

Human-Heart-Models for Formal Verification and Hardware-in-the-Loop Validation of Pacemakers

DISSERTATION

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Abstract

Pacemakers are an integral component of cardiovascular therapy. They are employed when a patient's cardiac rhythm is insufficient to meet the individual demands. Given the considerable patient-specific variability over a day and throughout the lifespan, this long-term implant has to adapt to the individual patient's changing needs and regulate the appropriate heart rate. In order to avoid potential risks to the patient, several factors have to be considered when pacing the heart. Stimulation at an inappropriate temporal phase can result in potential life-threatening adverse effects. Similarly, uncoordinated contraction among the heart chambers can lead to complications such as exercise intolerance, significantly impacting the patient's quality of life. The growing complexity of pacemakers is driven by the need to accommodate the unique needs of patients. This has led to an increased reliance on pacemakers to perform their functions with greater autonomy, necessitating comprehensive testing to ensure their reliability in diverse scenarios. The complexity of this process is further compounded by the multitude of factors that affect the pacemaker. Consequently, it is essential to develop a comprehensive testing and verification environment that can reflect the diverse range of influencing factors and borderline cases the pacemaker may encounter over its lifetime.

In this thesis, a heart model is presented that is capable of mirroring the [Electrical Conduction System of the Heart \(ECSH\)](#), the chambers and the valves of the heart. The model is capable of including the status of the chambers and valves as a function of the stimulation interval and the [Action Potential Duration \(APD\)](#). This enables the investigation of diverse scenarios, including pacing in the [vulnerable phase](#), the coordination of the chambers, the number of contractions for various diseases concerning the [ECSH](#) and the heart chambers. The model is demonstrated to be capable of modeling 14 diseases concerning the [ECSH](#), the generation of pulses within the heart and the heart chambers, such as various atrioventricular blockages, bradycardia, premature contractions, [flutter](#), and variances in the [QT interval](#) due to the menstrual cycle. The objective is to demonstrate the value of formal verification and [Hardware-in-the-Loop \(HIL\)](#) techniques for the development and improvement of increasingly complex medical devices in the future.

The proposed heart model is transformed into a formal verification model and a [HIL](#) model. The latter is then evaluated in interaction with a real pacemaker. A formal verification model of a pacemaker is constructed to assess the interaction between the formal verification model of the heart and a pacemaker. A particular challenge is to incorporate the various impact factors while keeping the model executable, especially since it is essential that the heart model interacts with the pacemaker in real time for [HIL](#) testing.

The [HIL](#) tests indicate the potential for life-threatening conditions concerning the number of contractions per minute, pacing during the [vulnerable phase](#), and the coordination of the chambers of the heart. The results also show the impact on the patient's safety of different diseases, of the chamber monitored by the pacemaker, of the frequency of [sinoatrial node \(SA node\)](#) self-stimulation and of the replacement rhythms. Our pacemaker model for formal verification shows promising results for the double chamber pacemaker. The single chamber model, however, is not yet suitable for all diseases. To the best of our knowledge, the pacing during the [vulnerable phase](#) and the chamber coordination have not been evaluated before.

Zusammenfassung

Herzschrittmacher sind ein integraler Bestandteil der kardiovaskulären Therapie. Sie werden eingesetzt, wenn der Herzrhythmus des Patienten nicht ausreicht, um die individuellen Anforderungen zu erfüllen. Die Anforderungen an den Schrittmacher sind dabei patientenspezifisch und variieren über den Tag und die Lebensdauer des Systems hinweg. Dementsprechend, muss sich dieses Langzeitimplantat an die wechselnden Bedürfnisse des einzelnen Patienten anpassen, um die Herzfrequenz entsprechend zu regulieren. Bei der Stimulation des Herzens müssen mehrere Faktoren beachtet werden, um Risiken für den Patienten zu vermeiden. Stimulationen in die vulnerable Phase des Herzens können lebensbedrohliche Auswirkungen für den Patienten haben. Ebenso können unkoordinierte Kontraktionen der Herzkammern zu Komplikationen wie Belastungsintoleranz führen, welche die Lebensqualität des Patienten erheblich einschränken. Die Notwendigkeit Herzschrittmacher besser an die individuellen Bedürfnisse der Patienten anzupassen hat zu einer zunehmenden Komplexität und Autonomie der Systeme geführt. Umfassende Prüfungen sind notwendig, um die Sicherheit und Zuverlässigkeit dieser Systeme in verschiedenen Szenarien zu gewährleisten. Die Komplexität der Prüfungen wird durch die Vielzahl der Faktoren, die einen Herzschrittmacher beeinflussen können, erhöht. Folglich ist es unerlässlich, eine umfassende Test- und Verifizierungsumgebung zu entwickeln, die das breite Spektrum der Einflussfaktoren und Grenzfälle widerspiegelt, denen ein Herzschrittmacher während seiner Lebensdauer ausgesetzt sein kann.

In dieser Arbeit wird ein Herzmodell vorgestellt, das das elektrische Reizleitungssystem des Herzens (ECSh), die Herzkammern und die Herzklappen einbezieht. Das Modell berücksichtigt den Zustand der Kammern und Klappen als Funktion des Stimulationsintervalls und der Aktionspotentialdauer (APD). Dies ermöglicht die Evaluation verschiedener Faktoren, einschließlich von Stimulationen in die vulnerable Phase, der Kammerkoordination sowie der Anzahl der Kontraktionen der Herzkammern, unter Einfluss von verschiedenen Krankheiten. Das Modell ist nachweislich in der Lage, 14 Krankheiten zu modellieren, die das ECSh, die Impulserzeugung im Herzen und die Herzkammern betreffen, unter anderem Blockaden, Bradykardien, extra Systolen, Flattern und zyklusbedingte Veränderungen des QT-Intervalls. Ziel ist es, den Wert der formalen Verifikation und der Hardware-in-the-Loop (HIL) für die Entwicklung und Verbesserung immer komplexerer medizinischer Geräte zu demonstrieren.

Das vorgestellte Herzmodell wird in ein formales Verifikationsmodell und ein HIL-Modell überführt. Mit letzterem wird die Interaktion mit einem echten Herzschrittmacher ausgewertet. Zur Auswertung der Interaktion zwischen dem formalen Verifikationsmodell des Herzens und einem Herzschrittmacher wird ein formales Verifikationsmodell eines Herzschrittmachers erstellt. Eine besondere Herausforderung besteht darin, die verschiedenen Einflussfaktoren zu berücksichtigen und gleichzeitig das Modell ausführbar zu halten, insbesondere, da es für HIL unerlässlich ist, dass das Herzmodell in Echtzeit mit dem Herzschrittmacher interagiert.

Die HIL-Tests zeigen das Potenzial für lebensbedrohliche Zustände in der Interaktion zwischen dem Herzmodell und dem Herzschrittmacher, in Bezug auf die Anzahl der Kontraktionen pro Minute, die Stimulation während der vulnerablen Phase und die Koordination der Herzkammern. Die Ergebnisse zeigen insbesondere die Auswirkungen durch die Ausgangsbedingungen während der Interaktion, wie den Einfluss von verschiedenen Krankheiten, der vom Schrittmacher überwachten Kammer, der Häufigkeit der Selbststimulation des sinoatrialen

Knotens und der Ersatzrhythmen auf die Sicherheit des Patienten. Unser Schrittmachermodell für die formale Verifikation zeigt vielversprechende Ergebnisse für den Zweikammer-Schrittmacher. Das Modell des Einkammer-Schrittmachers ist jedoch nicht für alle Krankheiten geeignet. Soweit wir wissen, sind Stimulation während der vulnerablen Phase und die Kammerkoordination zuvor noch nicht durch Modelle untersucht worden.

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Acronyms

ABP Atrial Blanking Period. 22–24

AEI Atrial Escape Interval. 24

APAC Action Potential After Conduction. 51, 52, 54–57, 86

APBC Action Potential Before Conduction. 51–57, 86, 89, 90

APD Action Potential Duration. , 2, 10, 46–60, 84, 85, 88, 89, 93, 98, 99, 101, 105, 115, 117, 118, 121, 126, 136, 137, 149, 150, 171, 176

ARP Atrial Refractory Period. 22–24

AV block Atrioventricular blockage. 89

AV Block 1 first-degree AV block. 10, 18, 19, 53, 54, 90, 106, 124–126, 138–145, 168, 170, 171

AV Block 2 h second-degree AV block higher grade. 10, 18, 19, 55, 91, 107, 124, 126, 127, 135, 138–143, 168, 170

AV Block 2 m second-degree AV block mobitz. 10, 18, 19, 56, 92, 107, 108, 124, 126, 127, 138–145, 150, 151, 168, 170

AV Block 2 w second-degree AV block wenckebach. 10, 18, 19, 27, 54, 90, 91, 106, 107, 127, 138–143, 168, 170

AV Block 3 third-degree AV block. 10, 18, 19, 57, 92, 124, 125, 168

AV Block 3i third-degree AV block infrahisary. 10, 124, 138–143

AV Block 3s third-degree AV block suprahisary. 10, 124, 138–143

AV node atrioventricular node. 8–10, 15, 29, 53, 87, 89, 92, 102, 105–108, 124, 143, 151, 170, 179

AV Valve atrioventricular valve. 2, 14, 45–48, 50, 85, 86, 95, 99, 101, 120

AVI Atrioventricular Interval. 24

BDD Binary Decision Diagram. 36, 40

BMI Body Mass Index. 17

BPEG British Pacing and Electrophysiology Group. vi, 22

bpm Beats Per Minute. 16, 18

CLS Closed-Loop Stimulation. 187

CTL Computation Tree Logic. 36, 39, 40

ECG ElectroCardioGram. 15–17, 123, 136, 149, 171, 187

ECSH Electrical Conduction System of the Heart. , 2, 6, 8, 14, 15, 18, 20, 27, 45, 46, 51, 52, 57, 59, 66, 68, 78, 83–88, 90, 92, 93, 97–108, 115, 121, 122, 124–126, 128–131, 133, 134, 136, 137, 143–145, 149, 150, 168, 169, 171

EIS Electrical Intrinsic Signal. 21–25, 27, 29, 45, 61, 64, 67–70, 72, 77–81, 94, 113, 115, 116, 119, 144, 167, 168, 185

FDA US Food and Drug Administration. 30, 31, 167

HIL Hardware-in-the-Loop. , 1–5, 8, 13, 31–34, 83, 87, 88, 91–94, 117, 119, 120, 126, 127, 131, 136, 145, 147, 149, 150, 170–173, 193–201

HRV Heart Rate Variability. 10, 16

IVDR In-Vitro Diagnostic Medical Device Regulation. 30

LabVIEW Laboratory Virtual Instrument Engineering Workbench. 4, 13, 34, 35, 83–92, 94, 95, 117, 119–121, 136, 145, 167, 169–171

LRI Lower Rate Interval. 22–24

LTL Linear Temporal Logic. 36

MDR Medical Device Regulation. 30

NASPE North American Society of Pacing and Electrophysiology. vi, 22

NBG-Code NASPE/ BPEG Generic Pacemaker Code. 22, 175

PAC Premature-Atrial-Contraction. 17, 59, 88, 105, 131, 132, 141, 142, 180

PAVRP Post-Atrial Ventricular Refractory Period. 23, 24

PCCD Prolonged Cardiac Conduction Disease. 19

PEA Peak Endocardial Acceleration. 187

ph value potential of Hydrogen. 188

PMT Pacemaker-Mediated-Tachycardia. 9, 10, 25, 27

PVABP Post-Ventricular Atrial Blanking Period. 26

PVARP Post-Ventricular Atrial Refractory Period. 23, 24, 27

PVC Premature-Ventricular-Contraction. 17, 59, 88, 105, 131, 132, 141, 142, 180

RMV Respiratory Minute Volume. 28, 187

SA node sinoatrial node. , 8, 9, 15–18, 28, 58, 87, 103, 121, 122, 124–134, 137, 138, 143, 145, 171–173, 180, 193–201

TCTL Timed Computation Tree Logic. 39, 43

URI Upper Rate Interval. 22–24

VBP Ventricular Blanking Period. 23, 24

VI Virtual Instrument. 34, 35, 121, 167

VO2max maximum amount of oxygen absorbed by the body during a maximum workload. 19

VRP Ventricular Refractory Period. 23, 24

VV Valve ventricle-vessel valve. 14, 46, 48, 50, 101

Introduction

The implantation of electrical medical devices can significantly enhance the quality of life for patients. In some instances, these devices may be a matter of life and death, as malfunctions can have serious and potentially fatal consequences. As medical devices become increasingly sophisticated in order to meet the individual needs of patients, it is crucial to establish validation and verification approaches that meet the requirements of medical regulations. This will ensure that the system is comprehensively validated and verified, thus preventing malfunctions.

Modern technical devices such as pacemakers represent a vital component of contemporary medicine. It is, therefore, imperative that their functionality is verified to ensure reliability and safety while at the same time minimizing the risk for animals and humans in the testing phases. This can be achieved by using software models of human organs interacting with the real devices. As an example of this approach, this thesis presents the model of a human heart to interact with pacemaker models and physical pacemakers. This thesis presents a system model of the heart and a pacemaker for the validation and verification of cardiac pacemakers. The implementation of this model is achieved by two distinct approaches: firstly, as a [Hardware-in-the-Loop \(HIL\)](#) model, and secondly, as a formal verification model. Additionally, a dedicated cardiac pacemaker model is designed for formal verification purposes. Subsequently, safety queries are defined, and the heart models are employed to evaluate pacemakers.

The complexity of biological systems and their intricate interdependencies present significant challenges to the integration of pacemakers. Even minor alterations in input parameters can result in a vast array of potential outcomes. Moreover, the full extent of the biological, chemical, and physiological interdependencies within these systems is not yet completely understood. Individual patients may also experience varying symptoms and show deviating measurement results, even when subjected to identical physiological conditions during medical examinations. As a result, many parameters required to model human organs are currently defined by relatively broad limits, and these limits may even vary depending on the reference. Furthermore, such a model requires an extensive state space, encompassing all potential variations. The system described here provides a framework for conducting well-defined and reproducible tests.

We demonstrate how a [HIL](#) model can be employed in conjunction with formal verification to validate and verify the functionality and safety of pacemakers and ensure their correct operation. In particular, the modular structure of the heart model allows one not only to confront the pacemaker with a regular healthy heart but also with a variety of diseases. Moreover, the model is suited to simulate different contextual conditions, such as gender-specific features based on the influence of hormones on the performance of the heart.

We develop a heart model that can be employed as a component of a [HIL](#) system to assess pacemaker functionality under realistic conditions. The [HIL](#) tests are conducted by integrating our heart model with a physical pacemaker, forming a closed-loop system. Additionally, the model can be transferred into a formal verification model. The verification model of the heart would give the opportunity to verify the satisfaction of defined safety criteria under diverse circumstances for the interaction between the heart and the pacemaker.

1.1 Context and Motivation

It is a common medical practice to surgically implant electrical medical devices, such as pacemakers, into patients for extended periods, often lasting years or even decades. To guarantee the patient's well-being and survival, it is essential that the pacemaker is capable of adapting to fluctuations in electrical resistances and frequencies. There is a pressing need for pacemakers to become more versatile in order to accommodate a broader range of patient activities, including cycling, illness, the variation of hormone levels, and relaxation. All these necessitate the development of more sophisticated and autonomous pacemaker algorithms, accompanied by a corresponding demand for more comprehensive validation and verification of heart-pacemaker interactions in situations that fall between the extremes.

The practice of using [HIL](#) is common within the automotive, aerospace, and railway industries [1]. However, this is not the case within the field of medical device certification, where neither [HIL](#) testing nor formal verification against biological models is currently a requirement [2]. The incorporation of [HIL](#) assessments facilitates the execution of authentic simulations, thereby enabling the identification of deficiencies at an early stage, without putting animals or humans at risk and at relatively low costs.

To the best of our knowledge, the current heart models for the testing of pacemakers do not take into account the states of the chambers and valves within the heart models, as outlined in Chapter 2. It is thus not possible to test the pacemakers for their probability of pacing into the [vulnerable phase](#), which could potentially result in [ventricular fibrillation](#) and significant adverse outcomes for the patient.

1.2 Objectives and Contribution

Our model characterizes the heart as a modular, parallel system of discrete, time-driven automata operating in unison while communicating asynchronously. To elucidate the dynamics of the heart's electrical conduction system, we employ a set of eleven parallel, single-parameter automata. Additionally, four parallel automata with distinct parameter sets are utilized to elucidate the chamber dynamics. The incorporation of supplementary modules models malfunctioning regions of a human heart. These modules can be incorporated into a user interface, thereby facilitating the generation of disparate timing characteristics and failure modes.

The proposed model is an effective method for identifying errors in the interplay between the pacemaker and the heart, as it calculates the [vulnerable phase](#) and valve state based on the current [Action Potential Duration \(APD\)](#). Additionally, patients may experience an inefficient coordinated pumping of the heart, medically referred to as [pacemaker syndrome](#). By employing our model, it is possible to study and visualize the effect of various abnormalities within the [Electrical Conduction System of the Heart \(ECSH\)](#), with or without the effect of a pacemaker. Our findings suggest both that current pacemakers may stimulate during the [vulnerable phase](#) and that atrial contractions against the closed [atrioventricular valve \(AV Valve\)](#) may occur, with the potential to cause adverse effects for patients.

The system described here provides a framework for conducting well-defined and reproducible tests.

Hardware-in-the-Loop The deployment of our [HIL](#) model permits the testing of physically available pacemakers in real-time, thereby facilitating the evaluation of their performance under conditions that approach the limits of their operational range. Furthermore, the examination of the corner cases identified through the verification process enables the enhancement of our verification model.

Formal Verification The formal verification of the interaction between the heart model and the pacemaker model allows for comprehensive verification across the full range of parameters defined for the models while incorporating boundaries for certain parameters by defining safety queries, which have to be satisfied during the interaction of the two models.

1.3 Publication List

Some of the results presented in this work were already presented in the following publications:

Conference presentations

J. Heuer, R. Krenz-Baath and R. Obermaisser (2022), "Modeling Bio-Electronic Systems", at 34. ITG/ GMM/ GI - Workshop Testmethoden und Zuverlässigkeit von Schaltungen und Systemen (TuZ 2022). Bremerhaven, Germany

J. Heuer, R. Krenz-Baath and R. Obermaisser (2023), " Verification of Bio-Electronic Systems", at 35. ITG/ GMM/ GI -Workshop Testmethoden und Zuverlässigkeit von Schaltungen und Systemen (TuZ 2023). Erfurt, Germany

J. Heuer, R. Krenz-Baath and R. Obermaisser (2023), "Verifying Bio-Electronic Systems", In Proc. of the 26th International Symposium on Design and Diagnostics of Electronic Circuits and Systems (DDECS). Tallinn, Estonia

J. Heuer, R. Krenz-Baath and R. Obermaisser (2023), " A software-based Heart Model for Formal Verification and Real-Time Validation of Medical Devices", 4th Young Researchers Academy MedTech MedTech Symposium (YRA MedTech Symposium). Jülich, Germany

Journal paper

J. Heuer, R. Krenz-Baath and R. Obermaisser (2024), "Human-Heart-Model in a Hardware-in-a-Loop Setup for Testing and Validation of Pacemakers" in Computers in Biology and medicine

1.4 Thesis Structure

The following section outlines the structure of the work.

- Chapter 2 introduces the fundamentals of human heart physiology, pacemaker technology, and domestic requirements, with a focus on the current state of technology for cardiac pacemaker systems. It also presents an overview of the background to [HIL](#) and formal verification and their added value for the approval process of medical devices.

- Chapter 3 provides a comprehensive account of the requisite specifications for a heart model designed to interact with a pacemaker. It offers an in-depth examination of the existing models in this domain and a systematic classification of the proposed model in the context of the prevailing state of the art.
- Chapter 4 presents the modules forming our model of the human heart as a system model.
- Chapter 5 presents the pacemaker model that has been developed as a system model.
- Chapter 6 delineates the defined safety queries, which have to be satisfied for the interaction between the heart and the pacemaker.
- Chapter 7 presents the heart model as a [HIL](#) model in [LabVIEW](#).
- Chapter 8 presents the heart and pacemaker models as formal verification models for [UPPAAL](#).
- Chapter 9 presents the results of the [HIL](#) tests and the formal verification.
- Chapter 10 considers the implications and limitations of the models and provides a summary of the most significant findings. In addition, possible future extensions of the model are discussed.

Related Work and Research Gap

2

The following chapter presents an overview of the challenges and requirements that arise in the context of modeling bioelectronically interacting systems. This is followed by a description of the essential specifications for a heart model that is to be used for pacemaker verification purposes. Subsequently, a summary of contemporary approaches to modeling the heart will be presented. To conclude, this project will be contextualized within the broader field of study, with a particular focus on its unique characteristics.

2.1 Modeling the Interaction between Heart and Pacemaker

In order for a model representing a human organ to be suitable for testing medical devices, it is essential to ensure that it accurately reflects the features of the organ. Given the complexity of the human body, the level of detail incorporated into the model must be tailored to align with the specific medical device undergoing evaluation. While a model structured at the cellular level may be deemed appropriate in principle, it is not feasible to fully consider all components of the heart for certain tests due to the high level of complexity. The model should accurately reflect the chronological and temporal sequences of a variety of processes occurring within the organ. Furthermore, the model should be capable of interacting with the medical device at the interface. On the one hand, this necessitates the provision of all of the parameters the medical device would receive from the human organ at the interface in order for the medical device to recognize it as the organ. On the other hand, it is essential that the model of the organ records and processes the responses of the medical device in a manner consistent with that of a real organ. This bidirectional process allows for the identification of potential risks to the patient resulting from interactions with the medical device.

In the context of modeling human physiology, the high degree of individuality inherent to the human organism necessitates the adaptability of a human organ model in a multitude of dimensions. This allows for the representation of a range of borderline cases, which is crucial for accurately replicating the nuances of human biology.

Specifications for a Hardware-in-the-Loop Testing Model

To facilitate the implementation of a [HIL](#) test environment, the simulated organ has to be capable of perceiving the reactions of an interacting medical device and emulating appropriate reactions in real-time. Therefore, the biological processes of the implemented model have to be designed to meet the required speed. For the interaction between a pacemaker and a heart the required speed for data transmission is milliseconds.

2.1.1 Requirements for a Heart Model

In order to represent the processes occurring within the heart, which is the most relevant organ for evaluating a pacemaker, the following elements should be included in the model. [Chapter 3](#) provides a further description of the heart, possible diseases, and the pacemaker treatment.

Electrical Conduction System of the Heart (anterograde/ retrograde) The [Electrical Conduction System of the Heart \(ECSH\)](#) serves as a coordinating system for the heart, facilitating an efficient pumping action. It transmits electrical stimulation pulses to activate the different areas along the system, ultimately resulting in contractions of the heart chambers. In order to accurately model the potential conduction direction, it is essential to consider both the [anterograde](#) and [retrograde](#) directions. Furthermore, different areas of the [ECSH](#) exhibit disparate timing behaviors, and some areas may permit self-stimulation followed by a probabilistic pulse transmission. It is thus imperative that all areas of the [ECSH](#) are included with their respective range of properties.

Heart Chambers and Valves The incorporation of dynamic alterations in the chamber and valve status into the model represents a crucial step in the investigation of the pumping efficiency of the heart and a number of potentially life-threatening scenarios, including [pacemaker syndrome](#) and pacing into the [vulnerable phase](#). The temporal parameters of the [vulnerable phase](#), including its duration and onset, depend on the timing of the respective chambers. This, in turn, is dependent upon the timing of the respective stimulation interval provided to the chamber by the [ECSH](#) and the pacemaker. A parallel dependency on the progression of contraction in the chamber is apparent in the status of the heart valves and the coordination of the [ventricles](#). These parameters are responsible for the cardiac output. Recent studies have indicated that the cardiac output exerts a greater influence on athletic performance than an increase in heart rate [3, 4]. It is, therefore, essential to be able to predict the dynamic alterations in chamber activity and, based on that, the altered timing of the [vulnerable phase](#) and the change in the chamber dynamics.

Heart Structure and Interfaces (internal and external) The individual components of the heart, including the various areas of the [ECSH](#) and the [ventricles](#), operate independently of one another, communicating via a range of interfaces. Consequently, when modeling the heart, the individual components have to operate independently and in parallel, connected via asynchronous channels. The same principles apply to the communication with a cardiac pacemaker. The heart model has to be capable of providing a signal that the pacemaker is able to recognize. Concurrently, the heart model should continue its intrinsic processes while the pacemaker detects and responds to the signal. Therefore, communication at the pacemaker interface should be as asynchronous and parallelized as the communication employed between the individual components of the heart model.

Diseases Malfunctions within the [ECSH](#) or timing of the heart chambers and valves may manifest in a number of ways, including dizziness, unconsciousness, and, in severe cases, death. As the underlying diseases are to be treated by a pacemaker, it is necessary to incorporate them into the heart model in order to create the test scenarios required. This allows for the interaction and treatment to be verified and validated in terms of safety and sufficiency.

Interference Signals It is possible for interfering signals, originating from within the body or from the external environment, to affect the ability of the pacemaker to detect the electrical impulses of the heart and consequently influence the pacemaker's ability to regulate the heartbeat. These interfering pulses are perceived by the pacemaker as a superimposition of the measured electrical cardiac activity. They, therefore should be integrated into the electrical output of the heart model.

2.1.2 Pacemaker Model Requirements

The model of a pacemaker should be as closely aligned with the actual system as possible. It is essential that the internal processes, including process sequences, intervals, and potential algorithms, are accurately represented. Additionally, the interface to the biological model and any interference signals should be provided.

Interface, Sensing and Pacing The interface between the pacemaker and the surrounding environment should be accurately represented in the model. This requires the inclusion of a cardiac interface, as well as the incorporation of electrodes and potential filters for the pacemaker.

Intervals, Modes, Algorithms and Mode Switch The pacemaker interacts with the heart by monitoring cardiac activity and emitting impulses in accordance with the sensed activity or as required. These processes are controlled by various intervals, modes, and algorithms. These processing elements, their probabilities, and settings are of decisive importance for the success of pacemaker therapy. Accordingly, these parameters should also be modeled by the pacemaker.

Energy Consumption and Aging Processes of the Device The function of a pacemaker is based on the delivery of energy to the heart; thus, the pacemaker should have a sufficient energy supply to stimulate the heart and execute the various algorithms. In the event that the energy is no longer sufficient, the device will be unable to execute various modes and should be surgically removed from the body and replaced with a new one. Accordingly, the behavior of the medical device should be modeled and verified during energy consumption and at low energy. Furthermore, the effects of aging should be modeled.

2.2 Related Work

Given the considerable complexity of biological structures and the substantial computational resources their modeling demands, it is necessary to reduce the level of detail in the models to enhance their computational feasibility, ensuring their execution within the requisite time frame for testing.

The following sections present an overview of the heart models developed by various research groups in order to provide a comprehensive overview of the current state of research in this field.

2.2.1 Simulation of the Heart

In recent decades, there have been notable advances in the field of pacemaker technology, including the development of novel pacemaker systems and their corresponding models. For example, Li et al. [5] developed a model for simulating biological pacemakers that were designed to replace electronic pacemakers in the future. However, their models have thus far focused on the modeling at the sub-cellular level.

Jiang et al. [6–10] presented a heart model designed for real-time interaction with pacemaker models from timed automata in Simulink. The virtual heart model is composed of distinct nodes and pathways that collectively represent the [ECSH](#). The individual sections are emulated by characterizing the action potentials of the respective section with ordinary differential equations. The pacemaker model, also developed by Jiang et al., then interacts with the aforementioned model-generated action potentials. Nevertheless, the model’s capacity to represent arrhythmias is constrained by the exclusive occurrence of electrical stimulus conduction in the [anterograde](#) direction.

Paoletti et al. [11] expanded the model proposed by Jiang et al. by incorporating probabilistic factors, thereby facilitating a broader spectrum of tests. Also, Roux et al. [12] built upon the cardiac model of Jiang et al. by incorporating [retrograde](#) pathways and additional nodes, enabling a more precise characterization of arrhythmias. However, neither of these approaches encompasses the trajectory of the electrical activity within the [ventricles](#), which is essential for assessing risks such as pacing into the [vulnerable phase](#) or the synchrony of the [ventricles](#).

Chen et al. [13] combined the Roux et al. model with the hybrid input-output automatic cell model presented by Smolka et al. with the objective of enhancing the fidelity of the individual model components. However, the model is constrained by the absence of [retrograde](#) conduction pathways, impairing its capacity to represent arrhythmias, as previously described. Yip et al. [14] extended the model proposed by Chen et al. (see also [15]) by incorporating additional models described above, thus creating a model capable of simulating the behavior of individual nodes with respect to their action potentials with high fidelity and exhibiting [retrograde](#) conduction. However, real-time interaction with a pacemaker is not feasible due to the extensive computational effort required to simulate a single cardiac cycle. The simulation of a single cardiac cycle requires approximately 30 seconds of actual computation time.

Hardware-in-the-Loop Models

In addition to software-based heart models interacting with software-based pacemaker models, Barker et al. [16] and Biasi et al. [17] conducted experiments including a [HIL](#) setup in which the pacemakers were represented by a micro-controller.

Barker et al. evaluated the power efficiency of pacemaker algorithms in interaction with a heart model but did not investigate the effects on the heart. Biasi et al. present a comprehensive model of cardiac anatomy based on partial differential equations. The model encompasses the [SA node](#), the [AV node](#), the [atrium](#), as well as the [endocardium](#) and [myocardium](#). Nevertheless, this level of detail is not practical for real-time implementation. Moreover, the model is incomplete in its coverage of other crucial regions of the [ECSH](#), such as the [bundle of his](#) and the [tawara bundle](#), which are required for accurate representation of a number of disease cases.

2.2.2 Formal Verification

Jiang et al. [6] also developed a model for formal verification, which was a highly abstract variant of their Simulink model. In order to circumvent the issue of [state explosion](#), this model was constrained to intervals of the heart chambers. Consequently, the inclusion of the intrinsic electrical conduction of the heart, endogenous replacement rhythms, and potential errors that may arise during the process cannot be incorporated into the verification.

2.3 Research Gaps

Table 2.1 provides an overview of the human heart models from different groups, including a comparison to our model. The characteristics of the model are enumerated on the left-hand side. The cells marked in green indicate the inclusion of specific properties in the model. A more detailed explanation of the colors and codes can be found at the bottom of the figure. Table 2.1 is divided into distinct categories. The particular specifications that a heart model must exhibit or encompass within each category are outlined in the following.

Physiology Implemented for the ECSH All heart models simulate [anterograde](#) conduction, the direction of conduction from the top to the bottom of the heart. Most models also include [retrograde](#) conduction from the bottom to the top of the heart. Only one other model proposed by (Ai et al. [18]) models area-specific self-stimulation, however, only for the [AV node](#). The probabilistic factor of self-stimulation is only included in our model. Heart rate variability is only in the model proposed by Chen et al. [15] and our model.

Physiology Implemented for the Heart Chambers As the following section demonstrates, our model is the only one that incorporates the [vulnerable phase](#) of the heart chambers and the status of the heart valves in accordance with the action potential duration.

Diseases - Pulse Generation Related In the modeled diseases, only Biasi et al. [17] include the possibility of [sinus arrest](#), in addition to our model. All other models include [bradycardia](#) and [tachycardia](#) originating from the [sinoatrial node](#). Jiang et al. [7, 8] and Paoletti et al. [19] also include [flutter](#). The models of Jiang et al. [6–10, 20], Lian et al. [21], Paoletti et al. [11], Ai et al. [18, 22], and Biasi et al. [17] include premature contractions, although for some of the models these are limited to atrial or ventricular primary contractions.

Diseases - Conduction Related The models encompass various AV blocks, with the first-degree and second-degree AV-block being the most prevalent. The third degree AV block is only modeled by our model.

Diseases - Chamber Related In addition to our model, the models of Kwiatkowska et al. [23] and Paoletti et al. [11] also include [long QT](#) in the modeling process. However, our model is the only one that incorporates the parameters of the menstrual cycle and the coordination between atrial and ventricular contractions.

Diseases - Chronotropic Competence In the case of diseases that directly affect the chamber, our model employs a chronotropic incompetence of the force-frequency relationship. Chronotropic incompetence is only incorporated into the model of Kwiatkowska et al. [23] The force-frequency relationship, which encompasses the status of the heart valves, is modeled exclusively by our model.

Pacemaker Associated Hazards Our model is the only one that includes the elements that are required to model the [vulnerable phase](#) and the heart valves and, thus, the potential to evaluate stimulations in the [vulnerable phase](#) and the [pacemaker syndrome](#). [Pacemaker-Mediated-Tachycardia](#) (PMT) is incorporated by the models proposed by Jiang et al. [6–10, 20], Lian et al. [21], Chen et al. [13, 24], Kwiatkowska et al. [23], Paoletti et al. [11], Ai et al. [18, 22] and Biasi et al. [17].

Pacemaker Interference Signal The phenomenon of far-field sensing is incorporated by the models proposed by Jiang et al. [6–10, 20], Lian et al. [21], Chen et al. [13, 24], Kwiatkowska et al. [23], Paoletti et al. [11], Ai et al. [18, 22] and Biasi et al. [17].

Table 2.1: Overview and comparison of state of the art heart models.

	Our Model	Jiang 2010 [6]	Jiang 2010 [7]	Jiang 2011 [8]	Jiang 2012 [9]	Jiang 2012 [20]	Jiang 2014 [10]	Lian 2013 [21]	Chen 2013 [15]	Chen 2014 [13]	Kwiatkowska 2014 [23]	Barker 2015 [16]	Yip 2018 [14]	Paoletti 2018 [11]	Ai 2020 [22]	Ai 2020 [18]	Biasi 2022 [17]
Physiology Implemented for the ECSH																	
anterograde conduction	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
retrograde conduction	x	x	x	x	x	x	x	x					x	x	x	x	x
area-spec. self stimulation	x															av	
prob. self stimulation	x																
Heart Rate Variability	x								x								
Physiology Implemented for the Heart Chambers																	
APD calculation	x																
vulnerable phase	x																
status of the heart valves	x																
Diseases - Pulse Generation Related																	
sinus arrest	x																x
bradycardia	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
tachycardia	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
flutter	x		x	x										x			
premature Contractions	x	a	a	a		a	a	x						a	x	x	v
Diseases - Conduction Related																	
AV Block 1	x							x	x	x			x		x	x	x
AV Block 2 m	x										x	x					
AV Block 2 w	x	x									x	x		x			
AV Block 2 h	x										x	x					
AV Block 3	x																x
AV Block 3i	x																
AV Block 3s	x																
Diseases - Chamber Related																	
long QT	x										x		x				
QT adaption to menstrual cycle	x																
coordinated contractions	x																
Diseases - Chronotropic Competence																	
chronotropic incompetence	x										x						
force-frequency relationship	x																
Pacemaker Associated Hazards																	
stimulation in vulnerable phase	x																
pacemaker syndrome	x																
PMT	x			x	x	x	x			x	x			x	x	x	x
Pacemaker Interference Signals																	
Far-Field-Sensing	x			x	x	x	x			x	x			x	x	x	x
Pacemaker Management																	
bradycardia management	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
tachycardia management	x		x	x	x	x	x			x			x		x	x	x
mode switch	x		x	x		x	x	x									
oversensing	x			x													
undersensing	x																
energy consumption	x									x							

x Property implemented
 av Property implemented for the AV node
 a Property implemented for the atrium

Pacemaker Management All of the pacemakers described are capable of treating [bradycardia](#). Some are also able to deal with [tachycardia](#) or, at the very least, prevent [tachycardia](#) from being transmitted to the other chamber by the pacemaker. An important factor here is the [mode switch](#), which is modeled by Jiang et al. The model of Jiang et al. also deals with [oversensing](#), while the model presented by Chen also investigates the energy consumption of pacemakers.

Summary of the Research Gaps

As previously outlined in the specifications for the cardiac model, it is of significant importance to incorporate self-stimulation of the inferior regions of the heart and the various cardiac chambers into the modeling process in order to investigate the impact of pacemakers on the heart. Previous models were unable to adequately simulate pacing in the [vulnerable phase](#) or the [pacemaker syndrome](#) due to the absence of proper modeling of heart chamber activity.

Our model overcomes this limitation by incorporating the [vulnerable phase](#) and the alteration in valve status contingent on the action potential duration of the distinct chambers and the pacing interval. This enables the representation of disparate ratios of action potential duration to pacing interval. Furthermore, the potential risks associated with pacemaker stimulation at varying times can be evaluated. Moreover, the model incorporates area-specific self-stimulation of the inferior regions of the heart, clinically referred to as replacement rhythms, with a probabilistic factor to enhance the model's fidelity to clinical reality.

A significant challenge in the field of biological modeling is the trade-off between increasing accuracy and the associated complexity. The generation of the signals that the pacemaker responds to is typically achieved through a standard methodological approach involving the combination of action potentials originating from disparate regions of the heart. This necessitates the precise delineation and calculation of each discrete electrical action potential. Potse et al. calculated one electrical cycle of the [ventricles](#) in their high-fidelity model using a 2048K-core Cray supercomputer in 20 minutes [25]. Yip et al. simulated one second of heart activity on a desktop computer in 30 seconds with their more abstract Hybrid-Input-Output-Automata model [14].

Accordingly, in order to enable a feasible model of the entire heart that runs in real-time, it is necessary to simplify the description of the electrical behavior. Our approach is centered on the delineation of the aforementioned regions, with a particular emphasis on the timescales associated with their activation and conduction. This reduces the computational complexity required and increases the variability of the model in response to different conduction perturbations that may occur in a given region. The pacemaker interacts with the heart model via a defined impulse, as opposed to an integrated signal derived from complex calculations of electrical potentials modeling various regions of the heart. This approach enables us to attain the requisite performance while incorporating mechanical elements, such as the status of the chamber and valves or the presence of interfering signals.

We further enhance the spectrum of modeled diseases in cardiac models by incorporating additional delays and blockages, which can be inserted and combined for various regions. Furthermore, the disease representation can be expanded to include a prolonged [QT interval](#). This allows for even more complex disease patterns. Previous models were capable of modeling the mediation of [bradycardia](#) and [tachycardia](#), as well as external interference and [mode switches](#). In the domain of pacemaker modifications, our model can facilitate the simulation of diverse scenarios to which the pacemaker must respond and the examination of the risks associated with the pacemaker's response.

Background

This chapter provides background information on the physiology of the human heart, pacemakers, [HIL](#) and formal verification serving as the foundation for the concepts presented in this work. The chapter will open with an overview of the physiology of the heart. Subsequently, the operational modes, the adaptability in pacemaker programming, and the potential hazards associated with pacemakers are introduced. This is followed by an overview of the design and approval guidelines applicable to pacemakers. The chapter concludes with the concepts related to [HIL](#) and formal verification, as well as an introduction to the tools utilized in this context, namely [LabVIEW](#) and [UPPAAL](#).

3.1 Physiology of the Human Heart

The heart rate is an inherently variable physiological parameter influenced by a multitude of factors. Such factors include physiological characteristics, such as body size, age, and gender [26], as well as responses to a variety of vegetative, physical, and psychological states. In a healthy physiological context, there is a bidirectional relationship between heart rate and the state of the body, whereby each influences the other [27].

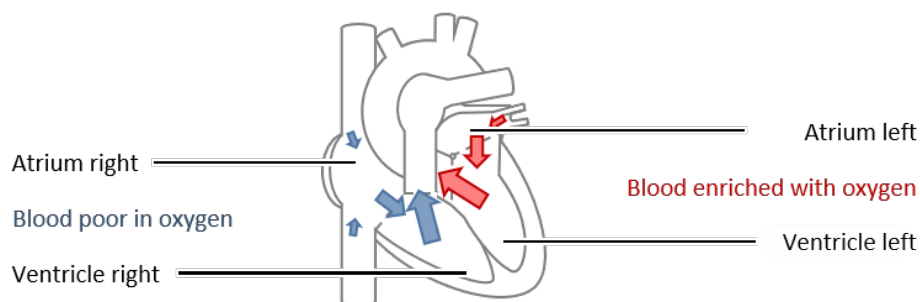


Figure 3.1: Schematic illustration of the division of the four cardiac chambers based on anatomical criteria, direction of the blood flow and the concentration of oxygen in the blood. As the heart is viewed from the perspective of the patient, the nomenclature is reversed.

The human heart can be divided into four chambers based on anatomical criteria, the blood flow and the concentration of oxygen in the blood. Figure 3.1 shows the four heart chambers and the pathway of the blood through the chambers. The illustration of the heart is presented from the perspective of the patient, which results in the image being reversed. As can be seen, the blood on the right-hand side of the heart is poor in oxygen, displayed in blue. Conversely the blood on the left hand side is rich in oxygen (displayed in red), since it has passed the lungs before entering these chambers. Subsequently, the two sides of the heart can be further subdivided into the [atrium](#) above and the [ventricle](#), the main chamber of the respective side.

3.1.1 Mechanical Sequence of a Pumping Action

The pumping process of the heart muscle can be conceptualized as a four-chamber suction-pressure pump. A contraction of a chamber, medically termed **systole**, results in the ejection of blood into the subsequent area of the cardiovascular system. Subsequent to the **systole**, the chamber undergoes a relaxation and extension phase, termed **diastole** [28, 29]. The rate of stimulation, and contraction impacts the duration of the aforementioned phases and the heart volume per minute, as will be discussed in Chapter 4. The direction of blood flow within this suction-pressure pump is primarily determined by the contraction direction of the chambers and the four heart valves, schematically represented in Figure 3.2.

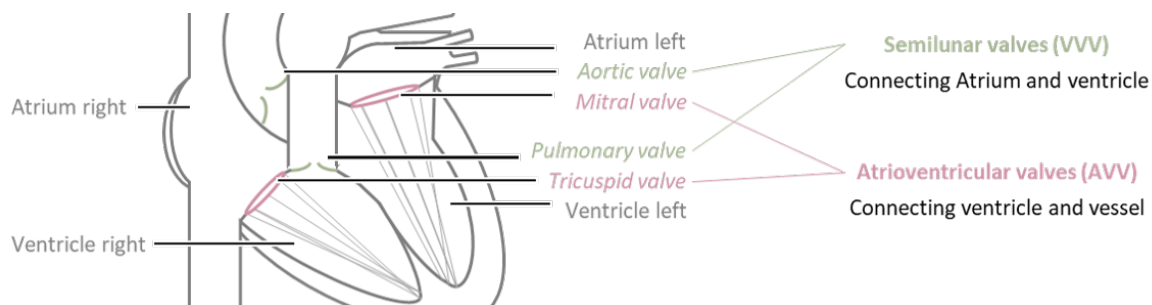


Figure 3.2: Schematic representation of the four heart valves and their association with the **ventricles**.

Systole

During a ventricular **systole**, the **ventricles** contract from the apex towards the center of the heart. In the initial stages of this contraction, the change in the shape of the **ventricle** closes the **atrioventricular valve (AV Valve)**, between the **atrium** and the **ventricle**, depicted in pink in Figure 3.2. The **AV Valve**, specifically the mitral valve (left) and tricuspid valve (right), are connected to the tissue of the **ventricles** and open and close in accordance with the changes in shape. Upon reaching the peak contraction the **ventricle-vessel valve (VV Valve)**, medically semilunar valve, opens due to the pressure exerted by the blood on the ventricular side.

Diastole

The subsequent expansion of the cardiac muscle during **diastole** generates a negative pressure gradient into the **ventricles**, thereby opening the **AV Valve** by reshaping the heart. Following the negative pressure gradient, the blood flows from the vessels through the atria and the open **AV Valve** into the **ventricles**. On the opposite side of the **ventricle**, the pocket-shaped **VV Valve** prevents the backflow of blood into the **ventricle**. As the blood flows back into the valve, the pocket-shaped valve becomes effectively sealed by the blood being drawn into it.

Chamber Coordination

The **AV Valve** has to be open throughout the process of re-filling the **ventricles**. This necessitates that the **ventricle** expands to a level that allows for a reopening of the **AV Valve**. Additionally, in a coordinated contraction of the heart muscle, the **ventricle** contracts after the **atrium**, which enables the **atrium** to increase the ventricular volume before the ventricular contraction closes the valve. The interval between the **atrium** and the **ventricle** is regulated by the **ECSH**, which is introduced in the subsequent section.

3.1.2 Electrical Conduction System of the Heart (ECSH)

The electrical connectivity and coordination of the heart chambers are facilitated by cells belonging to the **Electrical Conduction System of the Heart (ECSH)**. The ECSH can be subdivided into distinct regions, each exhibiting unique properties and localizations as illustrated in Figure 3.3. The time required for a pulse to traverse a given area depends on the distinctive combination of velocity and area dimensions. The regions highlighted in bold within Figure 3.3 are capable of generating electrical pulses and transmitting them to adjacent regions independently. These areas are capable of regulating the heart rate. The fastest rate of self-stimulation is typically observed in the **SA node**. A transmitted pulse stimulates the subsequent areas, preventing their self-stimulation [30–32].

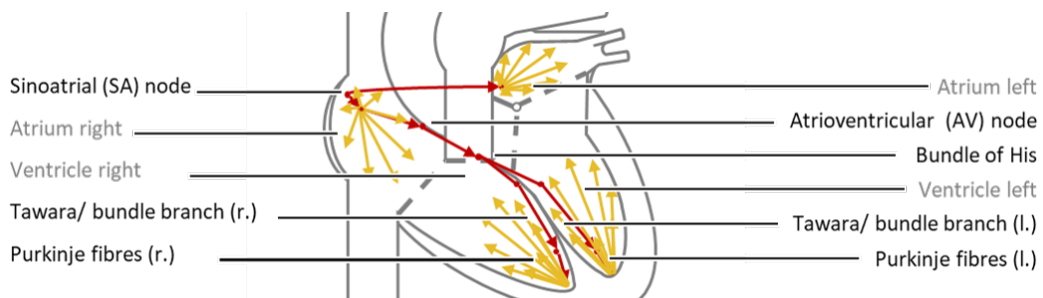


Figure 3.3: Schematic representation of the electrical conduction system of the heart.

In the event that the **SA node** fails to provide a pulse over a patient-specific time interval, deeper areas, such as the **AV node**, the **bundle of his**, and the **purkinje fibers**, may provide replacement rhythms. The aforementioned areas exhibit lower and less stable heart rates than the **SA node**. Furthermore, they are limited in their capacity to adapt to load with increasing depth within the ECSH. In particular, replacement rhythms are often insufficient to generate the requisite heart rate to maintain symptom-free or even survive.

visualization as ElectroCardioGram

An **ElectroCardioGram (ECG)** enables visualization of the electrical activity of distinct regions within the heart. The **P wave** is generated by the **depolarization** of the **atrium**. For a regular heartbeat, this is followed by the **QRS complex** and the **T wave**, originating from the **depolarization**, respectively, the **repolarization** of the **ventricles**. The **PR segment** and **PR interval** provide insights into atrial activity and the velocity of the pulse transitioning toward the **ventricle**. The subsequent **QT interval** combines the **QRS complex**, the **ST segment** and, the **T wave**. These intervals provide insight into the process of ventricular **depolarization** and subsequent **repolarization** of the **ventricle** [33].

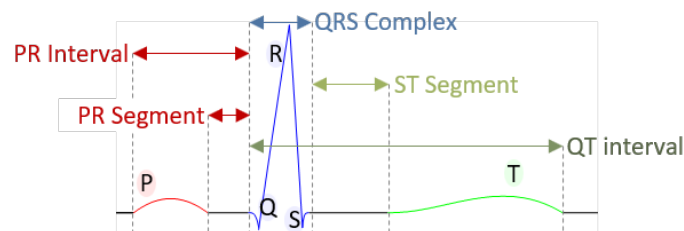


Figure 3.4: Schematic representation of the phases of a single heartbeat and their notations in an electrocardiogram.

QTc Interval In general, shorter **QT interval** intervals are observed at faster heart rates, while longer intervals are observed at slower heart rates. The **QTc interval** is a measure employed to identify **QT interval** intervals that are either excessively prolonged in comparison to the stimulation interval [33]. This is of particular importance, as a prolonged **QT interval** interval is associated with an increased risk of cardiac arrhythmia and a prolonged **vulnerable phase**.

A number of mathematical formulas have been developed, such as by Bazett, for calculating the **QTc interval** [33]. Notwithstanding their intrinsic limitations in including patient-specific factors such as the gender, these techniques remain widely employed in practice.

3.1.3 Adaptation and Variety within Hearts

The mean heart rate of healthy adults in **Beats Per Minute (bpm)** exhibits a range of 40 to 109 at rest [34]. Changes in body position and the performance of physical activity result in alterations in heart rate and **Heart Rate Variability (HRV)** [35]. Hereby, **HRV** is defined as the variation in time between consecutive regular heartbeats. The following examples illustrate the impact of various factors on cardiac activity.

Fluctuations in the Levels of Sex Hormones (Hourly, Monthly, Occasionally)

The interval for **SA node** self-stimulation is significantly shorter in women than in age-matched men with regular hearts [36]. Also, the morphology and duration of the action potential and **ECG** show differences based on gender [26], as can be seen in Figure 3.5.

A shortening of the **QT interval** by approximately 20 ms has been observed in males after the onset of puberty [37]. Since androgen deprivation therapy for prostate cancer increases the **QTc interval** interval [38], correlations between the **QTc interval** and testosterone levels are suggested. In women, the **QT interval** and the **QTc interval** are prolonged during pregnancy [39], and the **QTc interval** after intake of certain contraceptive pills. The use of oral contraceptives has been observed to result in a reduction of the **QTc interval** in cases of first- and second-generation oral contraceptives. Conversely, the use of fourth-generation oral contraceptives has been found to result in an increase in the **QTc interval** [40]. Also, the hormonal fluctuations over the menstrual cycle affect the heart rate [41], the **P wave** height [42], and the **QT interval** [43]. The relationship between the menstrual cycle and the incidence of ventricular premature beats, spontaneously occurring beats within the **ventricle**, is controversial [43, 44]. Furthermore, the amplitudes of **P waves** are significantly lower in women [45].

Physical Exercise

In response to an increase in load, the heart rate is elevated as a result of the initial activation of the parasympathetic nervous system. Moreover, an additional increase in heart rate is observed as a consequence of sympathetic activity when the workload reaches a level necessitating a heart rate of more than approximately 100 **bpm** [46–48]. Following the cessation of physical exertion, a decline in heart rate is anticipated over a period of up to 60 minutes [46, 49–51]. In individuals with regular hearts, intrinsic regulation causes a heart rate decline that is approximately exponential [52]. Measurements indicate no correlation between the heart rate and **HRV** during periods of rest, but there is a proportional relationship between heart rate and **HRV** at the beginning of the recovery phase following exertion [35].

The maximum heart rate during exercise depends on a number of factors. For instance, the heart rate declines with advancing age, and the range between maximum heart rates widens with elevated BMI. Additionally, there are discrepancies in the threshold values between men and women [53]. Some of these variances are visualized in Figure 3.5.

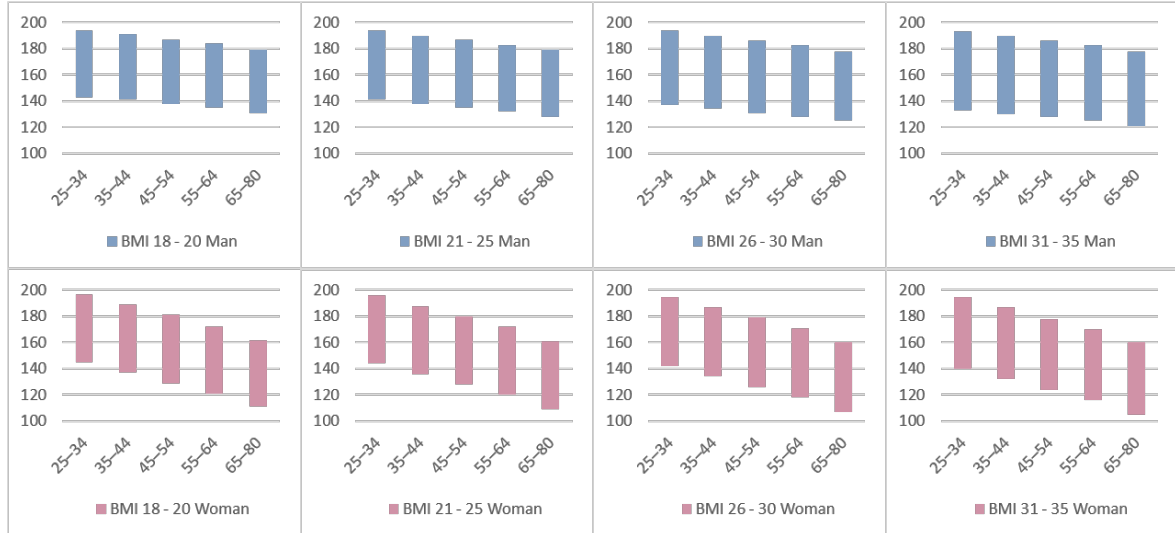


Figure 3.5: Differences in the heart rate at peak exercise based on age, gender and BMI, based on the data in [53].

Premature Contractions (Atrial and Ventricular)

A **Premature-Atrial-Contraction (PAC)** is an atrial activation originating from an **ectopic node** in an **atrium** rather than from the **SA node**. In the event that the **ectopic node** is situated in close proximity to the atrioventricular node, the atria are primarily depolarized by **retrograde** conduction. The majority of **PACs** reset the **SA node**, leading to a non-compensatory pause, and are conducted successfully, resulting in a ventricular contraction. A **PAC** is mostly asymptomatic and does not necessitate intervention. The occurrence of a **PAC** has a prevalence of at least one instance per 24 hours in 99% of the general population [54]. However, an association between frequent **PACs** and a number of adverse outcomes, including **atrial fibrillation**, ischaemic stroke, transient ischaemic attack, and mortality, is indicated [55].

A **Premature-Ventricular-Contraction (PVC)** occurs due to ventricular ectopic activity. The prevalence for a **PAC** to occur during a standard 12-lead **ECG** is 1% to 4% in a standard population. The prevalence in 24- to 48-hour Holter monitoring is up to 40% and 75% [56, 57]. However, there is a high prevalence in conjunction with structural heart disease, thereby indicating an elevated risk of mortality [58, 59]. In the absence of symptoms, **PVCs** do not necessitate intervention. In instances where the **PVCs** are symptomatic, **β blockers** can be employed to manage the associated symptoms [60].

Cardiac Arrhythmias

The classification of cardiac arrhythmias is based on their origin. Sinus rhythms originate in the **SA node**, atrial rhythms in the atria, and ventricular rhythms in the **ventricles**. In consideration of the underlying cause, sinus **bradycardia** and sinus **tachycardia** may be regarded as normal. However, arrhythmias originating from other parts of the atria are always considered clinical. The following section describes some of the pathological arrhythmias a pacemaker can be confronted with.

Atrial Flutter Atrial flutter is a supraventricular flutter characterized by a repetitive loop of a circulating electrical impulse, usually localized in the right [atrium](#). Each cycle of the loop causes a contraction of the atria, resulting in a fast and regular heart rate of 250 - 400 [bpm](#). The ventricular rate is slower due to the refractory properties of the AV node [61]. The prevalence of [atrial flutter](#) increases with age in children with cardiac disease [62].

Ventricular Flutter Ventricular flutter is typically the result of an [ectopic node](#) in one of the [ventricles](#), which emits regular and fast ventricular premature pulses with a range of up to 250 [bpm](#) [63]. A [ventricular flutter](#) episode with a duration of less than 30 seconds may occur without any accompanying symptoms. In the event that the episode persists for a period exceeding 30 seconds, immediate intervention is imperative to avert [cardiac arrest](#). Furthermore, [ventricular flutter](#) may progress to [ventricular fibrillation](#). Individuals with structural cardiac abnormalities, such as scarring, are more likely to experience [ventricular flutter](#).

3.1.4 Indications for Pacemaker Treatment

A pacemaker is indicated in case the heart is not able to generate an appropriate heart rhythm in the [atrium](#) and/or the conduction of pulses by the [ECSH](#) is interrupted. Defects and blockages along the [ECSH](#) can result in either temporary or permanent conduction abnormalities, which can pose a significant threat to the life of a patient [45].

Inappropriate Slow Atrial Rhythms

Possible diseases associated with inappropriate slow atrial rhythms are

- a disease concerning the [SA node](#) ([sick-sinus-syndrome](#)) [45]
 - Sinus [bradycardia](#) (heart rate < 40 [bpm](#), pauses > 3 s),
 - SA block, [sinus arrest](#),
 - bradycardia-tachycardia syndrome,
 - [chronotropic incompetence](#) (heart rate under stress below 100 to 110 [bpm](#) and/or continuous performance limit below 90 [bpm](#)),
- [atrial fibrillation](#) with [bradycardia](#) (slow ventricular rate (< 40 [bpm](#)) or long pauses (> 3 - 4 s) and suspected connection to clinical symptoms) [45]
- Post myocardial infarction [64] and
- the carotis sinus syndrome [45].

Conduction Diseases

The junction between the [atrium](#) and the [ventricle](#) may be partially or completely obstructed at various points along the [ECSH](#). Possible causes can be AV blockages [64, 65]. These are classified according to their impact on the cardiac output volume as

- [first-degree AV block](#) ([AV Block 1](#)), a delay,
- [second-degree AV block mobitz](#) ([AV Block 2 m](#)), an arbitrarily blockage,
- [second-degree AV block higher grade](#) ([AV Block 2 h](#)), a periodically blockage,
- [second-degree AV block wenckebach](#) ([AV Block 2 w](#)), a periodically progressive prolongation until a single complete blockage or
- [third-degree AV block](#) ([AV Block 3](#)), a complete blockage

within the pulse conduction. AV blockages are not inherently dangerous. In particular, an [AV Block 1](#) is typically not treated unless symptoms such as dizziness or other indications of dysfunction arise in the patient. An [AV Block 3](#), conversely, has the potential to rapidly become a life-threatening condition. Some forms of these AV blockages, especially of the second grade, are likely to progress to a higher and more severe and, therefore, potentially dangerous condition. This progression may occur suddenly. In the event that the generation and conduction of stimuli are insufficient to achieve an adequately high pulse rate and appropriate ventricular coordination, a pacemaker becomes a necessity.

There are guidelines for the majority of cardiac diseases, which define the conditions under which a pacemaker is indicated. However, it is essential to assess these conditions in the context of the individual patient, as not every patient requires the same therapy for the same underlying disease combinations. For example, congenital complete heart block, Long [QT interval](#) syndrome, hypertrophic cardiomyopathy, and heart failure are less common but possible indications for pacemaker implantation. The following is a summary of a guideline for [Prolonged Cardiac Conduction Disease \(PCCD\)](#) [66].

AV Blockage with a lower degree can be subject to treatment in case of co-morbidities like [PCCD](#). [PCCD](#) represents progressive conduction abnormalities without explanation on a structural or skeletal level in patients under 50 years. A pacemaker is indicated in case the [PCCD](#) occurs in parallel with

- an [AV Block 2 h](#) or an [AV Block 3](#),
- a symptomatic [AV Block 2 m](#) or [AV Block 2 w](#) or
- a bifascicular block with or without an [AV Block 1](#).

Chronotropic Incompetence

In patients with chronotropic insufficiency, the heart rate will not increase in case of physical load, resulting in a reduced exercise capacity and an elevated risk of mortality. This phenomenon is predominantly observed in patients with cardiac insufficiency [67–69]. The underlying cause remains uncertain. However, there is a potential association with an imbalance in the autonomic nervous system [67], morphological alterations [69], and [\$\beta\$ blocker](#) treatment [70]. The diagnosis of chronotropic insufficiency is based on the analysis of the heart rate response during an exercise test, which is ideally combined with an extended respiratory gas exchange analysis [67] since chronotropic insufficiency patients exhibit atypical patterns of gas exchange regarding the [maximum amount of oxygen absorbed by the body during a maximum workload \(VO₂max\)](#) and exercise oscillatory ventilation [69] for certain forms of chronotropic insufficiency [68]. The quality of life of these patients can be improved by exercise-based therapies [71].

The implementation of rate-adaptive pacemakers has been demonstrated to improve the exercise capacity and mortality of heart failure and [chronotropic incompetence](#) patients [67].

Chronotropic Incompetent AV Node In patients with a confirmed diagnosis of a COVID-19 infection, approximately 50% exhibited either paradoxical prolongation or absence of shortening of the [PR interval](#), in conjunction with an elevated heart rate. This aberrant [PR interval](#) behavior was associated with an elevated risk of mortality and the necessity for endotracheal intubation [72].

3.2 Pacemaker

The structure of a pacemaker can be divided into two main components: the signal processing pacemaker unit, containing the embedded electronics, software, and battery, and a connection linking the pacemaker to the heart muscle. The latest developments in pacemaker technology permit either transvenous implantation via electrodes or the utilization of leadless devices. In a transvenous implantation, the device is placed beneath the subcutaneous tissue in the region of the collarbone. From this position, it is connected to one, two, or three chambers of the heart via one to three electrodes, depending on the requirements of the patient. Initially, the electrodes are anchored to the chamber walls; subsequently, they are incorporated by the surrounding tissue. This process alters the electrical behavior of the lead-tissue interface.

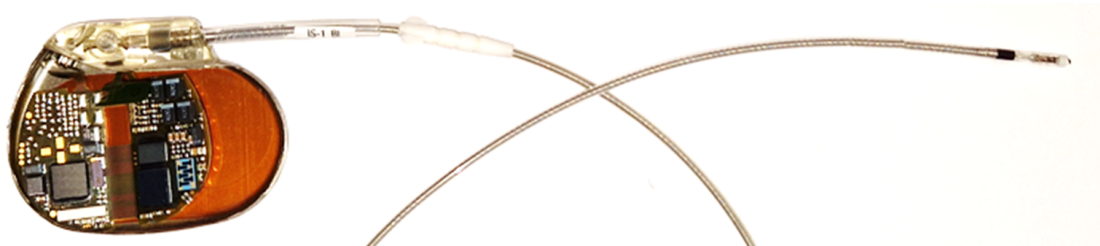


Figure 3.6: Implantable pacemaker with transvenous electrode.

Figure 3.6 shows a permanent pacemaker. A permanent pacemaker is typically worn for several years until the demands on the device change significantly, necessitating a replacement. This may occur due to the battery power becoming insufficient or due to changes in the patient's needs. In such cases, the electrodes are usually left in place, and a new device is connected to them.

The selection of a pacemaker is dependent upon the specific needs of the patient. A pacemaker may be programmed to interact with the heart in a variety of ways, depending on its abilities and connections to the heart.

- A Single-chamber pacemaker interacts with only one heart chamber, by one lead,
- a Dual-chamber pacemaker is connected to the [atrium](#) and the [ventricle](#), by two separate electrodes, while
- Biventricular systems comprise three leads that are attached to the two [ventricles](#) and the [atrium](#).

Single-chamber pacemakers are often indicated for a [sick-sinus-syndrome](#), yet conduction along the [ECSSH](#) remains intact. Dual-chamber systems are a common choice in cases of defective conduction in the [ECSSH](#) or proximal atrial arrhythmia. Biventricular pacemakers are indicated for cardiac resynchronization therapy.

3.2.1 Pacemaker Interface - Sensing and Pacing

The pacemaker paces the heart electrically to initiate a contraction of the muscle. Some pacemakers prioritize the **Electrical Intrinsic Signal (EIS)**, which has been found to yield several benefits for the patient, including a reduced risk of cardiac insufficiency. Therefore, the pacemaker senses for an **EIS** to adapt the time until the next stimulus. The following sections provide a concise overview of the characteristics and energy consumption of sensing and pacing.

Sensing

The occurrence of the **P wave** is monitored to assess atrial activity, while the **R wave** is considered a marker of ventricular activity. To accurately identify a heart signal and prevent it from interfering with other signals, hardware filters are employed:

- A **bandpass filter** is implemented with the highest input gain from 18 Hz - 150 Hz since the measured frequencies usually range from 20 - 50 Hz for the **R wave**, 40 - 90 Hz for the **P wave** and 2 - 10 Hz for the **T wave** [73] (The specifications are manufacturer and pacemaker model dependent).
- Area-specific thresholds are implemented to suppress all signals detected outside of 2 - 5 mV for the **atrium** and 10 - 20 mV for the **ventricle** [73].
- The **slew rate** enables a distinction between the **P waves** (usually ≥ 0.42 V/sec [74]) and the **R waves** (usually ≥ 1.4 V/sec [75]) against the **T waves** (usually ≤ 0.12 V/sec [75]).

A comparison of an electrogram (electrical recordings obtained from within the heart) recorded six months after implantation with those taken acutely revealed a reduction in both chronic voltage amplitude (by 15%) and slew rate (by 41%) [75]. The pacemaker must be adjusted or needs to adjust itself to ensure adequate sensing in accordance with the aforementioned changes.

Pacing

In the event that the pacemaker deems it necessary, it generates a rectangular voltage pulse to stimulate the heart muscle. The dimensions of the pulse, both in height and width, are adjusted by the physician and the pacemaker to exceed the stimulation threshold for the heart muscle. The energy output per pulse can be calculated by

$$E = U^2 \cdot \frac{t}{R}, \quad (3.1)$$

where E is the emitted energy in joule, U the amplitude in volt, t the duration in seconds, and R the impedance in Ohm [76]. Physicians and pacemakers have to adapt the parameters to the patient in the ranges of 1.5 - 3.5 V, which are applied over 0.2 - 0.6 ms. The total impedance for a pacemaker system and the heart tissue is approximately 300 - 1500 Ω for an intact lead and > 1000 Ω for high-impedance electrodes. Consequently, the energy emission is found to be within the range of 0.3 μ J to 24.5 μ J joules per pulse.

3.2.2 Adaptability - Modes, Intervals and Algorithms

A pacemaker is capable of operating in a variety of modes, contingent on the specific model. The physicians can set the modes and settings. In addition, the pacemaker is capable of switching between modes independently, contingent on the specific model and settings. The nomenclature of pacemaker modes is based on a generic code, designated as **NASPE/ BPEG Generic Pacemaker Code (NBG-Code)**, which is a combination of the **North American Society of Pacing and Electrophysiology (NASPE)** and **British Pacing and Electrophysiology Group (BPEG)** standards [77]. The aforementioned code is comprised of three to five letters, which represent the area in which the pacemaker senses, the pacemaker's pacing, the response to sensing an intrinsic signal, and whether the pacemaker is rate adaptable. Table 3.1 shows the potential values for the different positions and their respective meanings within the NBG code.

Table 3.1: Values and their respective meanings for the different positions in the **NBG-Code** [77].

Letter 1 Chamber(s) paced	Letter 2 Chamber(s) sensed	Letter 3 Response to sensing	Letter 4 Rate adaptiveness	Letter 5 Multisite Pacing
A (atrium), V (ventricle), O (none), D (dual - A & V) S (single - A or V)	A (atrium), V (ventricle), O (none), D (dual - A & V) S (single - A or V)	O (none), I (inhibited), T (triggered) D (dual - I & T)	O (none), R (rate adaptive)	A (atrium), V (ventricle), O (none), D (dual - A & V)

S is a manufacturer-specific notation for a single-chamber pacemaker suitable for the atrium and the ventricle

Exemplary modes for a single-chamber pacemaker connected to the atrium are

- **A00** - Rigid frequency (Paces atrium at programmed rate regardless of the **EIS**),
- **AAT** - Triggered (Senses in the atrium and paces atrium in case of sensed **EIS**),
- **AAI** - Inhibited (Senses in the atrium and inhibits atrial pacing in case of sensed **EIS**),
- **AAIR** - Inhibited with rate adaption.

The selected mode determines the applicable software-based intervals, limits, and (manufacturer-specific) algorithms, which can be adapted by the physician to suppress the sensing of interfering pulses and identify the optimal heart rate. An experienced physician is required to efficiently adapt a pacemaker to a given patient's requirements. The following examples demonstrate the functionality and intervals of some of the available modes and their adjustable intervals.

Single Chamber Modes

The following discussion focuses on the inhibited mode, as it is one of the most prevalent settings. Table 3.2 shows the intervals associated with a single-chamber pacemaker and the events triggering their onset and termination. Figure 3.7 depicts three stimulation scenarios.

Table 3.2: Abbreviations mentioned in Figure 3.7.

Abbreviation	Definition	Triggered by	Terminated by
ABP	Atrial Blanking Period	event (A sense or A pace)	time
ARP	Atrial Refractory Period	event (A sense or A pace)	time
URI	Upper Rate Interval	event (A sense or A pace)	time
LRI	Lower Rate Interval	event (A sense or A pace)	event (A sense or A pace) or time

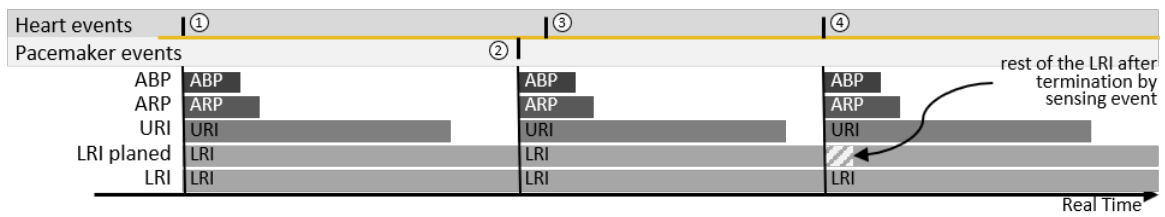


Figure 3.7: Intervals in a single-chamber inhibited pacemaker mode. **EIS** is represented above the yellow baseline, whereas pacing is indicated below. The x-axis represents the time, while the y-axis depicts the pacemaker intervals, triggered and partially terminated by events shown on the base line. The abbreviations are described in Table 3.2.

The three pulses above the yellow baseline are **EIS**. The impulse in the middle, below the axis, represents a pacemaker-mediated stimulation of the **atrium**. Each chamber atrial activity sensed as **EIS** or paced by the pacemaker initiates the intervals **Atrial Blanking Period** (**ABP**), **Atrial Refractory Period** (**ARP**), **Upper Rate Interval** (**URI**), and **Lower Rate Interval** (**LRI**). **ABP** and **ARP** are time-controlled intervals designed to prevent the double sensing of a cardiac impulse. During **ABP**, the corresponding electrode is fully deactivated. Subsequently, during **ARP**, the electrode identifies sensed pulses as interference signals. Meanwhile, **URI** is a time-controlled interval restricting the stimulation rate by establishing the minimum duration until the next stimulation. This interval has no influence on sensing. It just prohibits pacing. Conversely, **LRI** ensures a sufficient heart rate by limiting the time between simulations. An expiration of **LRI** is followed by a stimulation of the heart muscle by the pacemaker. **LRI** is event-controlled and, it is reset by chamber activity.

The initial pulse in Figure 3.7, sensed by the pacemaker, initiates a reset of all aforementioned intervals. The second pulse is provided by the pacemaker due to the expiration of the **LRI**. All intervals are reset again. The third pulse is not registered by the pacemaker, as it occurs within the blanking period and thus does not affect the intervals. The fourth pulse occurs prior to the conclusion of the **LRI**, resulting in the termination and reset of the **LRI** and all associated intervals.

Dual Chamber Modes

Table 3.3 presents the intervals of a dual-chamber pacemaker configuration, exemplified by the **DDD** mode. This mode enables the pacemaker to sense and pace within both **atrium** and **ventricle**. When no pacing is required, it inhibits the stimulation. Figure 3.8 illustrates the sequence of events and the interaction between the individual intervals and the cardiac and pacemaker events.

In addition to the intervals in Figure 3.8, the sequence for the **DDD** mode is extended by the inclusion of the **Ventricular Blanking Period** (**VBP**) and the **Ventricular Refractory Period** (**VRP**). These intervals exhibit a similar occurrence and sequence to **ABP** and **ARP** presented for the **atrium**. They commence with ventricular activity and conclude after a defined time period. Electrical events in one chamber can be perceived at the electrode of the other chamber. Consequently, atrial pacing initiates a **Post-Atrial Ventricular Refractory Period** (**PAVRP**), while any ventricular event is followed by a **Post-Ventricular Atrial Refractory Period** (**PVARP**). Atrial sensing is not followed by a **PAVRP** since the pulse is insufficiently strong to be sensed in the **ventricle**.

Table 3.3: Abbreviations mentioned in Figure 3.8.

Abbr.	Definition	Triggered by	Terminated by
AVI	Atrioventricular Interval	event (A sense or pace)	event (V sense)
AEI	Atrial Escape Interval	event (V sense or pace)	event (A sense)
ABP	Atrial Blanking Period	event (A sense or pace)	time
ARP	Atrial Refractory Period	event (A sense or pace)	time
PVARP	Post-Atrial Ventricular Refractory Period	event (A pace)	time
VBP	Ventricular Blanking Period	event (V sense or pace)	time
VRP	Ventricular Refractory Period	event (V sense or pace)	time
PAVRP	Post-Ventricular Atrial Refractory Period	event (V sense or pace)	time
URI	Upper Rate Interval	event (A sense or pace)	event (A sense or pace)
LRI	Lower Rate Interval	event (A sense or pace)	event (A sense or pace)

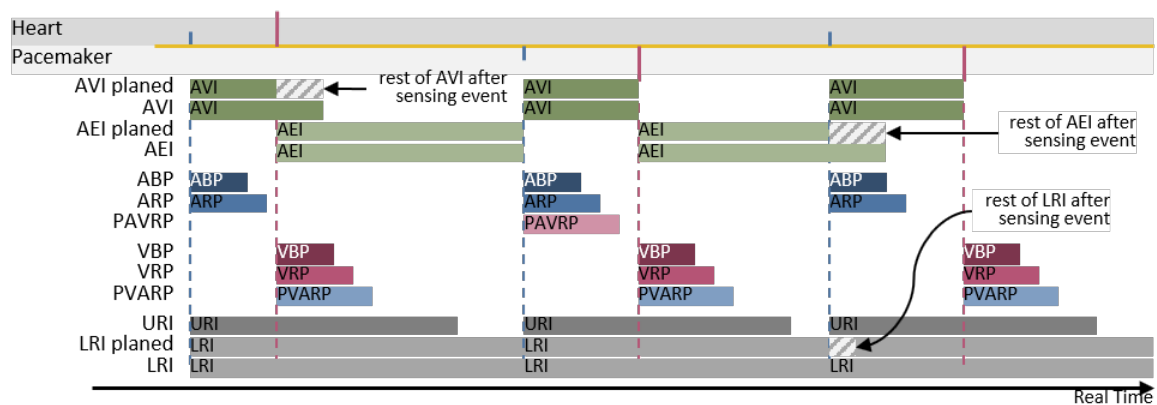


Figure 3.8: Intervals in a double-chamber inhibited pacemaker mode. Blue marks indicate atrial activity, pink marks ventricular activity. Cardiac events are represented by lines above the yellow baseline, whereas pacemaker events are indicated by lines below. The x-axis represents the time, while the y-axis depicts pacemaker intervals, which are triggered and partially stopped by events shown on the base line. The abbreviations are described in Table 3.3.

In order to ensure coordination between the [atrium](#) and the [ventricle](#), an [Atrioventricular Interval \(AVI\)](#) is added, which controls the conduction time between the [atrium](#) and the [ventricle](#). The [AVI](#) is initiated by an atrial event and terminated either by the sensing of a ventricular event or by expiration. In the event that the [AVI](#) expires the [ventricle](#) is paced by the pacemaker. In the case of an [AVI](#), a distinction is made subsequent to the sensing and pacing of the [atrium](#). Given that the pulse has already been transmitted at the time of sensing, it is necessary to set a longer conduction time following the atrial pacing in order to achieve the same conduction time as after sensing an [EIS](#) in the [atrium](#). Moreover, the [Atrial Escape Interval \(AEI\)](#) is introduced. This interval is initiated by a ventricular event and terminated by the perception of atrial activity. In the event that no atrial activity is discerned prior to the expiration of the [AEI](#), the [atrium](#) is stimulated.

Figure 3.8 presents a schematic overview of the pacemaker's response to three atrial (blue) and ventricular (pink) events. The pacemaker senses the initial atrial event, prompting the initiation of blanking intervals in the [atrium](#). Prior to the expiration of the [AVI](#), a ventricular activity is perceived. This terminates the [AVI](#) and initiates all sensing-related intervals associated with ventricular activity and the [AEI](#). As a result of the expiration of the [AEI](#), the pacemaker generates the second atrial impulse. The atrial stimulation initiates all sensing prevention intervals for the [atrium](#), the [ventricle](#), and the [AVI](#). Subsequently, the [ventricle](#) is stimulated by the pacemaker due to the expiration of the [AVI](#) interval.

3.3 Hazards and Challenges in Heart-Pacemaker Interaction

Malfunctions of pacemakers have been associated with adverse outcomes, including [cardiac arrest](#), syncopal seizures, heart failure, and death. Despite technological advancements, accurately detecting malfunctions remains a significant challenge. Therefore, monitoring is imperative [78], even in patients with uncomplicated clinical courses and no overt symptoms. In a postop evaluation by Nasir et al. [79], 26.4% of patients experienced complications over the reviewed timeframe of 36 – 96 months. Common postoperative complications are

- dislocation of pacemaker electrodes [45, 79, 80],
- [Pacemaker-Mediated-Tachycardia \(PMT\)](#) [79],
- early battery depletion [79],
- asystole [45],
- [ventricular fibrillation](#) [45],
- pocket hematoma [45],
- pneumothorax and haematothorax [45, 81] and
- device infection [45].

The considerable prevalence of lead malfunctions, particularly in pediatric [82] and female [79] patients, requires the swift identification of lead and generator issues. The most frequent complications are electrode dislocation (numbers vary from 3.1% [80] to 6.6% [79]), [PMT](#) (5.5% [79]), and early battery depletion (5.5% [79]). Identified correlation factors for complications are

- being female [79],
- being young (< 12 years) [82] or of increased age [79],
- the presence of structural congenital heart disease [82],
- previous heart surgery [83],
- blood thinning medication [83],
- additional diseases such as diabetes disease and chronic kidney failure [83] and
- dual chamber pacemakers [79].

Furthermore, delayed recalls result in syncopal episodes due to loss of pacing in patients with biventricular systems. The underlying causes of the pacing loss were determined to be high internal battery impedance and the failure of stripped bond wires within the electronic circuitry. The former is caused by the accumulation of a resistive film on the cathode current collector, which results in an increase in the internal impedance of the battery. The latter is caused by a degradation of the bond at the aluminum/gold intermetallic interface [84].

Sensing

On the sensing side, interfering signals are typically situated beyond the specified ranges, as described in Section 3.2.1. However, in some instances, they traverse the aforementioned chamber-specific [bandpass filter](#), [slew rate](#), and voltage thresholds and can be recognised as an [EIS](#), medically referred to as [oversensing](#). Conversely, the aforementioned chamber-specific [bandpass filter](#), [slew rate](#), voltage thresholds, and blanking intervals can blank out occurrences of [EIS](#). This is medically referred to as [undersensing](#). The following section delineates the underlying causes and resultant effects.

Oversensing Oversensing may result from the perception of a signal emitted from another heart chamber, medically referred to as crosstalk. Far-field **R wave** sensing (a ventricular **R wave** misidentified as a **P wave**) is a significant contributing factor to inappropriate switching to an alternative pacing mode in dual-chamber pacemakers [85, 86]. The risk of far-field **R wave** sensing is particularly elevated for short **Post-Ventricular Atrial Blanking Period (PVABP)** and high atrial sensitivity. Furthermore, instances of misinterpretation of **P waves** or **T waves** as **R waves** are documented. The prevalence of **oversensing** the **P wave** is increased for an implantation [87] or an insulation defect due to friction [88] of a ventricular electrode in close proximity to the **atrium**. The probability of exercise-related **T wave oversensing** is increased for a reduced ventricular threshold. In such cases, the slew rate is a sufficient parameter to differentiate between the **R wave** and the **T wave** at rest, but not during exercise [89].

In addition to the internal cardiac crosstalk, electromagnetic fields or electrical impulses originating external to the heart can result in interference-related **oversensing**. Medical devices, for example, impedance-based respiratory monitoring [90] and transcutaneous electrical nerve stimulation (a pain management device) [91], emit signals that affect the functioning of the pacemaker by interference. Bipolar electrodes reduce the probability of malfunctions due to electromagnetic fields to the extent that no specific precautions are advised when employing common household appliances [92, 93]. Nevertheless, devices positioned at a distance of less than 5 cm from the pacemaker generator can cause interference, and prolonged exposure to electromagnetic fields can induce functional anomalies. Welding equipment, electric motors, and demagnetization coils are examples for tools that inhibit pacemakers.

The consequence of **oversensing**, contingent on the operational mode of the pacemaker, is either an increase or a decrease in stimulus delivered by the pacemaker. In the event that it is not possible to resolve the issue of **oversensing** by extending the voltage threshold or the blanking periods, the electrodes and/or the pacemaker must be replaced.

Undersensing In contrast, **undersensing** is defined as the inability of the pacemaker to accurately sense the electrical activity occurring within the chamber. The consequences of **undersensing** can vary from no discernible effect over a reduction in exercise tolerance and an overall decline in quality of life ($\geq 10\%$) [94] to life-threatening ventricular arrhythmias in patients with intermittent atrial **undersensing**.

Vulnerable Phase

The interval of the **vulnerable phase** emerges during the electrical **repolarization** of the **ventricle** and varies in length, contingent on the duration of the action potential for each beat. Stimulation during the **vulnerable phase** has the potential to result in the development of **atrial fibrillation**, **tachyarrhythmias**, or, in the most severe cases, **ventricular fibrillation** [95]. The uncoordinated stimulation of the **ventricles** during **ventricular fibrillation** can result in **cardiac arrest**, defined as the complete inability of the **ventricles** to contract, leading to a significant reduction in cardiac output. In the absence of rapid resuscitation measures, there is a high risk of potentially fatal consequences, including brain injury and death [96]. Given the required fluctuations in heart rate throughout the day in response to various physiological and psychological factors, the pacemaker has to adapt its pacing rate gradually in order to accommodate these changes. This enables the chemical and biological muscle processes to align with the new pacemaker frequency, thereby ensuring optimal cardiac function [97]. The probability of pacing into the **vulnerable phase** is significantly elevated if the pacemaker is **undersensing**, for example, due to an unsuitable blanking period [98].

Pacing

The challenges in determining the patient-specific threshold for pacing occur from the multiple factors on which the electrical properties of the tissue and the heart-pacemaker interface are dependent. Some of the predictable influencing factors are the changes due to the growth of the electrode into the muscle in the days following the surgical procedure, the conductor material-specific properties of the lead, the properties of the active electrode surface, the patient-specific contact resistance from lead to tissue and the patient-specific tissue resistance [76]. Additional factors may also influence the overall impedance over the course of the pacemaker's lifespan, like technical defects (such as electrode fracture/ insulation defects) and physiological disorders (such as myocardial necrosis, electrolyte/metabolic imbalance, and medications). Consequently, the threshold values considered by these filters have to be adjusted constantly.

The occurrence of complications in the efficiency of pacing pulses can be reduced by increasing the pacing threshold. In order to identify the most energy-saving settings, the minimum pulse amplitude required to induce a reliable myocardial [depolarization](#) for a selected pulse duration for a given patient must be determined.

Pacemaker Syndrome

In the event of atrial contractions occurring against closed heart valves, blood is pumped back into the vein instead of into the [ventricle](#). This results in a reduction of the cardiac output volume, which in turn causes a decline in blood pressure and the potential for collapse. This condition is medically referred to as [pacemaker syndrome](#). The underlying causes for this can be attributed to two primary factors: firstly, the replacement of a portion of the [ECSH](#) with a pacemaker programmed with an inadequate conduction time [98], and secondly, a failure in the proper adjustment of the interference settings to align with the specific circumstances [99].

Force-Frequency Relationship at Rate Adaptation and Physical Exertion

In their meta-study, Clark et al. [4] demonstrated that rate-adaptive pacing increases the heart rate in patients with chronic heart failure. However, optimal cardiac output is of greater importance in achieving peak exercise [3, 4]. Rate adaptation may be more beneficial for the low loading range than for the generation of peak levels of load. The relevance of the force-frequency relationship can be seen, for example, in exercise intolerance or presyncope, as well as dizziness during exercise, in patients with AV blockage reported in [19]. In the reported cases, the patients experienced pacemaker-induced [second-degree AV block wenckebach](#) during exercise while being symptom-free at rest. Following the modification of the [PVARP](#) and the AV intervals, the patients remained symptom-free in their usual lifestyle [19].

Pacemaker-Mediated-Tachycardia

A [tachycardia](#) in which the pacemaker is a key component is classified as [Pacemaker-Mediated-Tachycardia \(PMT\)](#). In these cases, the pacemaker senses atrial [tachyarrhythmia](#), electromagnetic disturbances or retrograd-conducted ventricular signals as atrial [EIS](#) at the atrial electrode and paces the [ventricle](#) accordingly. The latter is referred to as endless loop [tachycardia](#) [100]. Acute [PMT](#) can result in a range of symptoms, including palpitations, chest discomfort, dizziness, syncope, or even a worsening of heart failure symptoms, depending on the rate of [tachycardia](#) and its impact on hemodynamic efficiency. [PMT](#) can be effectively treated, for instance, by prolonging the atrial blanking interval, with no long-term effects.

3.3.1 Adaptive Pacing

Rate response or rate-adaptive pacing represents a dynamic and evolving area within the domain of pacemaker development. These approaches are indicated for patients exhibiting **chronotropic incompetence**, defined as the heart's inability to adequately increase its rate in response to heightened activity or elevated **metabolic** demand, such as resulting from impairment in the **SA node**, and are observed in approximately 30-50% of patients with heart failure [68, 101]. This condition frequently results in an inability to engage in physical exertion. Conversely, the pacemaker's frequency can be adjusted to a more comfortable level for the patient by enabling the night mode. This mode reduces the pacemaker's stimulation rate during periods of sleep or during rest or sleep phases.

Sensors for Rate Adaption

Approaches, including sensors, are designed to detect changes in motion or ventilation, thereby ascertaining the patient's activity level and adjusting the heart rate accordingly. An ideal sensor would be capable of adapting and reacting in a manner analogous to that of the **SA node**, exhibiting rapid adaptation, precise sensing, and the ability to differentiate and adapt to physical, vegetative, and psychological loads. New approaches, such as the novel pacing algorithm PressurePace™, which modulates the atrial pacing rate based on blood pressure, have demonstrated promising results in a comparative study versus conventional methods [102].

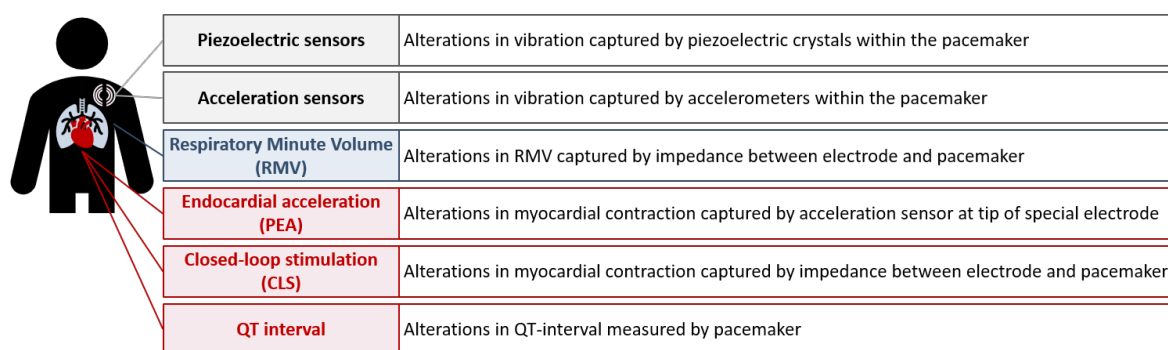


Figure 3.9: Schematic overview regarding the sensors for rate adaptive pacing and the organs and parameters utilized as references for load detection.

Figure 3.9 depicts a selection of conventional sensors in rate adaptation proposed in [103]. A more detailed description of the functions, advantages, and disadvantages of the sensors can be found in Chapter A of the Appendix. Currently, no sensor meets the criteria for an ideal sensor. Vibration sensors are capable of rapid response to changes but are not capable of adequately recognizing movements for certain postures, for example, if the upper body is at rest during cycling or when exposed to external vibrations (such as from streetcars). Moreover, they are incapable of discerning stress. The **Respiratory Minute Volume (RMV)** sensors, which predict the stress based on respiratory rate, are more effective in stress detection but require constant calculations, which makes them slow in response to changes and energy-intensive. Other methods employ alterations in cardiac parameters, such as contractility or the interval between **atrium** and **ventricle**, but necessitate specialized probes and also exhibit delayed responsiveness due to constant calculations. Moreover, the underlying disease may disable conclusions regarding the requisite heart rate based on the conduction interval between **atrium** and **ventricle**.

3.3.2 Mode Switch

A variety of stimulation modes are available, differing based on the pacemaker model. The physician selects and sets the appropriate mode, based on the patient's needs. Some pacemakers are able to alter the mode, based on the selected setting. Figure 3.10 provides an exemplary overview of common modes, along with a selection of parameters influencing the choice of the most suitable mode and the potential risks associated with the respective mode.

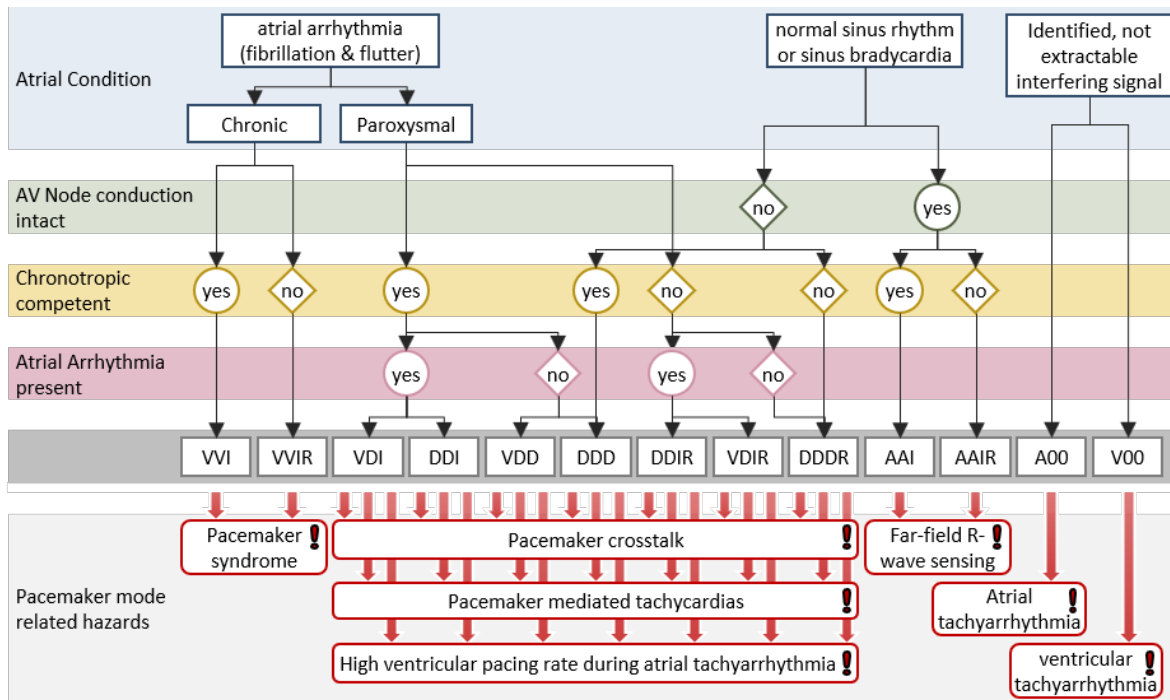


Figure 3.10: Exemplary and schematic overview of the commonly available modes, indicated in the dark gray bar. The colored bars above represent a selection of parameters and paths for choosing the pacemaker mode based on [64]. Below, the modes potential risks associated with the respective modes can be seen.

Figure 3.10 demonstrates that the occurrence of arrhythmia in the atrium (blue), the status of the AV node (green), the potential of chronotropic incompetence, and the current presence of atrial arrhythmia (pink) should be considered in choosing the optimal mode at the present moment. Specific difficulties for the pacemaker are encountered when the parameters undergo alteration. For instance, in the event of an atrial arrhythmia while the pacemaker is in DDD mode, a switch to either VDI or DDI is recommended to prevent an excessive pacing rate from being transmitted to the ventricle based on atrial sensing. A so-called mode switch can be programmed by the physician in anticipation of a potential tachyarrhythmia in the atrium.

Nevertheless, even when the selected mode is most appropriate for the given scenario, such as performing a mode switch to fixed-frequency mode (AOO, VOO, or DDD) in the presence of an interfering signal that cannot be mediated by the pacemaker, there are still inherent risks. In this case, failure to switch from an inhibitory mode to a fixed-frequency mode could result in the pacemaker inhibiting pacing, assuming the interfering signal as an EIS. However, if the switch takes place, there is a risk of triggering atrial or ventricular tachyarrhythmia by stimulating the vulnerable phase or causing pacemaker syndrome. Especially ventricular tachyarrhythmia can be as fatal as the absence of pacing is life-threatening.

3.3.3 Electronics and Energy Consumption

As previously outlined, surgical replacement of the pacemaker generator is indicated when the energy output is no longer sufficient to meet the necessities of the patient. These replacements are associated with the considerable risks mentioned at the beginning of Section 3.3 and high costs. The current design of pacemakers incorporates lithium batteries, which occupy over half of the total volume. To increase the lifespan of these batteries, they are often integrated with microcontroller circuits designed to consume minimal power. Nevertheless, the development of rechargeable batteries that can be implanted in the body represents an area of active research. A variety of approaches are currently under evaluation, including some that have already been tested on animals. For example,

- solar-powered systems that employ solar panels beneath the skin [104–106],
- harvest excess energy from heart movement captured via a linear generator in an electrode [107],
- miniaturized thermoelectric generators [108], and
- mass imbalance oscillation generators [109]

represent promising approaches of research.

The development of effective charging systems for pacemakers represents a significant challenge. It is of paramount importance that these systems do not interfere with the pacemaker's sensing. Misinterpretation by the pacemaker as a cardiac signal could lead to the aforementioned inhibition of the pacemaker, while the identification as interference could result in the pacemaker entering a mode that does not provide optimal care for the patient, as described in Section 3.3.

3.4 Pacemaker Development Process

The approval of medical devices by the [US Food and Drug Administration \(FDA\)](#) and in accordance with European standards differs in particular with regard to the parties involved. While the [FDA](#) is responsible for approving products, the manufacturer is required to confirm the conformity of the medical device with the relevant guidelines as part of the European approval process. In the case of high-risk products, the manufacturer is obliged to include a [notified body](#) in the European Union approval process. Moreover, the duration of the approval process varies. Once a product has been approved, it remains approved by the [FDA](#), provided that no significant alterations have been made to the product. In accordance with European guidelines, a product is granted approval for a period of five years. Subsequently, a reevaluation of compliance with the prevailing guidelines is necessary, and if required, the product must be modified accordingly.

In both approval procedures, guidelines or standards for the development of medical devices are provided. The manufacturer's technical documentation is examined by the relevant authorities ([FDA](#) or notified bodies) to ascertain its compliance with the aforementioned documents. In certain cases, additional testing at an accredited laboratory may be required. Both procedures allow for the approval of products that are already on the market. However, the [FDA](#) procedure [510\(k\)](#) is less demanding than the European Union procedure in accordance with the [Medical Device Regulation](#) and [In-Vitro Diagnostic Medical Device Regulation](#). All products, whether newly approved or based on a previously approved product, must be registered.

3.4.1 Tests in the Pacemaker Approval

As previously stated, a pacemaker is comprised of a signal processing pacemaker unit, which incorporates the integrated electronics, software, and batteries, in addition to a connection to the heart muscle. The software and hardware of pacemakers are designed with the objective of keeping the patient safe while optimizing energy consumption in order to avoid the necessity of replacing the unit and thus avoiding a repeated medical operation for as long as possible. As previously described, replacing the unit is a stressful and costly process for the patient. Ideally the pacemaker would also provide the patient with the best possible care by adapting to its needs. The fulfillment of these characteristics requires validation and verification prior to the implementation of the pacemaker in the patient. The device is evaluated in its entirety, rather than undergoing individual tests. As the categories of tests outlined in the European standards and the American guidelines are notably similar, Figure 3.11 presents the test categories of the FDA guidelines as an illustrative example. In 1990, the FDA published guidelines for the testing of [110, 111]. The framework enables the validation of pacemaker design via a series of tests that assess both safety and efficacy of the implementation. Moreover, a number of biological tests are conducted to ascertain the suitability of the device for implantation in the human body and for transportation.

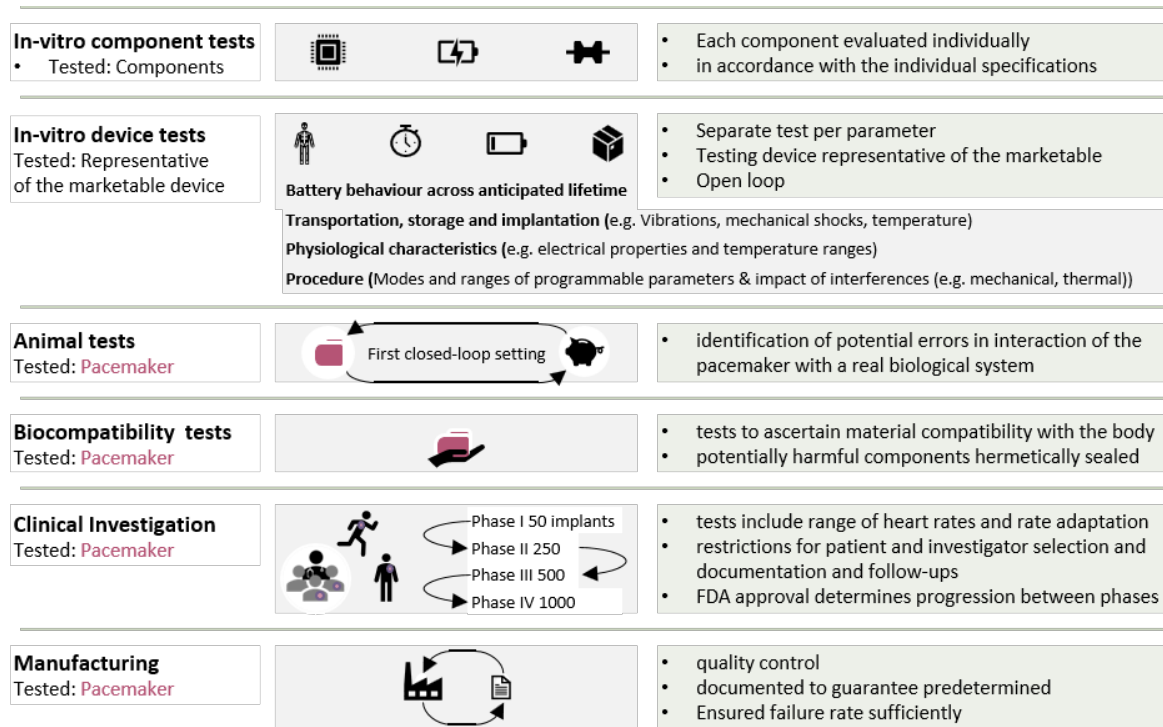


Figure 3.11: Test categories regarding the FDA guidelines.

3.4.2 Added Value to the Process of Software Development

Formal verification and HIL testing can improve the design and approval process for high risk medical devices, such as a pacemaker. In the initial stages of developing new pacemaker components or algorithms, these can be tested and modified directly. For advanced development steps they could assist in evaluating borderline and long-term scenarios. The following section describes the possible benefits in more details.

There is no established, industry-wide standardized procedure for the development of software in the field of medical technology. Nevertheless, software developed for use in this field is required to comply with the specifications, assuring the quality of software development outlined in the ISO 9001 [112], ISO/IEC 25010 [113], and ISO/IEC 12207 [114]. A variety of frameworks are aligned with the pertinent standards throughout the software development process. Frameworks that are well-established examples for the development of software in the medical technology sector are for example the waterfall model, in which each clearly defined phase must be completed before the next one begin, and the V-model, in which testing is defined as a part of the development process and each development phase is connected to the corresponding testing phase. The following section will examine the role of HIL and formal verification in the context of the V-model.

V-Model Figure 3.12 shows the stages of the V-model. The V-model is characterized by a clearly defined structure and traceability, with each development stage linked to a corresponding test phase. The parallel planning of tests ensures that potential errors are identified at an early stage in the development process. The approach is well suited for projects that require strict documentation, such as those involving safety-critical systems, due to both the planning and documentation that begins at the early stages. However, the model is not particularly flexible, as changes to the requirements are challenging to implement due to its highly sequential structure. Additionally, development times are lengthy, as all requirements must be defined at the outset, and it can take a considerable amount of time before the first results are visible. Moreover, it is not suitable for agile projects: The V-model is less practicable in dynamic environments, where requirements change frequently. Accordingly, this approach is well suited to projects with stable requirements and few changes.

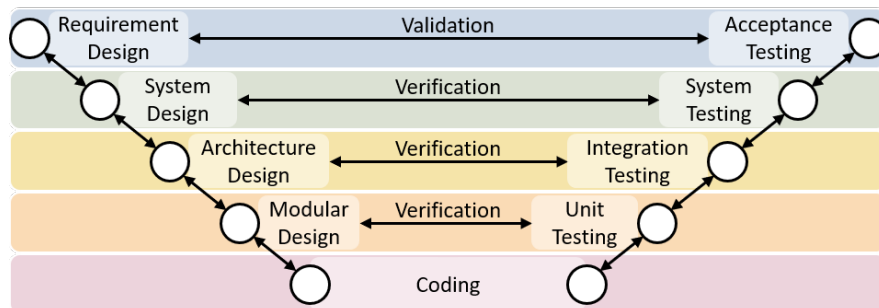


Figure 3.12: Representation of the V-model.

Formal Verification and Hardware-in-the-Loop in the Development Process

A notable benefit of both approaches is the capacity to incorporate additional disease patterns that have not yet been considered, should the need arise. The generated information about the physiological or environmental processes can then be included in the verification model to further extrapolate, identify, and investigate borderline cases. While HIL measurements must be conducted in real-time, formal verification is capable of processing a vast number of properties and extended time periods within seconds or minutes, verifying diverse requirements and borderline cases. Identified cases and approaches to mediate them can subsequently be evaluated in the HIL model to test them under environmental conditions.

Formal Verification In the V-model, formal verification can be employed to substantiate the system design specifications. This is the second stage of the V-model, marked in green in Figure 3.12. This stage ensures that the stipulated requirements have been adequately considered and that no contradictions exist within the design. A standardized model providing the boundaries of the human organ, extended by safety queries, which must be met by the interaction with the model, establishes a framework that supports the design and verification in the early stages.

Regarding the tests demanded by the FDA for the approval of a medical device, shown in Figure 3.11, formal verification could improve vitro component tests and in vitro device development and tests. In the in vitro component test, the components are selected and verified against standardized properties and requirements, including modeled borderline cases. Subsequently, the components are combined to form an overall system to verify that the requirements in interactions and under different boundary conditions are met.

Hardware-in-the-loop Testing The third phase of the V-model, the integration test of the V-model (Figure 3.12), is to ascertain whether the software interacts correctly with the hardware. In this context, HIL can be employed to evaluate the system's performance in a simulated environment, encompassing the full range of interactions and potential boundary and borderline cases between the heart and the pacemaker.

In the case of component and in vitro device tests mentioned in Figure 3.11, a standard HIL model improves the development performance in a later development stage by finding flaws at a lower level of detail and in the physical design. This enables the evaluation of the influence of a component or modification without the requirement for implantation in an animal or human, thereby reducing the probability of adverse effects and risks. Evaluated conditions can also include environmental factors, like heat or vibrations. HIL cannot be considered a substitute for the mandatory tests on animals of a new device (Figure 3.11) required for the approval of a medicinal product. Nevertheless, the physical pacemaker, including all software and hardware components, can be tested in a closed-loop before the implantation, and the risk for animals experiencing harmful effects of malfunctioning new devices or algorithms arising in closed-loop implementation can be reduced. Furthermore, the HIL model can be utilized to evaluate borderline cases regarding the patients and the environmental conditions the pacemaker can be confronted with over its life cycle.

3.5 Hardware-in-the-Loop

Hardware-in-the-loop testing represents a methodology for conducting tests on a system by connecting it to a test system, emulating the physical interfaces and conditions of the real environment. By enabling the evaluation of system functionality and interoperability in a manner that more closely resembles actual usage, this methodology overcomes the limitations of testing in operation, including the confounding effects of factors such as costs, time, and risks to the patient.

The aforementioned significant advantages have led to the increasing implementation of [HIL](#) in a multitude of fields, including the development of novel mechanical systems [115]. Early examples of this date back to 1967, when a [HIL](#) setup was employed to evaluate the actual Gemini digital computer [116] in real-time. The Gemini Guidance Computer was developed as the first onboard computer for a manned spacecraft, with the objective of optimizing the control and monitoring of flight maneuvers.

3.5.1 Advantages of a HIL Model for Pacemaker Testing

In order to provide the pacemaker with physical input as if the physical heart were present, the counterpart for testing a commercial pacemaker, in this case, is a model of the heart that transmits input/output signals that the pacemaker is able to understand. Modifications to the pacemaker or the interconnections between the heart and pacemaker can be rapidly incorporated and evaluated in a closed-loop manner, thus facilitating rapid iteration and optimization in real-time. Another advantage of this test procedure is the adaptability and variability of a [HIL](#). Extensions that simulate additional output signals of the heart or other parts of the heart or even the environment, such as smartwatches for additional input or interference signals, can be incorporated. This enables the evaluation of the effectiveness of innovative sensors, techniques, and algorithms for improving pacemakers in conjunction with the heart model.

3.5.2 LabVIEW

[Laboratory Virtual Instrument Engineering Workbench \(LabVIEW\)](#) is a technology developed by National Instruments [117]. It is a customizable combination of software and hardware-based components designed for the acquisition, analysis, and visualization of data. The software is employed in a variety of settings, including industry, academia, and research laboratories. An individual [Virtual Instrument \(VI\)](#) is written in a graphical programming language, facilitating the calculation, execution, and recording of software and hardware components. [VIs](#) can be linked, controlled, and read out via their inputs and outputs. In addition to pre-existing [VIs](#), users can also create and link their own [VIs](#) with inputs and outputs that are tailored to their specific needs. Each [VI](#) is designed with a front panel that serves as a user interface and a block diagram. The aforementioned front panel is composed of control elements, such as buttons and input fields, as well as displays that illustrate various statuses within the program sequence. Meanwhile, programming is carried out in the block diagram, where multiple [VIs](#) are selected and linked in order to execute the required functions.

Programming in LabVIEW

The program flow is represented as a diagram consisting of VIs and data flow lines between them. Each VI represents a subroutine embedded in the program, performing various functions, such as reading and recording data, performing mathematical calculations, and saving data. A function palette lists predefined nodes with categories and subcategories. Once a node has calculated its output, it is passed along the output wires to the waiting nodes. Nodes feature input connections on the left and output connections on the right. Accordingly, the data flow along the wires from left to right.

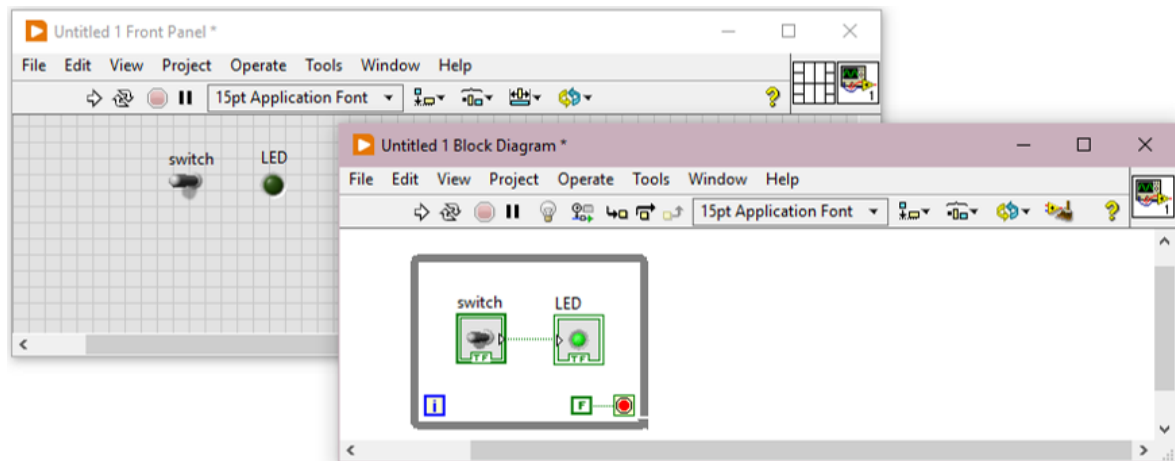


Figure 3.13: Block diagram and a front panel of a miniature VI in LabVIEW, including a switch and an LED controllable by the switch.

Figure 3.13 depicts a miniature VI with a block diagram and a front panel. The front panel, depicted in gray, includes the two interaction components, a switch, and an LED. When the switch button is clicked, the LED illuminates or extinguishes in accordance with the switch button's state. The block diagram on the right illustrates the networking of the two components. The switch and the LED each possess their own discrete block connected to the other. The data flow from left towards right, meaning from the switch into the LED, which assumes the same value as the switch. The two components are surrounded by a gray box, which represents a while loop. While loops run until they are terminated externally or by another condition.

3.6 Formal Verification

In contrast to the verification of medical products, which is conducted to ascertain whether a product aligns with the specifications outlined by a company during its development, formal verification in the context of hardware and software systems entails the rigorous examination of a given system's adherence to a specific formal property through the application of formal mathematical methods. One approach is model-checking, which involves a systematic and exhaustive statistical investigation of the mathematical model. Another approach is deductive verification, which involves a dedicated system, the requisite specifications, and a collection of mathematical proof obligations.

The models we designed for the formal verification process in [UPPAAL](#) were constructed with the intention of being verified by model-checking. [UPPAAL](#) is a well-established tool for modeling timed automata, combining temporal logic with temporal extensions. This enables the modeling of time-dependent behavior in complex systems with time constraints and hard real-time requirements. These are vital features for the formal verification of medical devices. Moreover, [UPPAAL](#) models can be augmented with probabilistic behavior, which is of paramount importance because of the considerable inter-individual variability in humans and the fluctuations within a single individual. The capacity to construct models that are readily comprehensible facilitates communication between developers, engineers, and medical experts, thereby expediting the incorporation of modifications and adaptations.

The concept and verification environment [UPPAAL](#) is described in further detail below.

Model-Checking

model-checking is a procedure for the fully automatic verification of a system description (model T) against a specification (formula φ). The formal definition for deterministic verification is

$$T \models \varphi.$$

If the system is found to satisfy the specified conditions deterministically, the property is successfully verified. In the event that the system does not satisfy the specified conditions, a counterexample is generated to demonstrate the violation. The specification is often expressed in the form of a logical formula, which is written in accordance with the conventions of temporal logic. Two such logics are [Computation Tree Logic \(CTL\)](#) and [Linear Temporal Logic \(LTL\)](#). For [CTL](#) and [LTL](#), a system is described in the form of a transition graph and verified against a specification expressed in a formula, formulated in accordance with the respective logic [118]. In contrast to deterministic model-checking, the statistic model-checking approach determines whether a property is satisfied with a certain probability, formally defined as

$$T \models P_{\geq p}(\varphi),$$

by performing a combination of simulation and statistical methods, such as hypothesis testing [119]. As the deterministic verification approach of [UPPAAL](#) is based on a modified form of symbolic verification on [Binary Decision Diagram \(BDD\)](#) in [Computation Tree Logic](#), the subsequent section will initially present an overview of the fundamental principles of automata theory, which serves as a foundation for [CTL](#) verification. Subsequently, the [CTL](#) verification procedure is presented. This is followed by an introduction of statistical model-checking, which is the [UPPAAL](#) approach to manage the [state explosion](#) problem for models with probabilistic components. In conclusion, the [UPPAAL](#)-specific extensions and applications of the aforementioned fundamentals will be described.

3.6.1 Automata Theory

In order to represent finite and infinite systems, transition graphs are employed. The system properties within these graphs are defined by logic, thereby offering the benefits of formally defined semantics. Moreover, the system states are reduced to a finite number of properties, thereby rendering the system decidable. The following sections present the various theories, with Figure 3.14 serving as an illustrative example. The Figure depicts the process of opening the camera mode on a the smartphone in natural language. The system initiates with a black screen. Upon pressing the smartphone's lock button, the screen is activated. If the button is pressed again immediately, the transition to the camera mode occurs. However, if the button is pressed with a time delay or not at all, the system returns to deactivated mode. Once the camera mode is engaged, the system has the option of returning to the previously selected mode by pressing the lock button again or after a certain waiting period.

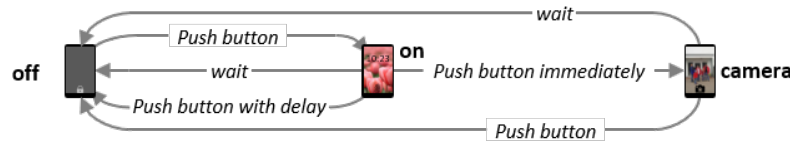


Figure 3.14: Schematic representation of a shortcut for camera activation on smartphone.

Finite Automata

A finite automaton is a model representing a system as an interconnected network of states and transitions, depicted in the form of a transition graph. This work defines an infinite automaton and the potential transitions that are possible for it:

Definition 1 A finite automaton is a tuple $T = (V, \Pi, \delta, s_0)$ with V as a finite set of states, Π as a finite alphabet, $\delta \subseteq V \times \Pi \times V$ as the transition relation and $s_0 \in V$ as the initial state. In accordance, the transition $v \xrightarrow{\pi} v'$ is possible if $(v, \pi, v') \in \delta$, with π as an element from the set Π .

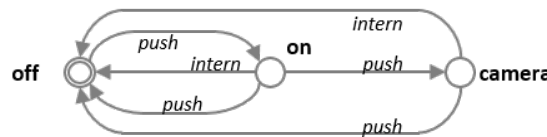


Figure 3.15: Finite automata based on the process depicted in Figure 3.14.

The exemplary representation of a transition graph for the aforementioned example is depicted in Figure 3.15. The sequence comprises three states: off, on, and camera. Here, off represents the initial state, indicated by a double circle. The transitions (edges) are extended by push and intern, representing internal and external actions. The system can revert to its initial state from the states on and camera by an internal event or by awaiting push. The exemplary automata can be specified by the aforementioned definition:

- $V = \{\text{off, on, camera}\}$
- $\Pi = \{\text{push, intern}\}$
- $\delta = \{(\text{off, push, on}), (\text{on, push, camera}), (\text{on, push, off}), (\text{on, intern, off}), (\text{camera, push, off}), (\text{camera, intern, off})\}$
- $s_0 = \{\text{none}\}$

Timed Automata

A timed automaton is an extension of the finite automaton that incorporates temporal components. These are integrated in the form of **invariants** and guards against which the time variables can be compared. Additionally, options for resetting the time variables ($t = 0$) are provided. Invariants impose a limit on the permitted length of time spent in a given state; for instance, a state may have the **invariant** $t \leq 2$, indicating that a state may only be visited for a maximum of two timesteps. In this instance, the variable must exit the state as soon as the aforementioned condition is no longer met. Guards function similarly; a transition may only be executed when the previously described conditions are met in conjunction with fulfillment of the time component, such that $t == 2$ is true. Figure 3.16 shows an accordingly extended version of Figure 3.15.

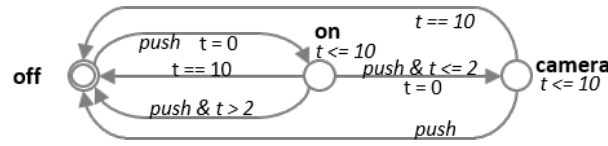


Figure 3.16: Timed automata based on the process depicted in Figure 3.14 and Figure 3.15.

Consequently, the transition from on to camera can only be executed if $t < 2$ and the push action occurs. In the event that t exceeds 2 when push occurs, a transition to off is initiated. Should no action occur until the specified period of time ($t > 10$) has elapsed, then the system will transition back to off via the internal path at exactly $t == 10$. It is possible for the system to remain in off indefinitely, as no **invariants** are imposed.

An extension of the automaton described in Definition 1 by a time component yields the following definition for the timed automaton:

Definition 2 A *timed automaton* is a tuple $T = (V, E, \delta, s_0, C, I)$ with V as a finite set of states, E as a finite alphabet, $\delta \subseteq V \times P(C) \times E \times 2^C \times V$ as the transition relation and $s_0 \in V$ as the initial state, C as a finite set of clocks and $I : P(C)$ is a mapping that assigns **invariants** to states, with $P(C)$ being a predicate over C .

The expansion of properties and limitations for a transition due to including timed values leads to the inclusion of constraints on time, actions, and resets of clocks. This means a transition $v \xrightarrow{\pi, \gamma, \zeta} v'$ is possible if $(v, \pi, \gamma, \zeta, v') \in \delta$, with π as an element from the set E , γ as the clock constraints by guards and $\zeta \in C$ as a set of clocks. Including the aforementioned definition, the example automation can now be specified by:

- $V = \{\text{off}, \text{on}, \text{camera}\}$
- $E = \{\text{push}, \text{intern}\}$
- $\delta = \{(\text{off}, \text{push}, t = 0, \text{on}), (\text{on}, \text{push}, t < 2, t = 0, \text{camera}), (\text{on}, \text{push}, t > 2, \text{off}), (\text{on}, \text{intern}, t == 10, \text{off}), (\text{camera}, \text{push}, \text{off}), (\text{camera}, \text{intern}, t == 10, \text{off})\}$
- $s_0 = \{\text{none}\}$
- $C = \{t\}$
- $I: I(\text{on}) : t \leq 10, I(\text{camera}) : t \leq 10$

3.6.2 Symbolic Model-Checking (CTL and BDD)

The following section describes the syntax and operators that apply to **Computation Tree Logic** (CTL) and its extension, **Timed Computation Tree Logic** (TCTL), which is used in **UPPAAL**. In order to verify the transition graph with CTL, a tree diagram is constructed. Each node and transition is transferred from the transition graph to the tree diagram until redundancies are obtained. Subsequently, the properties that are applicable to the individual nodes of the transition graph are transferred to the nodes of the tree diagram. Subsequently, it is verified whether the changes in the properties along the paths satisfy the conditions of the CTL formula.

CTL formulas are composed of a set of propositions (Π), logical connectives ($\neg$, $\wedge$ and $\vee$), and temporal operators. The set of CTL formulas with Π as a finite quantity of propositions and $\Sigma = 2^\Pi$ is defined inductively as follows [118]:

Definition 3 *The set $CTL(\Pi)$ of all CTL formulas over Π is with respect to inclusions the smallest set of formulas with $\Pi \subseteq CTL(\Pi)$, which means φ and ψ are CTL formulas, when $\varphi, \psi \in CTL(\Pi)$. Additionally, if $\varphi, \psi \in CTL(\Pi)$ then $\neg\psi, (\varphi \vee \psi), (\varphi \wedge \psi), X\psi, (\varphi U \psi) \in CTL(\Pi)$.*

With $\varphi, \psi \in CTL(\Pi)$ the temporal operators for paths are defined as:

Table 3.4: Temporal operators in CTL

Textual	Description
$\forall\psi$	ψ holds on each path
$\exists\psi$	ψ holds on a least one path

while the additional path specific operators are defined as:

Table 3.5: Path specific operators in CTL

Textual	Symbolic	Description
$X\psi$	$\bigcirc\psi$	Next, which signifies that ψ holds in the next step
$G\psi$	$\Box\psi$	Global, which signifies that ψ on the entire subsequent path,
$F\psi$	$\Diamond\psi$	Finally, which signifies that ψ holds eventually,
$\varphi U \psi$		Until, φ has to hold at least until ψ holds in the current or next step
$\varphi R \psi$		Release, ψ has to hold until φ holds simultaneously (in case φ never holds ψ must hold forever)

By combining the path and path-specific operators formulas are generated, which can be run on the transition graph. To enable information about variable and clock properties, CTL is extended to TCTL by incorporating timing annotations. The incorporation of timing properties extends, for example, the formula

$$\exists\varphi U \psi$$

formulated in CTL, interpreted as there is a path on which φ holds, until ψ holds, to

$$\exists\varphi U_{\sim c} \psi$$

formulated in TCTL, with $\sim$ as a relation operator and $c \in \mathbb{N}$ representing the associated time units. The interpretation for the TCTL formula is that there is a path on which φ holds until ψ holds within the time units designated by c .

Binary Decision Diagram

A **Binary Decision Diagram** (BDD) is a data structure that may be understood as a kind of flow chart for evaluating functions. In each step, the value of the variable to be evaluated is queried with the two possible outcomes, true or false. This process generates a tree structure that continues to expand towards the bottom, with the lowest level representing the value of the Boolean function f under the selected variable assignment.

To formally verify if automaton T satisfies the **CTL** formula φ , formally

$$T \models \varphi,$$

by incorporating a **BDD**, the **BDD** is derived from the transition graph T . The **BDD** represents the alteration of the requested variable along the specified paths as a binary value for each node. Storing only binary expressions for each property results in a reduction in the required space for the resulting tree. The two reduction rules inherent to **BDD** allow for a further reduction in the state space utilized. In **BDDs**, it is possible to merge a state and its successor state, provided that both of the binary outputs from the upper state lead to the same successor state. Furthermore, neighboring states can be merged in case all of their outputs lead into the same following nodes. Subsequently, the **CTL** formula is employed to ascertain whether the alterations of the variable satisfy the formula φ .

3.6.3 Statistical Model-Checking

In statistical model-checking, the state space of the model is not fully exhausted in order to draw conclusions about the properties. In contrast, a combination of simulation and statistical methods, such as hypothesis testing, is utilized to estimate the probability of specific model properties. This approach is unable to provide an absolute answer, as is the case with symbolic model-checking with exhaustive search. However, this approach does not suffer from the problem of **state explosion**. Rather than attempting to ascertain with absolute confidence whether a specific formula is true within a given model, the objective is to determine whether it is true with a certain probability [119]. So instead of ascertaining whether φ holds T , formally written as $\varphi \models T$, where φ represents a formula from logic L and T is the transition graph, statistical model-checking ascertains whether

$$T \models P_{\geq p}(\varphi).$$

The approach to the Statistical-Model-Checking method in **UPPAAL** is based on Monte Carlo simulation. This type of simulation is employed to numerically solve problems that cannot be solved analytically or that can only be solved with a considerable expenditure of effort using samples. The fundamental premise of this approach is the law of large numbers [119].

In essence, a Monte Carlo simulation generates a model of potential outcomes by employing a probability distribution, such as a uniform or normal distribution, for any variable with intrinsic uncertainty. Subsequently, the outcomes are repeatedly recalculated on an iterative basis, with a distinct set of random numbers drawn between the minimum and maximum values employed in each iteration to obtain a substantial number of probable outcomes.

3.6.4 UPPAAL

The framework **UPPAAL** is a toolbox for modeling, simulation and verification of real-time systems. It is developed in cooperation of the Uppsala University in Sweden and Aalborg University in Denmark [120]. The tool is divided into the verification engine and the graphical user interface. The latter can be subdivided into an editor, a simulator and the verification component. In the editor, the automata of a model can be created, edited, and deleted. Here, states, transitions, clocks, variables, and their properties, like **invariants** and guards, can be declared, edited, and deleted. The simulator, represented in Figure 3.17, enables a step-wise simulation of the model, including all possible transitions and the current states. The verification component, represented in Figure 3.18, facilitates interaction with the verification engine, enabling the specification and verification of properties and the configuration of the model-checking engine. Upon completion of a verification process, the results are displayed in the form of either a probability for statistical model-checking or a green or red circle for deterministic model-checking. A red circle, indicating that the requested property could not be confirmed, is accompanied by a counterexample.

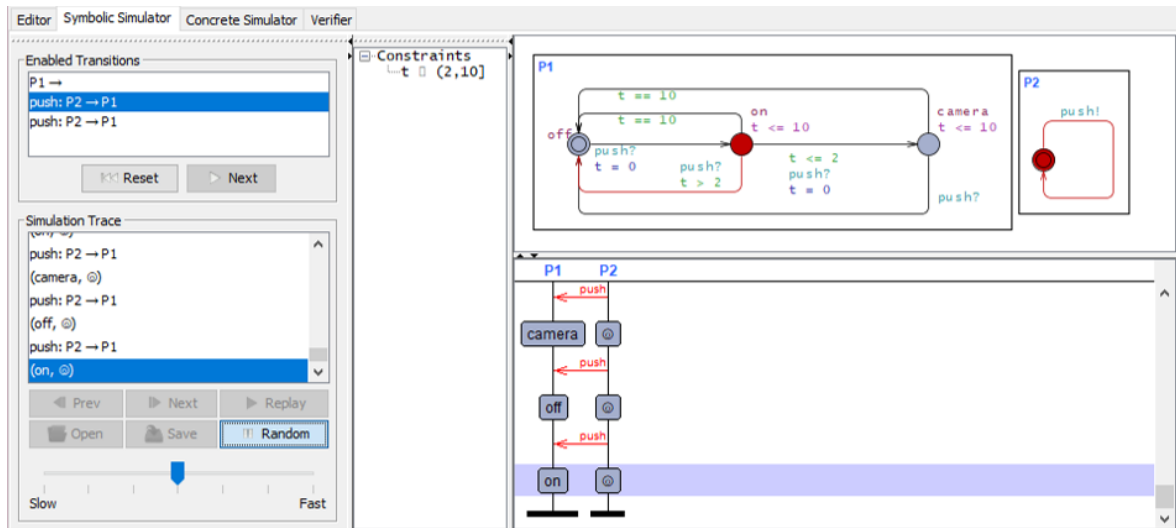


Figure 3.17: Simulation environment in **UPPAAL**.

In Figure 3.17, the speed of the simulation can be set via the scale located in the bottom left corner. To initiate a simulation, the button labeled **Random** is provided. This will result in a random selection between the subsequent potential transitions of the model during the simulation. The two displays situated above this button show the forthcoming potential transitions (white box at the top) and the previous transitions (white box below). The current values of the variables are displayed in the large white column situated in the center. In the top right-hand corner, the executed templates are displayed. The current status is indicated by the color red. If a transition is executed, both the transition and the subsequent status are displayed in red. Figure 3.17 shows the moment in which a transition is executed that leads to a synchronous transition in both automata (P1 and P2). Subsequently, a representation of the preceding and current states, transitions, and synchronization executions is displayed.

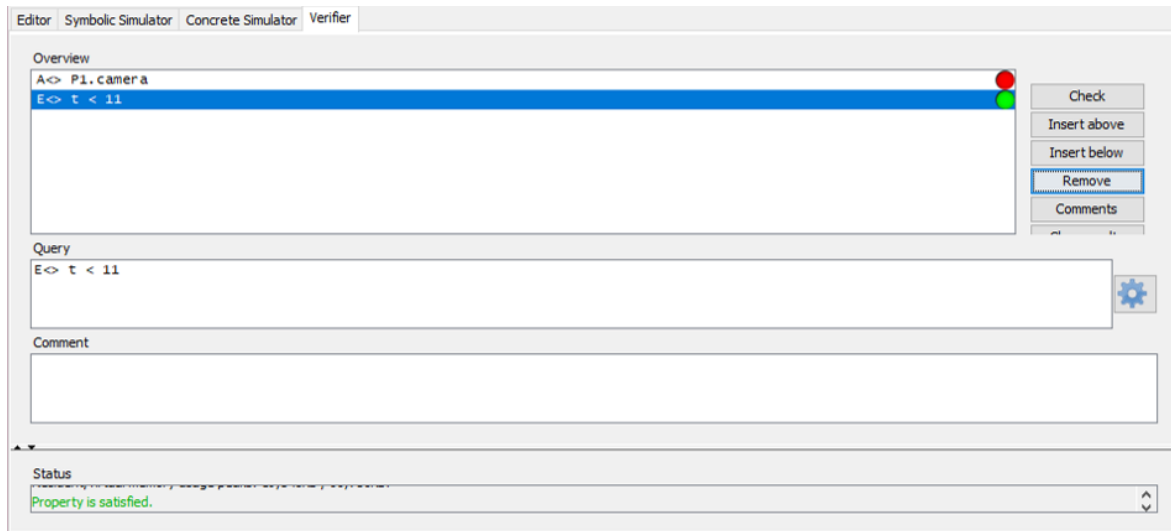


Figure 3.18: Verifying environment in UPPAAL.

Automata in UPPAAL

A system in UPPAAL is represented by a network of timed automata. Each automaton is visualized in its own template. To perform a simulation or verification, the user selects a set of templates before execution. The individual automata are processed in parallel and interact by channels and synchronization commands. The network of timed automata is extended by local (automata-related) and global (cross-automata) boolean and integer variables [121].

Figure 3.19 illustrates two exemplary automata implemented in UPPAAL. Both automata are designed in separate templates, indicated by the yellow borders. The template on the left-hand side represents the functionality of a lamp with three states: off, low, and high. The template on the right-hand side represents a human interacting with the lamp via the synchronization channel `press`. The `!` following the synchronization channel name indicates the emission of the command if the transition is taken. The reception of the synchronization command on the left-hand side, enabled for the transitions marked with the channel name extended by a `?`, would initially result in the transition from off to low for the lamp.

During the initial transition from off to low, the value of the clock `y` is reset to 0. Consequently, upon entering low, the clock initiates counting up. Depending on the value of the clock, during the reception of the synchronization command, the subsequent transition is either back to off or towards brightness. If the lamp is in the bright status, only the synchronization command `press` can result in a transition back to the off status.

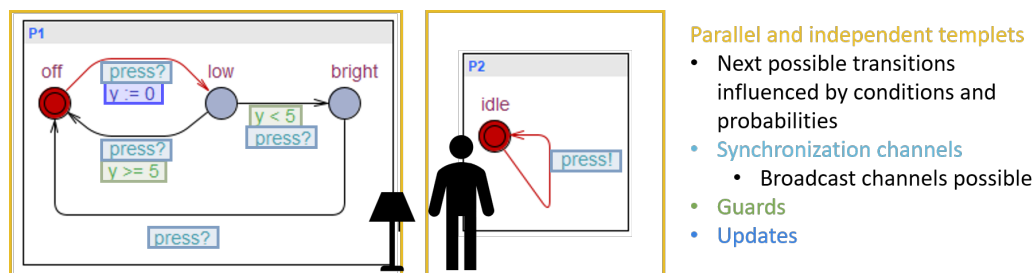


Figure 3.19: Example for two interacting templates in UPPAAL.

Query Language in UPPAAL

Queries in UPPAAL differ from the aforementioned formulas in TCTL as the query language in UPPAAL does not permit the nesting of path formulas.

Symbolic Queries Symbolic queries are formulated by symbolic operators based on the syntax of TCTL logic. Based on the requested properties, state or path formulas can be implemented as queries. State formulae describe the behavior of individual states within a model in a side-effect-free expression, evaluated for each individual state after each transition. The query

deadlock,

for example, evaluates to true if there is a state without a subsequent state reachable. Path formulas are employed to evaluate properties regarding the paths. Possible symbolic queries for path formulas in UPPAAL are displayed and described in Table 3.6.

Table 3.6: Semantics for the requirement specification language of UPPAAL.

Definition	UPPAAL Specifications	Description
Invariantly	$A[\]x \mid \text{not } E <> \text{not } x$	evaluates to true exclusively if every reachable state satisfies x
Possibly	$E <> x$	evaluates to true exclusively if at least one state reachable satisfies x
Potentially always	$E[\]x$	evaluates to true exclusively if there is a path on which x eventually is always satisfied. This is fulfilled by a loop on which each state satisfies x or a state with no outgoing transitions satisfying x
Eventually	$A <> x \mid \text{not } E[\]\text{not } x$	evaluates to true exclusively if there is at least one state satisfying x reachable on each path
Leads To	$x \text{ -- } > y \mid A[\](x \text{ imply } A <> q)$	evaluates to true exclusively if whenever x is satisfied eventually y will be satisfied (this is a special case in which nesting is supported)
	$\text{sup} : x, y$	computes the suprema of the listed expressions x and y (value for integer, bounds for clocks)
	$(\text{sup} \mid \text{inf})\{x\} : y, \dots$	computes the suprema respectively infimum of the listed expression y when x is satisfied in parallel (value for integer, bounds for clocks)

Statistic Queries Statistic queries can be formulated by extending the symbolic queries with probabilistic parameters, displayed and described in Table 3.7.

Table 3.7: Semantics for the requirement specification language of UPPAAL with δ representing the bounds (absolute global time, specific clock or number of action-transitions), sr as denoting the maximal number of runs to satisfying the state expression, x, y as expressions, v is a variable, κ as a constant, p as a probability bound, $\#$ as a number of simulation steps, and min : respectively max : minimum respectively maximum value over a run of the proceeding expression.

Definition	Specifications in UPPAAL	Description
Simulation	$\text{simulate } [\delta] \{x_1, x_2, \dots\} : sr : y$	gathers the valuations of list of expressions. If filtered by δ and satrun result includes probability confidence interval
Probability Estimation	$\text{Pr}[\delta]((\langle \rangle \mid \llbracket \rrbracket) x)$	quantitative model-checking generating a estimated probability confidence interval for the path expression
Hypothesis Testing	$\text{Pr}[\delta]((\langle \rangle \mid \llbracket \rrbracket) x)(\leq \mid \geq) p$	qualitative model-checking to validate the probability or the path expression against bound p
Probability Comparison	$\text{Pr}[\delta]((\langle \rangle \mid \llbracket \rrbracket) x) \geq \text{Pr}[(v \mid \#) \leq \kappa](\langle \rangle \mid \llbracket \rrbracket) x)$	indirectly compares two probabilities without estimation
Value Estimation	$E[\delta] ((\text{min} : \mid \text{max} : x)$	estimates the boundary value for an expression by running a given number of simulations

System Model of the Heart

Our model simplifies the electrical conduction system, chambers, and valves of the heart's complex structure, allowing for observation of chamber status and changes in pumping effectiveness due to [ECSH](#) adjustments. Specific diseases can be modeled by combining healthy and malfunctioning modules in the [ECSH](#). The modular structure of the heart model allows for the exchange of healthy and dysfunctional components, enabling the modification of conditions. Malfunctions in [ECSH](#) modules can include delays, deactivations, arrhythmias, and communication problems with the environment.

This chapter presents an overview of our heart model presented in [122], supplemented with additional modules. It includes the modules mirroring the [ECSH](#) and chamber behaviors, the calculation of different chamber status intervals with varying physiological properties of the heart, and the interaction between the [ECSH](#), the chambers, and the pacemaker by [EIS](#).

4.1 Sequence of a Pumping Action

Figure 4.1 provides an overview of the modules of our heart model and the timed interaction among the modules. The diagram displays modules of the [ECSH](#), an [atrium](#), and a [ventricle](#) with valves, marked by colored borders.

On the right-hand side of the valve, the diagram is extended to illustrate the blood flow and its effect on the valves. Each module is expressed by its own independent timed automaton, which operates in parallel with other modules. To ensure the independence of the stimulating and stimulated regions, the modules interact only through asynchronous channels.

The components of the [ECSH](#) are highlighted in yellow on the left side of the figure. Communication between modules is either orthogonal, top-down, or [retrograde](#), bottom-up. The [atrium](#) chamber modules (shown in pink) and the [ventricle](#) (outlined in green) are electrically connected to the [ECSH](#) via the [atrium](#) and Purkinje fiber modules. Horizontal arrows indicate the connection between the chambers and the [ECSH](#). The pink box highlights the atrial action of contracting and then expanding in response to pacing. The chamber fills with blood due to negative pressure as it expands after a contraction. If the [ventricle](#) below is expanding at the same time and the [AV Valve](#) is opened, the blood flows from the [atrium](#) directly into the [ventricle](#) below due to the [ventricle](#)'s negative pressure. The [ventricles](#) can only be filled by blood that has passed through the atria. Therefore, the coordination between the atria and the [ventricles](#) and their contractions is crucial, as it affects the ventricular blood volume. To further increase the volume of blood in the [ventricles](#), the atria must contract before the ventricular contraction closes the [AV Valves](#). This allows for an additional amount of blood to be pushed into the [ventricle](#) by atrial contraction. The [ECSH](#) modules provide the required delay between atrial pacing and ventricular pacing, as shown in Figure 4.1.

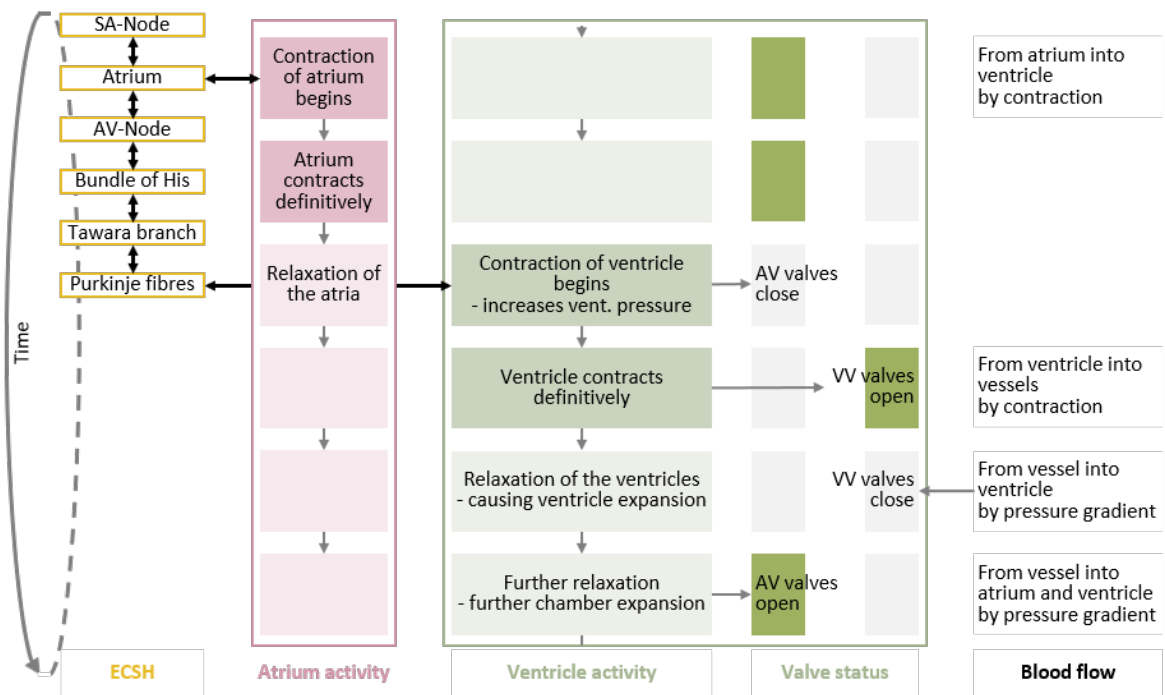


Figure 4.1: Schematic overview of the electrical and mechanical interaction of the heart including the **ECSH** (yellow), atrial contractions (pink), and contractions of the corresponding **ventricle** (green). The diagram of the **ventricle** also displays changes in the heart valves' status. Additionally, the column on the far right illustrates the blood flow through the heart, which affects the behavior of the heart valves. A box in the same color as the previous one indicates that the part remains in the same status [122].

The modeled relationship between the contraction of the **ventricle** and the opening and closing of the valves is shown in the green module. The **ventricle** contracts and then expands again in response to the stimulation. During contraction, the **ventricle**'s shape changes, which leads to the closure of the **AV Valves**. At the peak of the contraction, the high intraventricular pressure causes the **VV Valves** to open. Upon re-expansion of the **ventricle**, the **VV Valves** close due to the back-flow of blood from the vessel as a result of the negative pressure in the chamber. As the heart muscle relaxes, the **ventricle** expands, causing the shape of the **ventricle** to change, which results in the reopening of the **AV Valve**.

4.2 Chambers

The following sections describe the atrial and ventricular modules of the system model.

4.2.1 Atrium

The atrial module is schematically represented in Figure 4.2. Its initial state is **IDLE**, representing the diastolic phase where the **atrium** expands, and blood flows in or through it due to negative pressure. The module can only transition to the next state **Systole**, representing the first part of the **systole**, after receiving an incoming stimulation, represented by *Input : Stimulation by the **ECSH** or the pacemaker*. Since the timing of the physiological process in a human heart depends on the current **APD**, an **APD** recalculation, based on the previous **APD** and model-specific parameters, becomes necessary as soon as an incoming pulse triggers a transition towards **Systole**. The **APD** recalculation, based on the formulas described

in Section 4.2.3, is represented by *Update : recalculate APD* at the transitions from **IDLE** to **Systole** and from **Vulnerable Phase** to **Systole**.

The module remains in **Systole** for Δt_{vp} milliseconds, where Δt_{vp} is calculated as a fraction of the **APD** for the current chamber cycle. During the states **Systole** and **Vulnerable Phase**, the **AV Valve** status is monitored to determine if the valve is open. If the valve variable *AAV* indicates that it is open, the chamber synchronization variable *aRtovR* is set to true. Once Δt_{vp} milliseconds have elapsed, the model enters the **Vulnerable Phase**, which is still a part of the physiological **systole**. In our model, we separate the physiological **systole** into two states to account for the different effects that depend on the time of occurrence from a stimulation. In contrast to the **Systole** state, the state **Vulnerable Phase** allows for a transition back to **Systole** due to a re-stimulation of the chamber. A re-stimulation during this state can result in **tachyarrhythmias**. That is why this transition updates the variable monitoring stimulation in the **vulnerable phase**, *potArr*. As the **vulnerable phase** ends, the **atrium** returns to its initial state and remains in **IDLE** until the next stimulation.

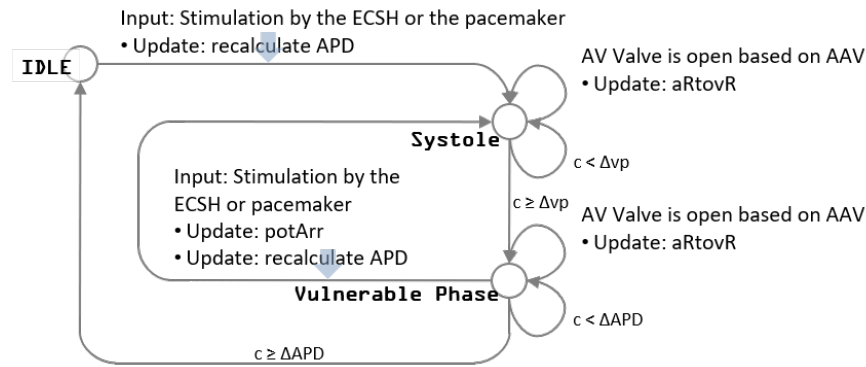


Figure 4.2: Schematic representation of the **atrium** module. States are represented by circles, while transitions are represented by arrows. Variables are explained in Table 4.1.

Table 4.1: Overview and descriptions of the variables in Figure 4.2.

Category	Variable	Definition
Clocks	c	Clock containing time since chamber activity
Time intervals	Δ_{vp} Δ_{APD}	Current interval for vulnerable phase Current interval for blanking resp. refractory
Monitoring variables	<i>AAV</i> <i>aRtovR</i> <i>potArr</i>	Monitoring the AV Valve status Monitoring the chamber synchronization Monitoring stimulation in the vulnerable phase

4.2.2 Ventricle

The ventricular module, shown in Figure 4.3, follows a pattern that is similar to that of the **atrium** in terms of modulation. Until stimulated, it remains in an **IDLE** state. Like in the **atrium**, a stimulation of the **ventricle** leads to a recalculation of the subsequent **APD**. Based on the newly calculated **APD**, the occurrences of the following ventricular events are determined. The cycle following a stimulation of the **ventricle** includes the **systole**, split into **Systole** and **Vulnerable Phase**, as in the **atrium**, extended by a state called **Diastole**, which allows us to include the closure of the **AV Valve**.

The timing of the onset of status changes associated with the ventricular valves is determined by fractions of the **APD**. As shown in Figure 4.3, the status of the **AV Valve** is changed to false right at the beginning of the **systole** and stored in the variable **AAV**. Here, the **ventricle** contracts, changing shape and closing the valve. Due to the high pressure of the blood in the **ventricle** during the peak of contraction the **VV Valve** opens. To represent this behavior, the variable **VVV** is set to true. After entering **Vulnerable Phase**, the **VV Valve** status variable **VVV** is changed to false, representing the closure of the valve due to back-flowing blood. As in the **atrium**, a stimulation in the **ventricle** during the **Vulnerable Phase** can lead to reentry into **Systole** and can lead to **tachyarrhythmias**. If the module passes through **Vulnerable Phase**, it enters **Diastole**, where it remains until the **AV Valve** variable **AAV** is set to true and the module transitions back to **IDLE**, waiting for the next stimulation. A reentry from **Diastole** into **Systole** is not associated with **tachyarrhythmias**. Therefore, this transition is only accompanied by an update of the current **APD**.

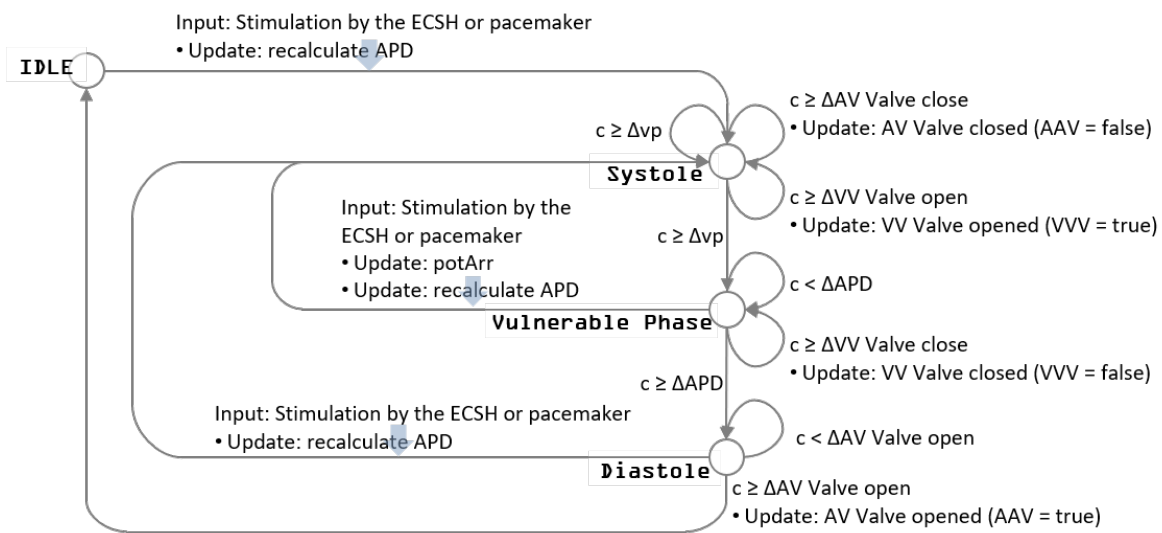


Figure 4.3: Schematic representation of the **atrium** module. States are represented by circles, while transitions are represented by arrows. Variables are explained in Table 4.2.

Table 4.2: Overview and descriptions of the variables in Figure 4.3.

Category	Variable	Definition
Clocks	c	Clock containing time since chamber activity
Time intervals	Δvp	Current interval for vulnerable phase
	ΔAV open	Current interval since chamber stimulation until the AV Valve opens
	ΔAV close	Current interval since chamber stimulation until the AV Valve closes
	ΔVV open	Current interval since chamber stimulation until the VV Valve opens
	ΔVV close	Current interval since chamber stimulation until the VV Valve closes
	ΔAPD	Current interval for blanking resp. refractory
Monitoring variables	AAV	Monitoring the AV Valve status
	VVV	Monitoring the VV Valve status
	aRtovR	Monitoring the chamber synchronization
	potArr	Monitoring stimulation in the vulnerable phase

4.2.3 Calculation of the APD

To properly integrate the evolution of the APD into our model, information on the pertinent time evolution in real patients is needed. For this, we parametrize the data samples provided in [123] based on long-term monitoring of monophasic action potentials originating from the human heart to investigate the impact of a single extra-stimulus, abrupt sustained rate acceleration and deceleration, and different steady-state cycle lengths on ventricular action potential duration in 17 patients. The data in [123] indicates that the APD in a given time interval $i + 1$ is strongly influenced by the previous APD (APD_i) in time interval i and the previous stimulation interval (S_i) within the chamber. Franz et al. found a linear relationship between the APD and the stimulation interval, with an adaption of the APD by 23 ms for a change of 100 ms in the stimulation interval [123]. This relationship is incorporated in our model as the factor ψ .

Upon examining the data provided in [123], we developed the following formulas to describe the evolution of the APD over time. It is noticeable that for each stimulation interval S_i , there is an asymptotic value

$$A_{inf} = APD_0 - (S_0 - S_i) \cdot \psi \quad (4.1)$$

towards which APD_i adjusts over time. The model parameters APD_0 and S_0 , which represent the initial APD and the initial stimulation interval in milliseconds, enable the creation of unique ratios between these parameters, as they may differ from heart to heart. The variable S_i contains the value of the time interval since the last chamber stimulation, also in milliseconds. S_i is recalculated during the run time of the model whenever the chamber is re-stimulated. By the variable ψ the effect of a patient-specific altering of the stimulation interval relative to the initial parameters is controlled. The value of the APD at a given time, APD_i in milliseconds, is represented by

$$APD_{i+1} = aid_{i+1} + dos_{i+1} . \quad (4.2)$$

The first term on the right (aid_{i+1} short for *ideal APD*) reflects the step-wise approach towards the current target value, to which the second term (dos_{i+1} short for *damped oscillation*) adds the influence of a damping step response. The former can be described by

$$aid_{i+1} = aid_i + \Delta A_i \cdot \beta_i, \quad (4.3)$$

with aid_0 initialized in milliseconds with the same value as APD_0 ,

$$\Delta A_i = A_{inf} - APD_i \quad (4.4)$$

and the mitigating model parameter

$$\beta_{i+1} = \begin{cases} \beta_i, & |S_i - S_{i+1}| < 1 \\ \gamma, & |S_i - S_{i+1}| > 1 \end{cases} , \quad (4.5)$$

with

$$\gamma = \begin{cases} \gamma_1, & S_i - S_{i+1} > S_{max} \\ \gamma_2, & S_i - S_{i+1} < S_{max} \end{cases} . \quad (4.6)$$

Here β_0 , γ_1 , γ_2 are additional model specific parameters, which have to be adjusted. The parameter S_{max} represents the threshold value for the difference between two intervals at which the value of the parameter β differs. The latter part of Equation 4.2 - the damped step response - is calculated via

$$dos_{i+1} = \frac{\Delta A_i}{\omega} , \quad (4.7)$$

where the parameter ω has to be adapted in the model. A comparison of the parametrization of the APD with exemplary data of [123] is presented in Chapter 3.

For the calculation of the atrial **APD**, the formulas described above are used, assuming that atrial adaptation follows the same process as ventricular adaptation - considering the same tissue and the inter-chamber synchronization. However, the variable A_{inf} is to be rescaled by a parameter α . To account for the shorter **APD** in the **atrium**. The values of all parameters mentioned in the section employed in the actual simulations and verifications are given in Table 9.1.

4.2.4 Calculation of the Time of the Occurrence of Valve Status Change

As shown in Figure 4.3, the opening and closing times of the heart valves are dynamically recalculated based on the current **APD** in our model. Given that the changes are dependent on the form change of the **ventricle**, which occurs over the course of the **APD**, the time after the onset of ventricular contraction, at which the status of the valves is expected to change, is calculated as a percentage of the respective total duration of the currently calculated **APD** of the respective **ventricle** in milliseconds.

Proportionality parameters for valve closure and opening can be introduced and selected according to the person in question, allowing for personalization of the model and accounting for potential differences in anatomy that may result in delayed or earlier valve closure. In terms of its control parameter, $AVVclose_{i+1}$ in milliseconds, this yields

$$AVVclose_{i+1} = APD_{i+1} \cdot \frac{AVVc}{100} \quad (4.8)$$

for the closure of the **AV Valve** in milliseconds, after the onset of ventricular contraction. Thereby, $AVVc$ is a patient-specific constant, determining the proportion in percent of the **APD** in which the **ventricle** has changed its shape so far that the valve is closed. The calculated $AVVclose_{i+1}$ is expressed as a proportion of the current **APD**. Analogous formulas with the patient-specific constants $VVVc$ and $VVVo$, respectively, apply to **VV Valve** closure ($VVVclose_{i+1}$) and ($VVVopen_{i+1}$) reopening. Notwithstanding the above, the reopening of the **AV Valve** in milliseconds is described via

$$AVVopen_{i+1} = APD_{i+1} \cdot \left(1 + \frac{AVVo}{100}\right), \quad (4.9)$$

with $AVVo$ as a patient-specific constant, determining the proportion in percent of the **APD** in which the **ventricle** has changed its shape so far, that the valve is opened. since the **APD** has already expired as the valve closes. The correlation of atrial contractions with atrioventricular valve status are used as an indication of the occurrence of **pacemaker syndrome**, as described in the context of Figure 4.2.

4.2.5 Calculation of the Vulnerable Phase

Our model calculates the interval from the stimulation of the respective chamber until the onset of the **vulnerable phase** as a function of APD_{i+1} via

$$vp_{i+1} = \frac{APD_{i+1} \cdot v_{onset}}{100} \quad (4.10)$$

with the adjustable parameter v_{onset} (expressed as a percentage of the current APD_{i+1}). At 70% of **APD** the earliest time a new stimulation can stimulate the area is [123]. The **vulnerable phase** interval typically ends when the clock monitoring the time since chamber activation reaches APD_{i+1} . The duration of the **vulnerable phase** is patient-specific.

4.3 Electrical Conduction System

The ECSH is divided into two types of modules in our model: those that conduct electrical pulses and those that can generate pulses on their own.

4.3.1 Conduction Module

Figure 4.4 provides a schematic overview of a conducting module. The module is divided into three states and is controlled by its own clock, c . Initially, the module starts in **IDLE** and remains inactive until it receives a stimulation pulse (*Input : ortho_stimulation* or *Input : retro_stimulation*) from a neighboring module. Upon receiving a stimulus, the module transitions to **Action Potential Before Conduction (APBC)**. The possible transitions are represented by two paths: the pink arrow stands for the orthogonal direction, and the blue arrow represents the **retrograde** direction. Depending on the path taken, the numeric variable containing the direction's status (ecd) is adapted.

The module remains in **APBC**, representing the time the area of the ECSH is active, but the stimulus has not yet been conducted to the neighboring area for the area-specific duration of dt_{BC} . After dt_{BC} elapsed, the module transitions to **Action Potential After Conduction (APAC)**. Depending on the status of ecd , the pink or blue path is taken, and the neighboring **anterograde** or **retrograde** module receives a synchronization pulse through an asynchronous channel represented by *Output : ortho_stimulation* or *Output : retro_stimulation*.

APAC represents the state in which the area remains electrically active and cannot be stimulated by a neighboring area. Remaining in the **APAC** region is necessary to prevent back-stimulation from the stimulated area and the generation and conduction of high pulse frequencies. The time interval dt_{AC} for this state is also area-specific. After the **APAC** state, the system transitions back to an **IDLE** state.

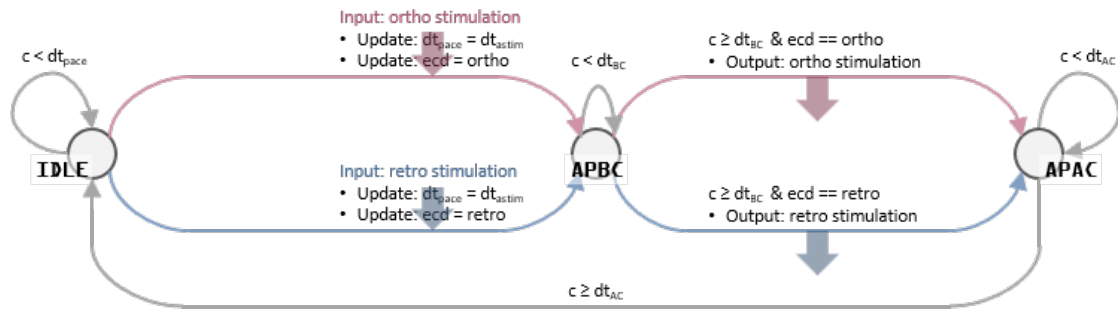


Figure 4.4: Schematic representation of a healthy area of the ECSH in our model. Variables are explained in Table 4.3.

Table 4.3: Overview and descriptions of the variables in Figure 4.4.

Category	Variable	Definition
Module sync.	<i>Input : ortho_stimulation</i>	Pulse from the module above
	<i>Output : ortho_stimulation</i>	Pulse to the module below
	<i>Input : retro_stimulation</i>	Pulse from the module above
	<i>Output : retro_stimulation</i>	Pulse to the module below
Clocks	c	Clock containing time since module activation
Time intervals	dt_{BC}	Current interval for the APD before conduction
	dt_{AC}	Current interval for the APD after conduction
Variables	ecd	Variable containing the conduction direction

4.3.2 Self-Stimulating Areas

In areas that can independently generate stimulation pulses and transmit them to their neighboring areas, there is an additional path through which the module can enter **APBC**, shown in Figure 4.5, which is marked in green. The green path is taken when the time interval required for self-stimulation (dt_{pace}) has expired. Since self-stimulation may not be reliable in certain areas, a probabilistic variable is added after the transition that follows the self-stimulation. If the probability of occurrence variable (p_{pace}) exceeds the adjustable threshold (val_{rnd}), the stimulation is successful, and the transition to **APBC** is performed. Otherwise, the module returns to the **IDLE** state. The time interval until self-stimulation and the probability of occurrence are dependent on the area.

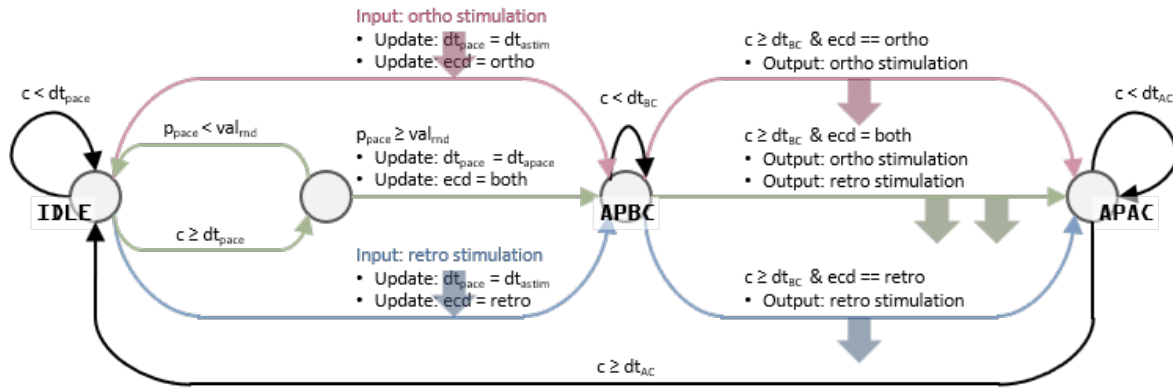


Figure 4.5: Schematic representation of a self-stimulating area of the **ECSH** in our model. Variables are explained in Table 4.4.

Table 4.4: Overview and descriptions of the variables in Figure 4.5.

Category	Variable	Definition
Module sync.	<i>Input : ortho_stimulation</i>	Pulse from the module above
	<i>Output : ortho_stimulation</i>	Pulse to the module below
	<i>Input : retro_stimulation</i>	Pulse from the module above
	<i>Output : retro_stimulation</i>	Pulse to the module below
Clocks	c	Clock containing time since module activation
Time intervals	dt_{pace}	Time interval required for self-stimulation
	dt_{BC}	Current interval for the APD before conduction
	dt_{AC}	Current interval for the APD after conduction
	dt_{apace}	Time interval required for self-stimulation after external stimulation
	dt_{astim}	Time interval required for self-stimulation after self stimulation
Variables	ecd	Variable containing the conduction direction
	p_{pace}	Probability for successfully self-stimulation
	val_{rnd}	Adjustable threshold - randomly generated within it's boundaries

The time interval between self-stimulation pulses is affected by the origin of the previous pulse, so the variable containing the time interval to self-stimulation is adjusted in relation to the origin of the module activation pulse. As soon as the time for the module in **APBC** has expired, the module stimulates both the orthogonal and the **retrograde** areas and transitions to the **APAC**. As in the conduction module the module remains non stimulateable in **APAC** for the area-specific duration before returning to the **IDLE** state. This cycle restarts upon receiving a new external or internal stimulation.

4.4 Conduction Disease Modeling Modules

In the described setup, modules simulating a healthy conduction area can be replaced with modules simulating a diseased conduction area. This includes various types of supra- and intrahisternal AV blockages, which can cause delays or interruptions in the conduction pathway. These malformations can affect the path from the **AV node** to the **bundle of his** or the conduction in the areas below.

4.4.1 First-degree AV Block

The **first-degree AV block** is characterized by a delay in the pulse transition to the following area. This type of delay often occurs in the region of the **AV node** or in the underlying areas and leads to a loss of synchronization between the **atrium** and **ventricle**.

This delay is represented in the modular implementation by an extension of the dt_{BC} time by dt_{delay} , which prolongs the dwell time in the **APBC** state, as shown in Figure 4.6.

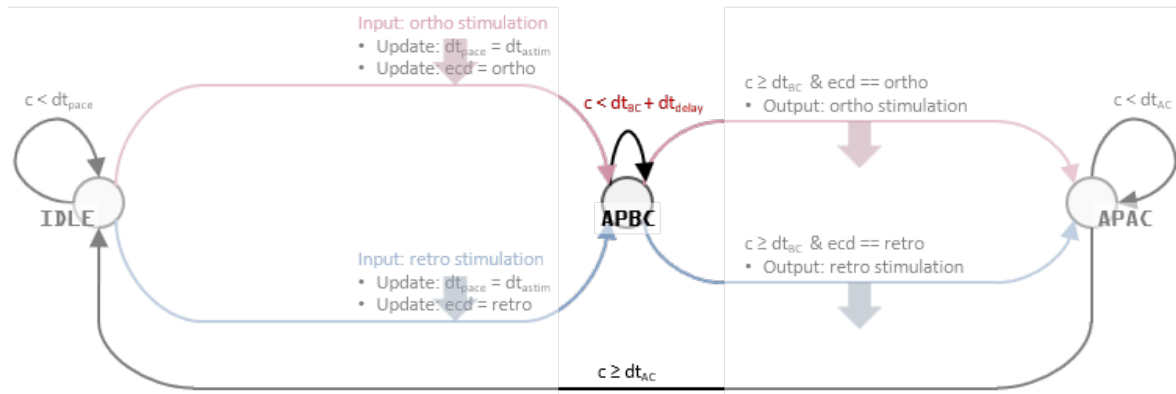


Figure 4.6: Schematic representation of a defective area of electrical conduction as represented in our model - an **AV Block 1** can be seen. Variables are explained in Table 4.5.

Table 4.5: Overview and descriptions of the variables in Figure 4.6.

Category	Variable	Definition
Module synchronisation	<i>Input : ortho_stimulation</i>	Pulse from the module above
	<i>Output : ortho_stimulation</i>	Pulse to the module below
	<i>Input : retro_stimulation</i>	Pulse from the module above
	<i>Output : retro_stimulation</i>	Pulse to the module below
Clocks	c	Clock containing time since module activation
Time intervals	dt_{BC}	Current interval for the APD before conduction
	dt_{AC}	Current interval for the APD after conduction
	dt_{delay}	Current interval for delay added to dt_{BC}
Variables	ecd	Variable containing the conduction direction

4.4.2 Second-degree AV Block Wenckebach

A [second-degree AV block wenckebach](#), is characterized by a progressive prolongation of conduction time with each beat until a point where the conduction in this area is completely blocked for one beat. This cycle then repeats.

To represent this in the module, a variable representing the delay dt_{delay} , the index n , and the threshold dtp are introduced. Index n contains the number of beats since the last full blockage which is offset against dt_{delay} to dynamically recalculate dt_{BC} . The module is visualized in Figure 4.7. The path of transition the module takes from [APBC](#) to [APAC](#) depends on the value of the index. If the index n is below the blockage threshold dtp , there is a prolonged stay in [APBC](#), as in [first-degree AV block](#). Afterward, the transfer time is extended, and the index is increased. When the index n matches the threshold dtp , the path for stimulating the neighboring areas is bypassed by the violet path and the index n and the time the module spends in [APBC](#) are reset.

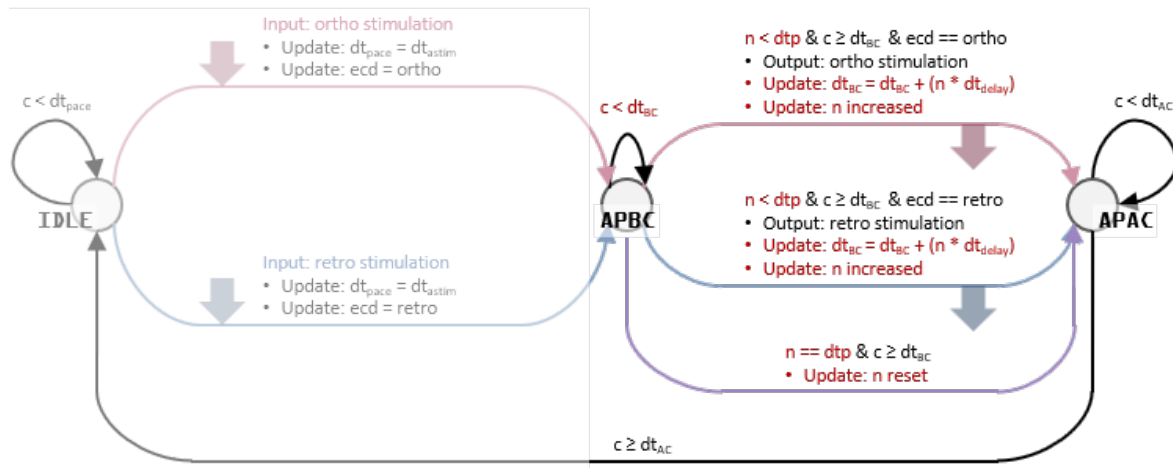


Figure 4.7: Schematic representation of a defective area of electrical conduction as represented in our model - an [AV Block 2 w](#) can be seen. Variables are explained in Table 4.6.

Table 4.6: Overview and descriptions of the variables in Figure 4.7.

Category	Variable	Definition
Module synchronisation	<i>Input : ortho_stimulation</i>	Pulse from the module above
	<i>Output : ortho_stimulation</i>	Pulse to the module below
	<i>Input : retro_stimulation</i>	Pulse from the module above
	<i>Output : retro_stimulation</i>	Pulse to the module below
Clocks	c	Clock containing time since module activation
Time intervals	dt_{BC}	Current interval for the APD before conduction
	dt_{AC}	Current interval for the APD after conduction
	dt_{delay}	Delay interval for recalculation of the current dt_{BC} for each pulse until complete blockage
Variables	ecd	Variable containing the conduction direction
	n	Index counting the beats since the last full blockage
	dtp	Number of transmitted pulses until complete blockage for one pulse

4.4.3 Second-degree AV Block Higher Grade

An area with a [second-degree AV block higher grade](#) blocks beats periodically.

To incorporate this behavior in our model, the index n and the threshold dtp are introduced. Thereby, the index n counts the beats since the last full blockage, and dtp is the number of transmitted pulses until the complete blockage for one pulse. Figure 4.8 shows the module mirroring this behavior in our model. Based on the status of the index n after passing [APBC](#), one of the neighboring areas will be stimulated or the module will just return back into [IDLE](#). If the index n is below the periodic threshold dtp , the path to [APAC](#) without stimulating the neighboring areas is selected. Conversely, if the index n matches the threshold dtp either the [anterograde](#) or the [retrograde](#) neighboring area will receive the stimulation pulse. During the transition marked in pink and blue, the index n is increased when the transition is executed. If the violet path is selected, the index is reset so that the period starts again with the next simulation of the module.

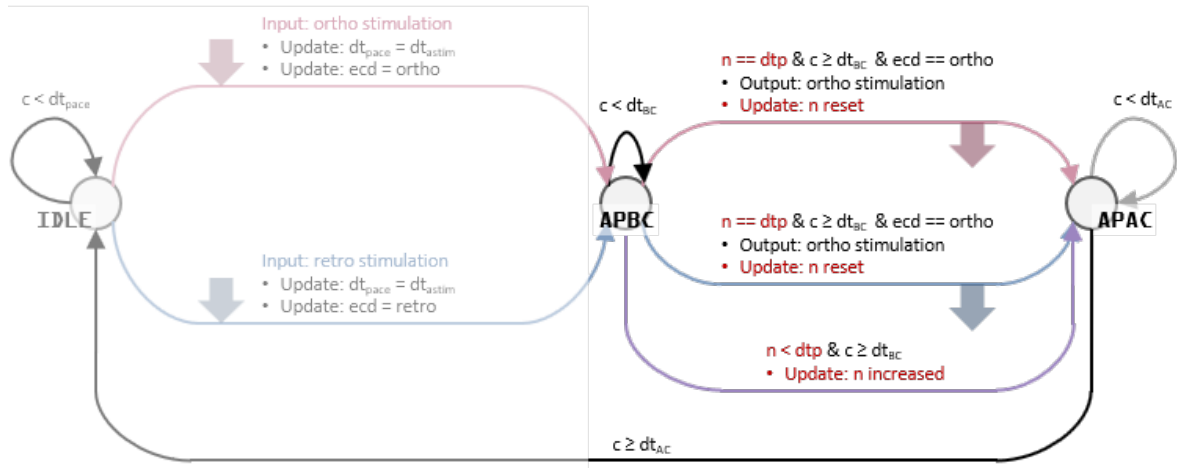


Figure 4.8: Schematic representation of a defective area of electrical conduction as represented in our model - an [AV Block 2 h](#) can be seen. Variables are explained in Table 4.7

Table 4.7: Overview and descriptions of the variables in Figure 4.8.

Category	Variable	Definition
Module synchronisation	<i>Input : ortho_stimulation</i>	Pulse from the module above
	<i>Output : ortho_stimulation</i>	Pulse to the module below
	<i>Input : retro_stimulation</i>	Pulse from the module above
	<i>Output : retro_stimulation</i>	Pulse to the module below
Clocks	c	Clock containing time since module activation
Time intervals	dt_{BC}	Current interval for the APD before conduction
	dt_{AC}	Current interval for the APD after conduction
Variables	ecd	Variable containing the conduction direction
	n	Index counting the beats since the last full blockage
	dtp	Number of transmitted pulses until complete blockage for one pulse

4.4.4 Second-degree AV Block Mobitz

In a [second-degree AV block mobitz](#), a blocked conduction of individual beats in the course of electrical conduction occurs. The affected area conducts or blocks beats more or less arbitrarily.

The module mirroring the behavior is extended by a random variable val_{rnd} , which influences the transition from [APBC](#) to [APAC](#), as can be seen in Figure 4.9. When the random variable val_{rnd} exceeds the blocking threshold p_{cond} , one of the transitions leading to the stimulation of the neighboring area (marked in blue and pink, respectively) is performed. If the value of the random variable does not exceed the threshold, the module will use the violet path to bypass the stimulation of the neighboring area to reach [APAC](#). From there, the system transitions to [IDLE](#) state as in the health module, after the time dt_{AC} in [APAC](#) has elapsed.

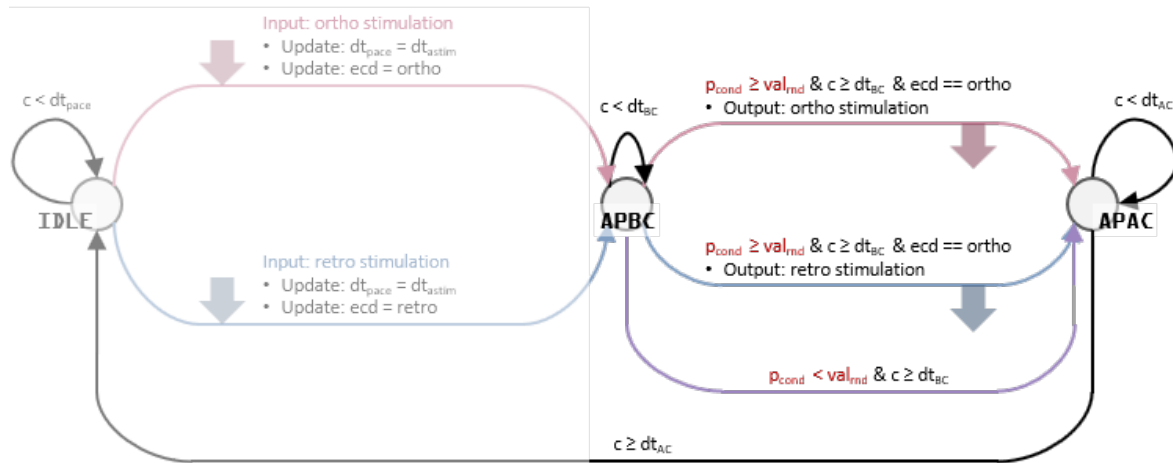


Figure 4.9: Schematic representation of a defective area of electrical conduction as represented in our model - an [AV Block 2 m](#) can be seen. Variables are explained in Table 4.8.

Table 4.8: Overview and descriptions of the variables in Figure 4.9.

Category	Variable	Definition
Module synchronisation	<i>Input : ortho_stimulation</i>	Pulse from the module above
	<i>Output : ortho_stimulation</i>	Pulse to the module below
	<i>Input : retro_stimulation</i>	Pulse from the module above
	<i>Output : retro_stimulation</i>	Pulse to the module below
Clocks	c	Clock containing time since module activation
Time intervals	dt_{BC}	Current interval for the APD before conduction
	dt_{AC}	Current interval for the APD after conduction
Variables	ecd	Variable containing the conduction direction
	p_{cond}	Variable containing the blocking threshold
	val_{rnd}	Random Variable - The value is calculated randomly

4.4.5 Third-degree AV Block

A [third-degree AV block](#) blocks the pulse from reaching the next area. Depending on the location of the blockage in the [ECSH](#), this can have fatal consequences, such as unconsciousness and, in the worst case, death if left untreated.

The module representing this disease in our model is represented in Figure 4.10. When transitioning from [APBC](#) to [APAC](#), the paths, including the commands for synchronizing and activating the neighboring area, are unavailable.

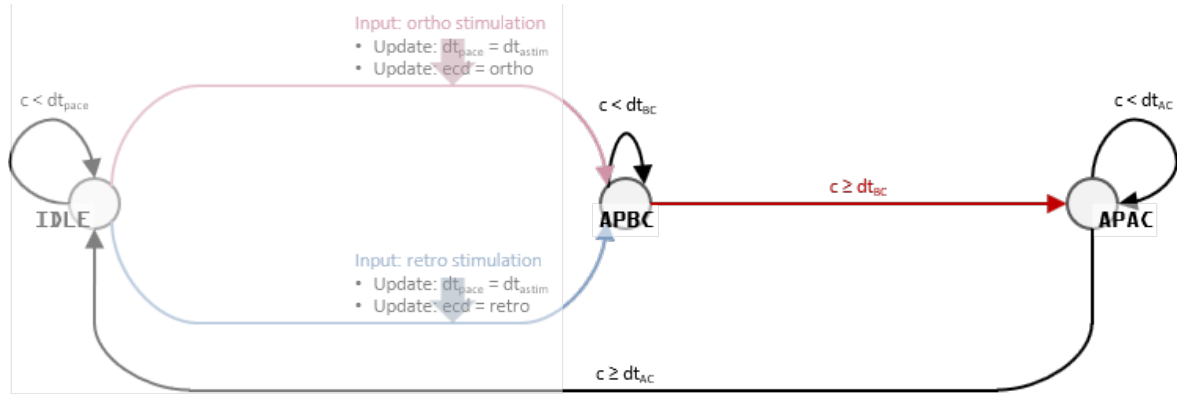


Figure 4.10: Schematic representation of a defective area of electrical conduction as represented in our model - an [AV Block 3](#) can be seen. Variables are explained in Table 4.9.

Table 4.9: Overview and descriptions of the variables in Figure 4.10.

Category	Variable	Definition
Module synchronisation	<i>Input : ortho_stimulation</i>	Pulse from the module above
	<i>Output : ortho_stimulation</i>	Pulse to the module below
	<i>Input : retro_stimulation</i>	Pulse from the module above
	<i>Output : retro_stimulation</i>	Pulse to the module below
Clocks	c	Clock containing time since module activation
Time intervals	dt_{BC}	Current interval for the APD before conduction
	dt_{AC}	Current interval for the APD after conduction
Variables	ecd	Variable containing the conduction direction

4.5 Diseased Rate Generation Modules

The following sections describe modules that are capable of modeling alterations in the heart, which lead to changes in the ability and frequency of pulse generation.

4.5.1 Bradycardia, Chronotropic Incompetence and Arrest

By adjusting the time required for a module to stimulate itself, dt_{pace} , and the probability for a successfully self-stimulation (p_{pace}), as seen in Figure 4.11, specific conditions such as sinus bradycardia, chronotropic incompetence and sinus arrest can be induced. Our model incorporates the behavior of various fast backup rhythms of the heart.

Bradycardia A **bradycardia** is a condition where the heart is stimulated at a decreased rate. To model this condition in one of the self-stimulating modules of our heart model the time until a self-stimulation (dt_{pace}) is increased.

Chronotopic Incompetence As the value for dt_{pace} can be controlled in each self-stimulating area, our model is capable of representing the successful adaptation of an area frequency or the absence of the corresponding adaptation (**chronotropic incompetence**) to external factors.

Arrest Sinus arrest is a complete failure of the **SA node** to generate a rhythm at all. To model this condition in one of the self-stimulating modules of our heart model, the probability for a successful self-stimulation (p_{pace}) is set to 0%.

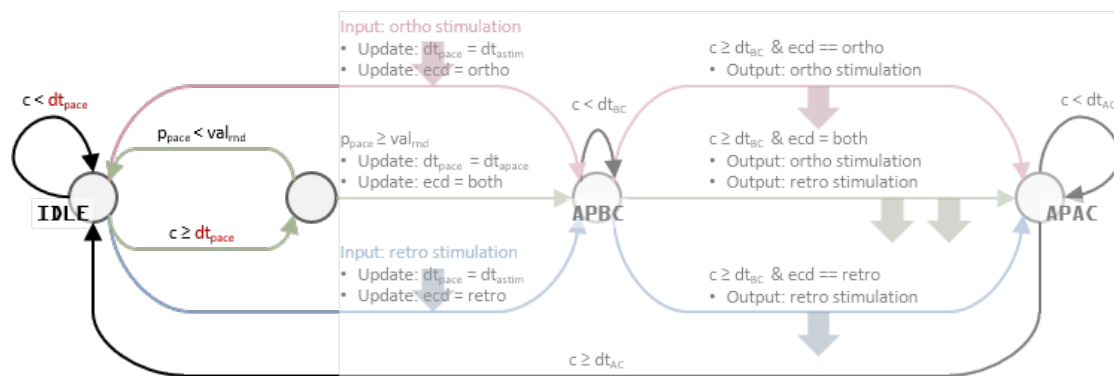


Figure 4.11: Schematic representation of a defective area of electrical conduction as represented in our model - an arrest of the area can be seen. Variables are explained in Table 4.10.

Table 4.10: Overview and descriptions of the variables in Figure 4.11.

Category	Variable	Definition
Module sync.	<i>Input : ortho_stimulation</i>	Pulse from the module above
	<i>Output : ortho_stimulation</i>	Pulse to the module below
	<i>Input : retro_stimulation</i>	Pulse from the module above
	<i>Output : retro_stimulation</i>	Pulse to the module below
Clocks	<i>c</i>	Clock containing time since module activation
Time intervals	<i>dt_{pace}</i>	Time interval required for self-stimulation
	<i>dt_{BC}</i>	Current interval for the APD before conduction
	<i>dt_{AC}</i>	Current interval for the APD after conduction
	<i>dt_{apace}</i>	Time interval required for self-stimulation after external stimulation
	<i>dt_{astim}</i>	Time interval required for self-stimulation after self stimulation
Variables	<i>ecd</i>	Variable containing the conduction direction
	<i>p_{pace}</i>	Probability for successfully self-stimulation
	<i>val_{rnd}</i>	Adjustable threshold - randomly generated within it's boundaries

4.5.2 Atrial and Ventricular Premature Contractions and Atrial Flutter

Figure 4.12 illustrates the module of the heart model able to mirror the behavior of premature contractions and [atrial flutter](#). The module is capable of self-stimulation after a time interval defined by dt_{pace} , with a probability determined by p_{pace} . As the module is part of the heart chamber, p_{pace} is reset by a stimulation of the chamber (*Input : chamber_ortho_stimulation*).

Since this module is not part of the [ECSH](#) configuration but is instead located within one of the chambers, it does not stimulate one of the modules of the [ECSH](#) but rather the chamber to which it is assigned. As the chamber is stimulated from within, the [retrograde ECSH](#) module is stimulated by a [retrograde](#) output of the chamber (*Output : chamber_ortho_stimulation*), while the connected pacemaker receives the pulse via the [anterograde](#) path of the chamber module (*Output : chamber_retro_stimulation*).

Atrial and Ventricular Premature Contractions Premature contractions are initiated by an [ectopic node](#) spontaneously generating pulses. Given that [PACs](#) and [PVCs](#) typically manifest sporadically, the interval preceding self-stimulation (dt_{pace}) is set to a duration greater than at least a minute, while the probability p_{pace} is set to 100% to ensure an occurrence.

Atrial Flutter [atrial flutter](#) is defined as a circulating pulse that stimulates the [atrium](#) each time it completes its circuit. To mirror the stimulation frequency due to [atrial flutter](#), the module emits a series of pulses mediated by dt_{pace} , reflecting the interval for a single circulation, with a probability of successful self-stimulation, represented by p_{pace} , of 100%.

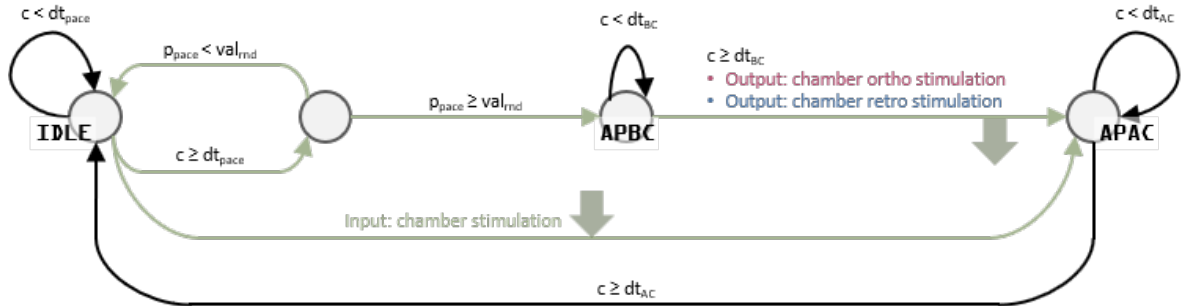


Figure 4.12: Schematic representation of a defective area of electrical conduction as represented in our model - the module representing premature contractions can be seen. Variables are explained in Table 4.11.

Table 4.11: Overview and descriptions of the variables in Figure 4.12.

Category	Variable	Definition
Module sync.	<i>Input : chamber_ortho_stimulation</i>	Pulse from the chamber
	<i>Output : chamber_ortho_stimulation</i>	Pulse to the chamber
	<i>Output : chamber_retro_stimulation</i>	Pulse to the chamber
Clocks	c	Clock containing time since module activation
Time intervals	dt_{pace}	Time interval required for self-stimulation
	dt_{BC}	Current interval for the APD before conduction
	dt_{AC}	Current interval for the APD after conduction
Variables	ecd	Variable containing the conduction direction
	p_{pace}	Probability for successfully self-stimulation
	val_{rnd}	Adjustable threshold - randomly generated

4.6 Variances in the QT Interval

Fluctuations in the **QT interval** affect the interval between heart chamber stimulation and the subsequent **depolarization** and **repolarization** of the chamber, including the **vulnerable phase**. The modeling of these fluctuations is conducted by modifying the **APD** in relation to the stimulation interval of the corresponding heart chamber by adapting the parameter APD_0 in Equation 4.1 in Section 4.2.3, repeated here to ease reading:

$$A_{inf} = APD_0 - (S_0 - S_i) \cdot \psi.$$

A_{inf} is the asymptotic value towards which APD_i adjusts over time, with S_i as the constantly recalculated time interval since the last chamber stimulation and the patient-specific constant ψ , which parametrizes the effect of an altering stimulation interval relative to the initial parameters.

As the model parameters APD_0 and S_0 represent the initial **APD** and the initial stimulation interval in milliseconds, variances in these intervals enable the model to create unique ratios between these parameters. This ratio is crucial to model the variances in the **QTc interval** correlated with **long QT** and the menstrual cycle.

4.6.1 Long QT

The condition of the heart chambers in the context of a **long QT** is characterized by a prolonged chamber activity following a stimulation. As a result, the **vulnerable phase** of the corresponding chamber is prolonged, which increases the probability of stimulation in the **vulnerable phase**.

In order to represent this extended chamber activity in our model, a longer initial **APD** is designated in relation to the stimulation interval in the respective chamber module of our model by increasing the APD_0 until the ratio of the initial parameters for APD_0 and S_0 results in a **QTc interval** associated with **long QT**.

4.6.2 Menstrual Cycle

The fluctuation of the **QT interval** due to the menstrual cycle affect the **APD** interval and the stimulation interval. For the varying phases, the ratio and the **QTc interval** is either lengthened or shortened.

In order to represent the changes in the **QTc interval** during the menstrual cycle in our model, different initial **APD** values are specified in relation to the stimulation interval in the respective chamber module. This is accomplished by modifying the APD_0 until the resulting initial parameter values for APD_0 and S_0 yield a **QTc interval** interval associated with the various phases of the menstrual cycle.

4.7 Heart Pacemaker Interface

In order to facilitate the generation of diverse signal forms at the interface of the heart model, the signal forms are emulated by partially defined functions, as described below. Those are then transferred by the interface between the heart model and the pacemaker.

4.7.1 Emulated Intrinsic Signal (EIS)

The triangular signal shown in Figure 4.13 represents the electrical activity of the chamber as a voltage waveform. In accordance with the European standard [124], this waveform is the appropriate waveform for pacemaker sensitivity/detection threshold testing. Therefore, this waveform can be expected to meet the criteria for pacemaker recognition as a model-generated EIS.

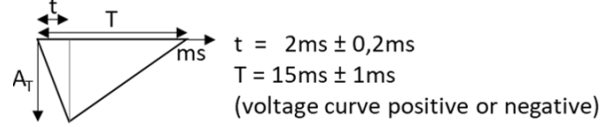


Figure 4.13: Triangle signal generated for the EIS following the standard [124].

The appearance of the signal in our model is determined by

$$f(i) = \left\{ \begin{array}{ll} A_i \cdot \frac{i}{t}, & 0 \leq i \leq t, \\ A_i \cdot \left(\frac{T-i}{T-t} \right), & t < i \leq T \\ 0, & i < 0 \text{ or } i > T. \end{array} \right\} \quad (4.11)$$

Here i is the time interval, A indicates the value for amplitude height, t represents the duration of the leading edge and T the duration of the entire triangle.

System Model of a Cardiac Pacemaker

This chapter presents pacemaker models, commencing with a description of the single-chamber pacemaker and continuing with a model of a inhibited dual-chamber pacemaker. The chapter then proceeds to illustrate the interaction between the pacemaker modules and the heart model via electrode modules. Figure 5.1 shows a schematic representation of the possible interaction interfaces between the heart and the pacemaker modules.

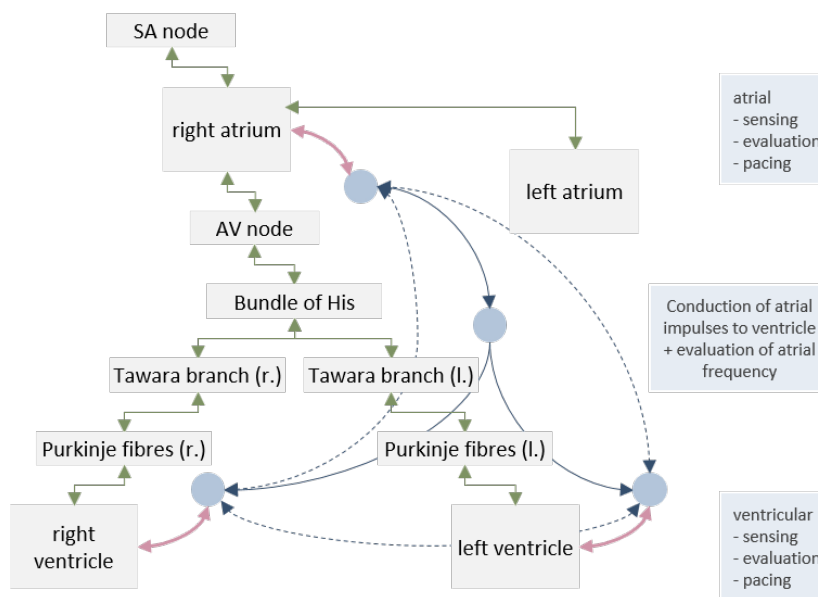


Figure 5.1: Schematic representation of the interaction interfaces between the individual modules of the pacemaker and the heart model: Solid lines indicate synchronisation commands between modules that lead to status changes in the following module. Dashed lines indicate an update of the variables that affect the module in the direction of the arrow. Blue lines represent the pacemaker and green lines the heart model. Pink lines indicate the interaction between the two modules via electrodes.

5.1 Inhibited Single-Chamber Pacemaker

A pacemaker with inhibitory properties ensures that cardiac activity is prioritized. Therefore, the pacemaker model remains in an **IDLE** state until it either detects an electrical pulse at the corresponding electrode or, if no cardiac activity is detected for an extended period, the pacemaker stimulates the heart. To prevent misperception or double perception, two additional states (**Blanking** and **Refractory**) follow the **IDLE** state, with different sensing properties to help to limit module perception. Figure 5.2 shows a inhibited single-chamber pacemaker. This module interacts with a single chamber of the heart model via an additional module representing the associated electrode.

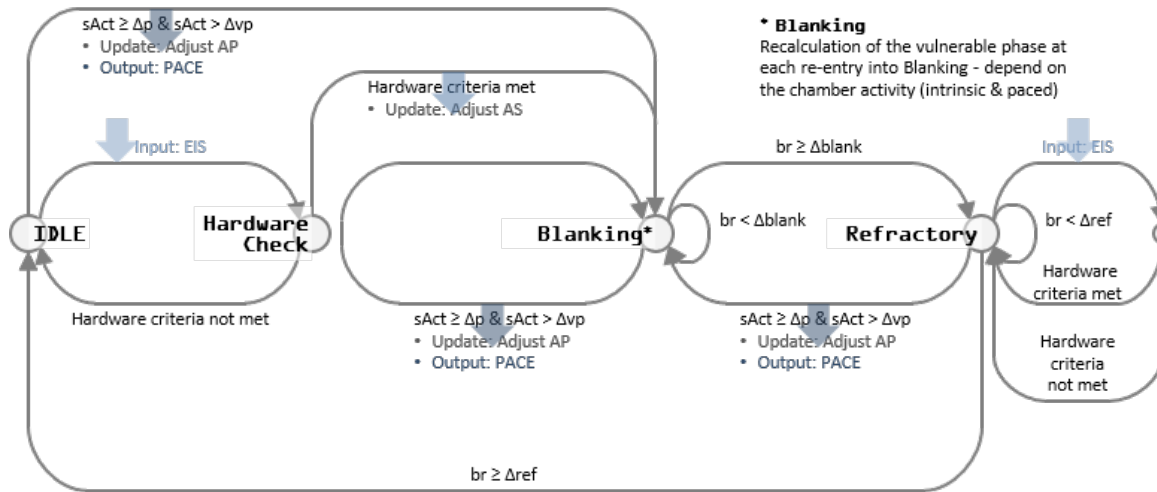


Figure 5.2: Schematic representation of a single-chamber pacemaker. Large circles represent states in which the pacemaker remains for a defined duration, whereas the small circle indicates a decision about the next path without a stay in the state. Arrows whose tip protrudes into the line of the model represent signals that enter this module from another module and can lead to a status change. Arrows whose tips point away from the line of the schematic represent the activation of other modules, with the output of the current module. Variables are explained in Table 5.1.

Adjust after AP = $\{sAct = 0, br = 0, \Delta t_b = PBP, \Delta t_r = PRP, n_{pmp}++\}$

Adjust after AS = $\{sAct = 0, br = 0, \Delta t_b = PBS, \Delta t_r = PRS, n_{pms}++\}$

Table 5.1: Overview and descriptions of the variables in Figure 5.2. Concrete values are given in Chapter 9.

Category	Variable	Definition
Module synchronisation	PACE	Pulse by the pacemaker → received by the modules: electrode
	EIS	Pulse by the electrode → received by the modules: pacemaker
Clocks	$sAct = 0$	Clock containing time since chamber activity
	$br = 0$	Clock containing time since heart activity
Time intervals	Δt_{vp}	Current interval for vulnerable phase
	Δt_b and Δt_r	Current interval for blanking resp. refractory
	Δt_p	Current interval for stimulating the heart chamber
Interval values	PBS and PRS	Duration for blanking resp. refractory interval after sensing
	PBP and PRP	Duration for blanking resp. refractory interval after pacing
Counter	n_{pmp}	Counter recording the pacing by the pacemaker
	n_{pms}	Counter recording the EIS sensed by the pacemaker

In our model there are two ways in which the pacemaker can exit the **IDLE** state:

IDLE to Blanking in Case of Sensing To enter this transition path, the pacemaker waits for a signal from its electrode (*Input : EIS*) to indicate the sensing of an **EIS**. Subsequently, its compliance with the hardware criteria is evaluated. In the event that the pulse does not fulfill the hardware criteria, it will revert to **IDLE**. Should the pulse meet the criteria, it will be classified as a cardiac signal and the pacemaker will transition to **Blanking**. During the transition from **IDLE** to **Blanking**, the variables are updated according to

$$AS = \{sAct = 0, br = 0, \Delta t_b = PBS, \Delta t_r = PRS, n_{pms}++\}$$

- The clock monitoring the time since the last chamber activity ($sAct$), which is constantly compared with the interval until pacing is necessary (Δt_p), is reset to maintain the programmed pacing rate.

- The clock for the blanking and refractory intervals (br) is reset and the corresponding intervals (Δt_b respectively Δt_r) are set to post-sensing. These intervals ensure that the pacemaker first remains in the blanking interval, unable to sense electrical activity for a defined period of time, to avoid sensing the same potential difference as additional chamber activity, and later in the refractory interval, for a defined period of time, to identify interfering pulses.
- The counter monitoring the sensed pulses (n_{pms}) is increased by one.

IDLE to Blanking in Case of Pacing If no ventricular activity is sensed by the pacemaker before the variable monitoring the time since last ventricular activity ($sAct$) exceeds the interval until pacing is required (Δt_p), the **ventricle** is stimulated by the pacemaker (*Output : PACE*) and the pacemaker passes to **Blanking** state. During the transition from **IDLE** to **Blanking**, the variables are updated according to

$$AP = \{ sAct = 0, br = 0, \Delta t_b = PBP, \Delta t_r = PRP, n_{pms}++ \}$$

- The clock that monitoring the time since the last chamber activity $sAct = 0$ is reset.
- The clock monitoring the blanking and refractory intervals (br) is reset and the corresponding intervals (Δt_b respectively Δt_r) are adjusted to post-stimulation, since the required time frames differ due to the tissue responses following the sensing or pacing pulses respectively.
- The counter monitoring the pacing pulses (n_{pms}) is incremented.

Blanking The pacemaker remains in **Blanking** for the defined period of time Δt_b . The duration of Δt_b depends on the path on which the pacemaker transitioned to this state. In this state, the pacemaker cannot receive any external pulses and is thus protected from sensing previously detected cardiac activity or any activity following its own electrical impulse. The pacemaker can re-enter the **Blanking** state, if the clock that stores the time since the last chamber activity $sAct$ exceeds the variable containing the interval until the next pacing pulse is required Δt_p . In this case, the updates as described for *AdjustAP* are performed.

Blanking to Refractory After the variable containing the interval for the blanking period Δt_b is exceeded by the clock containing the time since heart activity br , the module transitions into **Refractory**.

Refractory The module remains in this state for the duration of Δt_r . During this state, the module is capable of recognizing electrical pulses again. However, pulses recognised during this period are considered interfering signals, if they meet the hardware criteria to be identified as a heart signal. This is because there is no intrinsic heart signal expected in such a short time period after the latest chamber activity.

Refractory to Blanking The module can transition from the **Refractory** back to **Blanking** in case the clock storing the time since the last chamber activity $sAct$ exceeds the variable containing the interval until the next pacing pulse is required Δt_p . During this transition, the updates as described for *AdjustAP* are performed.

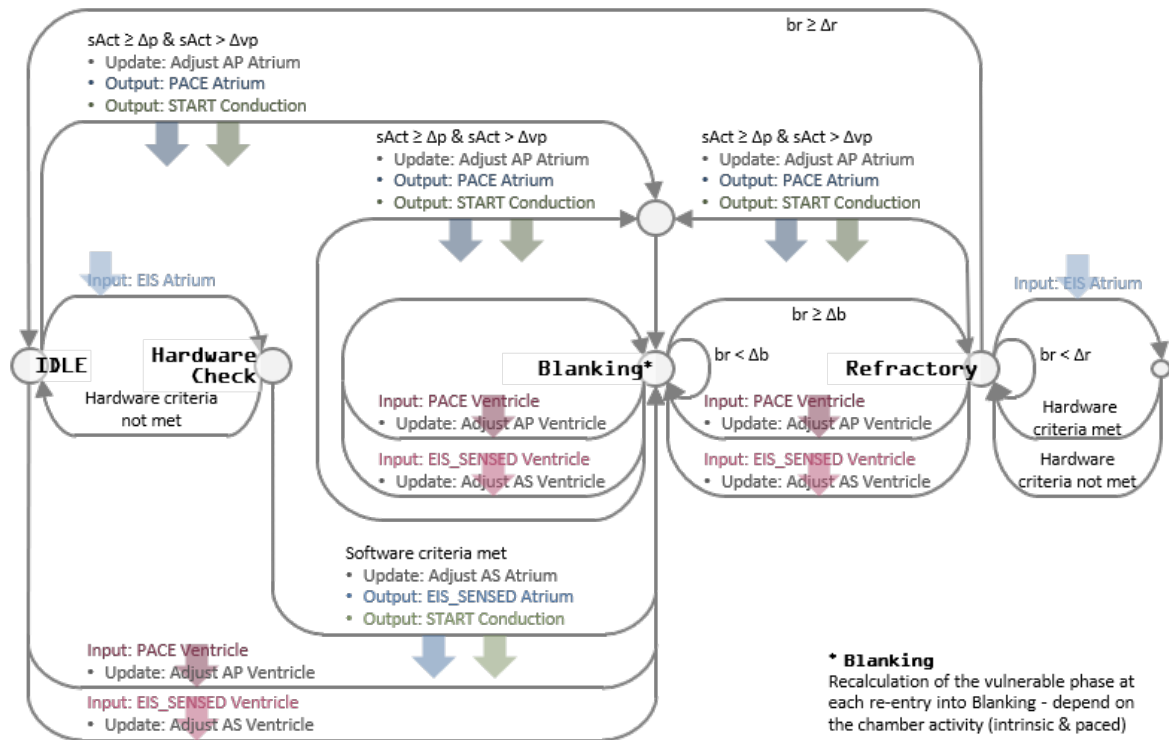
Refractory to IDLE In the event that the allotted time Δt_r in the **Refractory** state is extended by the variable monitoring the time since the latest cardiac activity br , the module transitions back from the **Refractory** to the **IDLE** state. It then awaits the occurrence of one of the two aforementioned events triggering a transition from **IDLE** to **Blanking**.

5.2 Inhibited Dual-Chamber Pacemaker

The model of the dual-chamber pacemaker described below consists of three modules: the atrial module, the ventricular module and a conduction module from the atrial module to the ventricular module. The atrial and ventricular modules are extensions of the inhibited single-chamber pacemaker described above. Each of them interacts with the corresponding ventricular modules by means of electrode modules. The conduction module is positioned between the two modules monitoring the chambers to achieve optimal ventricular synchronization. Conduction time and frequency are adapted to the variable atrial current values.

5.2.1 Atrial Module

Figure 5.3 shows the atrial module of the dual-chamber pacemaker model. The atrial module, starts in an **IDLE** state. It waits in this state for a heart signal to determine whether a stimulation of the chamber is required or whether the stimulation of the chamber by the **ECSH** is sufficient. The module remains in this state until one of four events occurs:



* **Blanking**
Recalculation of the vulnerable phase at each re-entry into Blanking - depend on the chamber activity (intrinsic & paced)

Figure 5.3: Representation of the atrial module of our dual-chamber pacemaker model. Arrows whose tip protrudes into the line of the model represent signals that enter this module from another module and arrows whose tips point away from the line of the schematic represent activation of other modules. The color blue represents actions regarding the atrium, pink, actions regarding the ventricle and green interactions with the conduction module. Variables are explained in Table 5.2.

Adjust after AP Atrium = {sAct = 0, br = 0, Δt_b = PAABP, Δt_r = PAARP, Δt_c = caP, $n_{pmp}++$ }

Adjust after AS Atrium = {sAct = 0, br = 0, Δt_b = PAABS, Δt_r = PAARS, Δt_c = caS, $n_{pms}++$ }

Adjust after AP Ventricle = {br = 0, Δt_b = PVABP, Δt_r = PVARP }

Adjust after AS Ventricle = {br = 0, Δt_b = PVABS, Δt_r = PVARP }

Adjust after APD = {APD recalculated, vp recalculated, s = 0 }

Table 5.2: Overview and descriptions of the variables in Figure 5.3. The section containing the synchronization commands provides an overview over the emitting and receiving modules for the synchronization commands respectively. Concrete values are given in Chapter 9.

Category	Variable	Definition
Sync.	EIS Atrium	Emitted by the atrial electrode module when receiving an activity → received by the modules: atrial pacemaker
	PACE Atrium	Emitted by the atrial pacemaker module when pacing the atrium → received by the modules: ventricular pacemaker, atrial/ ventricular electrode
	EIS Ventricle	Emitted by the atrial electrode module when receiving an activity → received by the modules: ventricular pacemaker, atrial/ ventricular electrode
	EIS SENSED Ventricle	Emitted by the ventricular pacemaker module when an input is identified as EIS → received by the modules: atrial pacemaker
	PACE Ventricle	Emitted by the ventricular pacemaker module when pacing the ventricle → received by the modules: atrial pacemaker, atrial/ ventricular electrode
	START Conduction	Emitted by the atrial pacemaker module when an input is identified as EIS → received by the modules: conduction module of the pacemaker
Clocks	$sAct$	Clock containing time since chamber activity
	br	Clock containing time since heart activity
Variables for Intervals	Δt_{vp}	Current interval for vulnerable phase
	Δt_b and Δt_r	Current interval for blanking resp. refractory for the atrial module
	Δc	Current interval for conduction
	Δt_p	Current interval for stimulating the atrial module of the heart
Updates for Variables	PAABP	Duration for the Δt_b in atrial module after pacing in the atrium
	PAABS	Duration for the Δt_b in atrial module after sensing in the atrium
	PVABP	Duration for the Δt_b in atrial module after pacing in the ventricle
	PVABS	Duration for the Δt_b in atrial module after sensing in the ventricle
	PAARP	Duration for the Δt_r in atrial module after pacing in the atrium
	PAARS	Duration for the Δt_r in atrial module after sensing in the atrium
	PVARP	Duration for the Δt_r in atrial module after pacing in the ventricle
	PVARs	Duration for the Δt_r in atrial module after sensing in the ventricle
Counter	n_{pmp}	Counter recording the pacing by the pacemaker
	n_{pms}	Counter recording the EIS sensed by the pacemaker

IDLE to Blanking in Case of Sensing in the Atrium When the atrial module senses an electrical signal (*Input* : *EIS Atrium*) from its lead, the module transitions to **Blanking**, after the hardware criteria confirm it as an atrial **EIS**. If the hardware criteria are not met, the module transitions back to **IDLE**. Upon identification as a cardiac signal, different variables of the atrial module have to be adapted according to

$$AS \text{ Atrium} = \{sAct = 0, br = 0, \Delta t_b = PAABS, \Delta t_r = PAARS, \Delta t_c = caS, n_{pms} ++ \}.$$

- The clock containing the time since the latest chamber activity $sAct$ is reset.
- The clock monitoring the time since the last heart activity br is reset and the durations for the intervals (Δt_{bA} and Δt_{rA}) are adjusted to prevent the electrode from double sensing the same electrical signal for multiple chamber activations.
- The module leading this pulse to the ventricular part is activated (*Output* : *STARTConduction*) and the conduction time (Δc) is adapted to the conduction time after sensing. This adaptation is required since a sensed pulse, has already passed a part of the chamber before being recognized on the electrode. When pacing the **atrium**, the **atrium** must contract from the beginning when the chamber is paced and the conduction has to be further delayed to maintain the interval duration.

IDLE to Blanking in Case of Pacing in the Atrium If no electrical signal occurs before the next scheduled stimulation of the chamber ($sAct$ reaches Δt_p), the pacemaker will stimulate the **atrium** (*Output* : *PACEAtrium*) and transition to **Blanking**. The parameters are adjusted to after pacing the **atrium** according to

AP Atrium = $\{sAct = 0, br = 0, \Delta t_b = PAABP, \Delta t_r = PAARP, \Delta t_c = caP, n_{pmp} ++ \}$

- Similar to after sensing the interval since stimulation $sAct$ is reset.
- The clock monitoring the time since the last heart activity br is reset and the blanking and refractory intervals (Δt_{bA} and Δt_{rA}) are adjusted.
- The stimulation of the **atrium** by a pacemaker involves higher energy than the intrinsic stimulation of the chamber by the **ECSH**, so the blanking and refractory periods not only of the **atrium** but also of the **ventricle** have to be reset to avoid double sensing and sensing in the other chamber. The pacing by the pacemaker in the **atrium** (*Output : PACEAtrium*) can therefore be received by the ventricular module and forces it to transition into **Blanking**.
- The conduction module is started by (*Output : STARTConduction*) and the conduction time (Δc) is reset. In case of pacemaker stimulation the conduction time is adapted to after pacing.

IDLE to Blanking in Case of Pacing Command in the Ventricular Pacemaker Module The incoming synchronisation command *Input: PACE Ventricle*, triggered by the ventricular pacemaker module in case the **ventricle** has been paced by the respective module, leads to the transition of the atrial pacemaker module from **IDLE** to **Blanking**, to prevent the sensing of the ventricular pacing pulse on the atrial electrode as an atrial signal. The parameters in the **atrium** for this transition are adjusted according to

$$\text{Adjust AP Ventricle} = \{br = 0, \Delta t_b = PVABP, \Delta t_r = PVARP \}$$

IDLE to Blanking in Case of Sensing of the Ventricular Pacemaker Module The incoming synchronisation command *Input: EIS SENSED Ventricle*, triggered by the ventricular pacemaker module in case a ventricular signal has been identified as **EIS**, leads to the transition of the atrial pacemaker module from **IDLE** to **Blanking**, to prevent the sensing of the ventricular pulse on the atrial electrode as an atrial signal. The parameters in the **atrium** for this transition are adjusted according to

$$\text{Adjust AS Ventricle} = \{br = 0, \Delta t_b = PVABS, \Delta t_r = PVARs \}$$

Blanking After entering **Blanking**, the pacemaker is unable to detect any cardiac activity. The module remains in this state until the blanking time (Δt_{bA}) exceeds br . The actual time spent in **Blanking** may vary as the state can be re-entered due to ventricular activity or in case $sAct$ reaches Δt_p . The transitions for reentering **Blanking** are identical to those mentioned for the possible transitions from **IDLE** to **Blanking**, except for the path that requires sensing.

Blanking to Refractory After the clock br reaches the value of the timing interval Δb while the module is in **Blanking**, the module transitions to **Refractory**.

Refractory In this state, for the duration of Δt_{rA} , the dual-chamber pacemaker mirrors the single-chamber pacemaker in terms of functionality. However, there is an important difference: The module can transition from **Refractory** back to **Blanking** triggered by additional events, mentioned above for entering **Blanking**.

Refractory to IDLE If the clock br reaches the value of the timing interval Δr in **Refractory** the module transitions back to **IDLE** state. Here it awaits for one of the four activation triggers to occur.

5.2.2 Conduction Module

Figure 5.4 shows the conduction module of the dual-chamber pacemaker. The mentioned synchronisation command, to start the conduction module from the atrial module (*START Conduction*), leads to the transition from **IDLE** to **PotModeSwitch** in the conduction module.

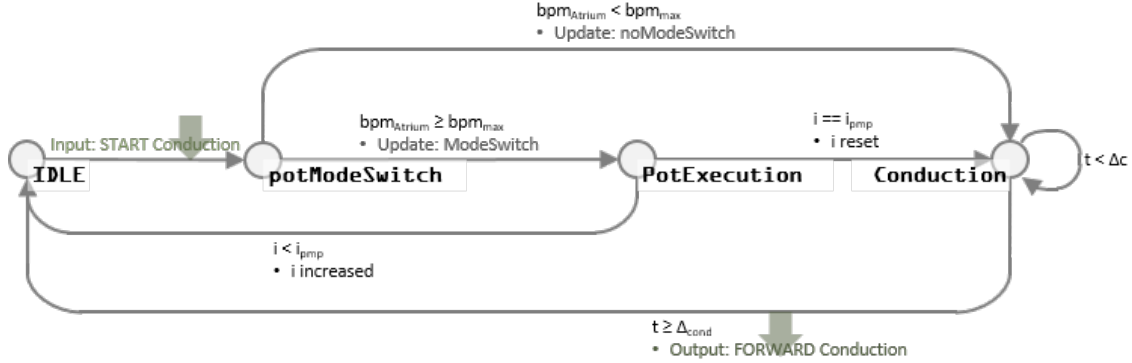


Figure 5.4: Representation of the conduction module of our model of a dual-chamber cardiac pacemaker. Symbols and colors are as described in Figure 5.3. Required updates can be found under the guards on the respective paths. Variables are explained in Table 5.3.

Table 5.3: Overview and descriptions of the variables in Figure 5.4. Concrete values are given in Chapter 9.

Category	Variable	Definition
Sync.	START Conduction	Pulse by the atrial pacemaker module → received by the modules: conduction module of the pacemaker
	FORWARD Conduction	Pulse by the conduction module of the pacemaker → received by the modules: ventricular pacemaker
Clocks	t	Clock
Intervals	Δc	Current interval for conduction
Counter	i	Counter recording the stimulations by the pacemaker
	n_{pmp}	Counter recording the pacing by the pacemaker
	n_{pms}	Counter recording the EIS sensed by the pacemaker
Variables	bpm_Atrium	Variable recording the total stimulations of the chamber per minute
	bpm_max	Threshold for the number of stimulations per minute initiating a mode switch

PotModeSwitch to Conduction In case the actual pulses in the [atrium](#) bpm_{Atrium} is below the maximal pulses to be conducted to the [ventricle](#) bpm_{max} , every pulse has to be conducted. Therefore, the module transitions from **PotModeSwitch** to **Conduction** directly, in case bpm_{max} exceeds bpm_{Atrium} .

PotModeSwitch to PotExecution If the actual beats in the [atrium](#) bpm_{Atrium} exceeds bpm_{max} the ratio of beats per minute to the maximum beats per minute over a single minute is calculated. The number of pulses to occur until a pulse is transmitted to the ventricular module is calculated via

$$i_{bpm} = \frac{bpm_{Atrium} \times bpm_{max}}{\text{milliseconds of a minute}}, \quad (5.1)$$

with

$$bpm_{Atrium} = n_{pmp} + n_{pms}. \quad (5.2)$$

Here, the values of n_{pms} and n_{pmp} contain the number of **EIS** sensed by the pacemaker perspectivevely the number of pulses emitted by the pacemaker. Both values are reset every minute minute. The value bpm_max contains the threshold for the number of stimulations to be conducted per minute.

The combination of i_{bpm} with an index i ensures a reduction and an evenly distribution of the pulses over time.

PotExecution to Conduction The module enters **Conduction**, if index i equals the number of pulses to occur until a pulse is transmitted i_{bpm} .

PotExecution to IDLE If index i does not match the value of i_{bpm} , index i is increased by one and the module returns to **IDLE**.

Conduction After reaching the **Conduction**, the module remains in this state until the clock t reaches the conduction time Δc , which depends on the sensing or pacing of the **atrium**, has expired.

Conduction to IDLE Following the ventricular module the synchronisation command *FORWARD Conduction* is emitted for the ventricular module and the conduction module transitions back to the **IDLE**.

5.2.3 Ventricular Module

Figure 5.5 shows the ventricular module of the dual-chamber pacemaker model. The states and transitions of the **ventricle** closely resemble those described for the **atrium**. The differences for the transitions into **Blanking** are described below.

IDLE to Blanking in Case of Ventricular Sensing For this, module **Blanking** is entered if a signal from the ventricular electrode is identified as **EIS**. This is followed by an update of the parameters according to

$$\text{Adjust after AS Ventricle} = \{br = 0, \Delta t_b = PVVBS, \Delta t_r = PVVRS\}.$$

IDLE to Blanking in Case of Pacing The transition due to the activation from the conduction module is initiated by the synchronisation command *Input: FORWARD Conduction*. Since the activation by the ventricular module of the pacemaker is supposed to be timely correlated to the activity of the atrial pacemaker module, the transition following $sAct > \Delta t_p$ is usually disabled for the ventricular module. In case the module has to operate without the atrial module as the time managing module, the transition can be enabled.

If one of the transitions is triggered in the ventricular pacemaker module, the **ventricle** of the heart model is stimulated by the pacemaker by the synchronation comand *Output: PACE Ventricle*. The updates for the stimulation of the **ventricle** are according to

$$\text{Adjust after AP Ventricle} = \{br = 0, \Delta t_b = PVVBP, \Delta t_r = PVVRP, n_{pmp} ++\}.$$

Figure 5.5: Representation of the ventricular module of our model of a dual-chamber pacemaker, using the same symbols and colors as those described in Figure 5.3. Variables are explained in Table 5.4.

IDLE to Blanking in Case of Atrial Pacing Furthermore the reception of the synchronisation command *Input: PACE Atrium* from the atrial module can lead to the transition into **Blanking**, including the updates of the variables according to

A transition to **Blanking** due to the sensing of the **atrium** is not necessary, since the atrial electrical impact is so low that it is usually not recognized in the **ventricle**.

- In case of the occurrence of a synchronisation command following atrial pacing (*PACE Atrium*) the variables are updated according to *AP Atrium* and the module re-enters **Blanking**.
- Following the occurrence of a synchronisation command from the conduction module *Input: FORWARD Conduction* the variables are updated according to *AP Ventricle* and the module re-enters **Blanking**.

Table 5.4: Overview and descriptions of the variables in Figure 5.5. The section containing the synchronization commands provides an overview over the emitting and receiving modules for the synchronization commands respectively. Concrete values are given in Chapter 9.

Category	Variable	Definition
Sync.	EIS Atrium	Emitted by the atrial electrode module when receiving an activity → received by the modules: atrial pacemaker
	PACE Atrium	Emitted by the atrial pacemaker module when pacing the atrium → received by the modules: ventricular pacemaker, atrial/ ventricular electrode
	EIS Ventricle	Emitted by the atrial electrode module when receiving an activity → received by the modules: ventricular pacemaker, atrial/ ventricular electrode
	EIS SENSED Ventricle	Emitted by the ventricular pacemaker module when an input is identified as EIS → received by the modules: atrial pacemaker
	PACE Ventricle	Emitted by the ventricular pacemaker module when pacing the ventricle → received by the modules: atrial pacemaker, atrial/ ventricular electrode
	START Conduction	Emitted by the atrial pacemaker module when an input is identified as EIS → received by the modules: conduction module of the pacemaker
Clocks	$sAct$	Clock containing time since chamber activity
	br	Clock containing time since heart activity
Variables for Intervals	Δt_{vp}	Current interval for vulnerable phase
	Δt_b and Δt_r	Current interval for blanking resp. refractory for the atrial module
	Δc	Current interval for conduction
	Δt_p	Current interval for stimulating the atrial module of the heart
Updates for Variables	PAVBP	Duration for the Δt_b in atrial module after pacing in the atrium
	PVVBP	Duration for the Δt_b in atrial module after pacing in the ventricle
	PVVBS	Duration for the Δt_b in atrial module after sensing in the ventricle
	PAVRP	Duration for the Δt_r in atrial module after pacing in the atrium
	PAVRS	Duration for the Δt_r in atrial module after sensing in the atrium
	PVVRP	Duration for the Δt_r in atrial module after pacing in the ventricle
	PVVRS	Duration for the Δt_r in atrial module after sensing in the ventricle
Counter	n_{pmp}	Counter recording the pacing by the pacemaker
	n_{pms}	Counter recording the EIS sensed by the pacemaker

5.3 Interface and Effects on the Pacemaker

The interaction between the modules of the heart model and the pacemaker model is facilitated by modules that route the synchronization commands back and forth between the heart model and the corresponding pacemaker modules. These modules reflect the electrodes that would perceive potential differences in a human heart.

Table 5.5: Overview and descriptions of the variables in Figure 5.6.

Category	Variable	Definition
Module sync.	ACT Atrium	Pulse by the atrial electrode and the atrial heart module → received by the modules: atrial electrode/ atrial heart
	PACE Atrium	Pulse by the atrial pacemaker module → received by the modules: ventricular pacemaker, atrial/ ventricular electrode
	INTERFERENCE Atrium	Pulse by interference module → received by the modules: atrial electrode
	PACE Ventricle	Pulse by the ventricular pacemaker module → received by the modules: atrial pacemaker, atrial/ ventricular electrode
	ACT Ventricle	Pulse by the ventricular electrode and the ventricular heart module → received by the modules: pulse by the ventricular electrode/ ventricular heart
	EIS Atrium	Pulse by the atrial electrode module → received by the modules: atrial pacemaker, atrial/ ventricular electrode

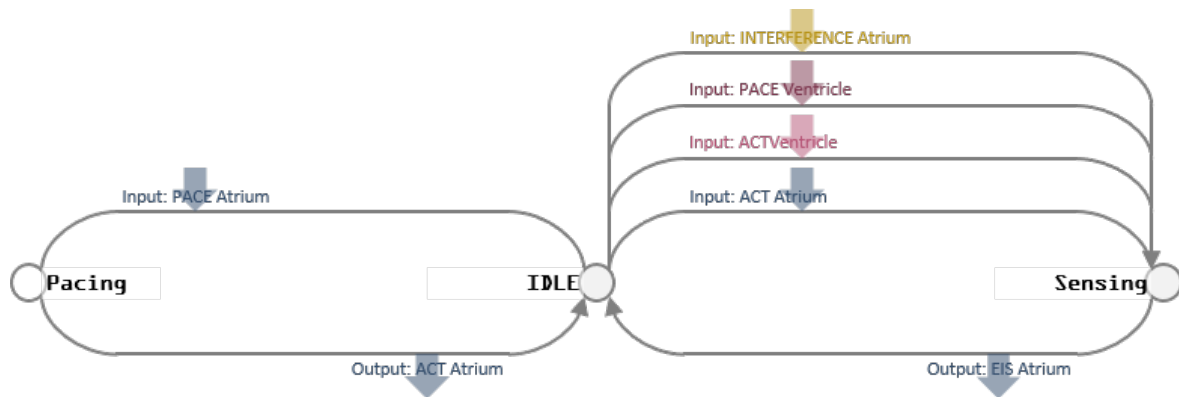


Figure 5.6: Representation of the module mirroring an atrial electrode. On the left hand side the conduction of a pacemaker module pulse into the chamber module, on the right hand side the conduction of pulses from cardiac and external modules into the respective pacemaker module are shown. The color coding is yellow for interference, pink for the *ventricle* and blue for the *atrium*. Variables are explained in Table 5.5.

Atrial Electrode

The module depicted in Figure 5.6 shows an atrial electrode. On the left side, the direction from the pacemaker to the *ventricle* is represented. The module receives the signal from the pacemaker to stimulate the *atrium* (*Input: PACE Atrium*) and transmits it to the atrial chamber module (*Output: ACT Atrium*).

The right-hand side represents the conduction of the signals received at the electrode into the pacemaker. The activities of

- an interfering signal (*Input: INTERFERENCE Atrium*),
- a stimulation of the *ventricle* (*Input: PACE Ventricle*),
- an intrinsic activation of the *ventricle* (*Input: ACT Ventricle*) and
- an intrinsic activation of the *atrium* (*Input: ACT Atrium*)

are conducted through the electrode into the pacemaker by *Output: EIS Atrium*. The electrical activities related to these events can be received at the atrial electrode located within the heart.

Ventricular Electrode

To represent a ventricular electrode, the synchronization commands on the left side are adapted to the *ventricle*. On the right side, the variable for the interference signal and the pathway for sensing and pacing of the *ventricle* is changed to pacing of the *atrium*. The pathway for sensing the *atrium* is omitted because the voltage of the electrical pulse emitted from the intrinsic activation of the *atrium* is too low to be measured in the *ventricle*.

Single-Pacemaker Electrode

The electrodes can also be used for a single-chamber pacemaker. The pacemaker stimulation paths of the other chamber are then unused.

Safety Queries

The following chapter describes the safety requirements we defined that must be met during the interaction between the heart model and the pacemaker. The safety requirements are presented in the following order: those that must be fulfilled in the stimulation intervals, the pacemaker's compliance with the required intervals (including both the stimulation and refractory intervals), and finally, the criteria for the [mode switch](#).PR These safety requirements naturally also apply to the real organ and the real pacemaker in the later application of both aspects as a bioelectronic system in the patient.

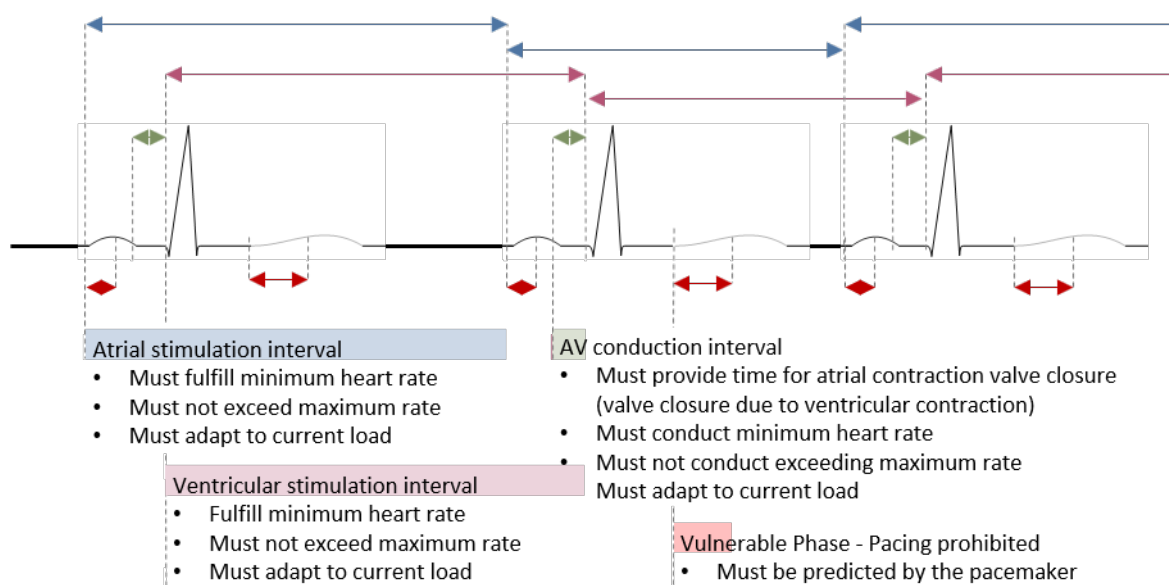


Figure 6.1: Schematic representation of the heart and pacemaker mediated intervals and their requirements.

Figure 6.1 provides a summary of the various intervals that the heart passes through with each beat, which must be taken into account when determining the next stimulation pulse and the total frequency to be generated by the pacemaker:

- the atrial interval and the ventricular pacing interval, which must experience a minimum number but must not exceed a maximum number of terminations and restarts per minute,
- the interval for pulse conduction between the [atrium](#) and the [ventricles](#), which must be adapted to the respective source of the atrial pulse and must maintain the specific coordination between the heart chambers depending on the circumstances and
- the [vulnerable phase](#), which occurs in both the upper and lower chambers, during which the pacemaker must not pace and which therefore has to be predicted precisely.

By modulating these intervals, the pacemaker can effectively elevate the heart rate and cardiac coordination of patients relying on a pacemaker, to the extent that they may survive or even experience a state of complete symptom-free remission.

6.1 Safety Queries for the Interaction of Pacemaker and Heart

The following safety criteria define the characteristics and limits that must be met on the heart side of the interaction between the heart and the pacemaker in order to compensate for the existing cardiac dysfunction or to enable a safe interaction between the heart and the pacemaker.

6.1.1 Heart Rate

To ensure adequate oxygenation of the body, it is essential to maintain a minimum heart rate. A heart rate below this threshold can result in a range of symptoms, including headaches, dizziness, nausea, vomiting, and, in rare cases, sudden loss of consciousness. The onset of these symptoms is influenced by individual factors. Conversely, an elevated heart rate can result in a number of adverse effects, including discomfort, lightheadedness, and chest tenderness. A persistently elevated heart rate exerts considerable stress on the cardiac muscle, which, over time, may result in the weakening of the muscle tissue and is also associated with an increased risk of developing heart failure, myocardial infarction, and atherosclerosis.

Accordingly, the heart rate, derived from the integrated heart rate signals and the pacemaker stimulation, must remain within the specified upper and lower heart rate limits for all cases. In order to verify this property, the following queries must be formulated:

Property 6.1.1 *Minimal heart rate* *The variable quantifying the number of beats per minute per chamber must not fall below the required minimum number of beats per minute for any chamber.*

Property 6.1.2 *Maximal heart rate* *The variable quantifying the number of beats per minute per chamber must not exceed the maximum number of beats per minute for any chamber.*

6.1.2 Heart Coordination

As described in Chapter 3.1.1, the efficient pumping of the heart necessitates the coordinated contraction and relaxation of the chambers. Inadequate ventricular filling, induced by atrial contraction against a closed ventricular valve, can reduce cardiac output and lead to symptoms such as palpitations, dizziness, and loss of consciousness.

Property 6.1.3 *Coordinated Contractions* *The variable quantifying the effective beats per minute must not fall below the minimal required number of effective beats per minute.*

6.1.3 Vulnerable Phases of the Heart

As mentioned previously, the stimulation of a cardiac chamber during its **vulnerable phase** can lead to **tachycardia**. To minimize the risk of triggering such a life-threatening cardiac arrhythmia, pacemaker stimulation during the **vulnerable phase** is to be avoided.

Property 6.1.4 *Vulnerable Phase* *The variable monitoring the occurrence of pacing during the **vulnerable phase** indicates no occurrences of pacing in the **vulnerable phase** by the pacemaker for any chamber.*

6.2 Safety Queries for Workflow Pacemaker Characteristics

The following queries are designed to ensure the safe operation of the pacemaker. They concern the occurrence, duration and reset of blanking intervals, with the aim of preventing the multiple perception of a signal. Additionally, they address the adaptation of the conduction module to atrial frequencies that may exceed the upper limit, as well as the adaptation of the conduction time during the sensing or stimulation of the [atrium](#).

6.2.1 Stimulation Interval

As described above, the beats per minute of the heart must fall within the specified minimum and maximum pulse ranges. Furthermore, it is imperative to reduce the number of pacemaker pulses to avoid the development of heart failure. It thus follows that the minimal duration until the next stimulation and the safety interval to prevent a stimulation during the [vulnerable phase](#) must be terminated exclusively by the clock. The maximal interval until stimulation must be terminated by the sensing of chamber activity or, in the event that the termination of the interval is initiated by the clock, it must be followed by pacing of the chamber. This interval must not be extended.

Property 6.2.1 *Sensed/ Paced bpm - Minimal* *The sum of the variables quantifying the [EIS](#) per minute and the paces per minute must not fall below the required minimum number of beats per minute for any chamber.*

Property 6.2.2 *Sensed/ Paced bpm - Maximal* *The sum of the variables quantifying the [EIS](#) per minute and the paces per minute must not exceed the maximum number of beats per minute for any chamber.*

Property 6.2.3 *Non-Essential Pacemaker Pulses* *The ventricular module should be able to enter the [systole](#) at the time a pacing pulse from the pacemaker occurs.*

Property 6.2.4 *Vulnerable Phase Protection Interval Duration* *The variable containing the interval until the next stimulation must always exceed the calculated duration of the [vulnerable phase](#) for any chamber.*

Property 6.2.5 *Termination of the Minimal Interval until Chamber Stimulation* *The minimum interval until chamber stimulation must not be terminated by any entity other than the extension of its associated clock for any chamber.*

Property 6.2.6 *Termination of the Maximal Interval until Chamber Stimulation* *The sensing of an [EIS](#) out of the blanking and refractory period must terminate the stimulation interval.*

Property 6.2.7 *Expiration of the Maximal Interval until Chamber Stimulation* *The expiration of the maximal interval until chamber stimulation must be followed by the pacing of the associated chamber.*

Property 6.2.8 *Termination of the Vulnerable Phase Protection Interval* *The [vulnerable phase](#) protection interval must not be terminated by any entity other than the extension of its associated clock for any chamber.*

6.2.2 Onset, Duration and Reset of Blanking/ Refractory Periods

The activation of a heart chamber, whether by the [ECSH](#) or the pacemaker, takes place via electrical pulses along the heart fibers through the chamber. In order to prevent the sensing of an activation of the chamber multiple times, a blanking time is necessary, which switches the pacemaker blind after the sensing of a cardiac signal or the stimulation of the [ventricle](#) by the pacemaker. In our model, each synchronisation command for the sensing of cardiac activity or stimulation by the pacemaker is followed by the entry into the blanking interval in the atrial and ventricular module (with the exception of the case of sensing in the [atrium](#), in which only the [atrium](#) must switch to blanking status).

In the event that the duration of the blanking or refractory state is either too long or too short, there is a discrepancy between the number of [EIS](#) that are recognized by the pacemaker and the actual number of [EIS](#), due to blanking during the occurrence of pulses or the incorrect identification of pulses as interfering signals. It is thus necessary that the intervals, which are set to determine these periods, are aligned with the event-specific time-frames, contingent on the event which initiated the respective adaptation. In addition, the clocks used to measure the duration of the current interval must be reset, when the blanking interval onsets.

Property 6.2.9 Onset of the Blanking Interval - After High Pulse *Each pacing of a heart chamber and the sensing of an [EIS](#) of the [ventricle](#) by the pacemaker is followed by a transition into blanking state for every pacemaker module in the subsequent step.*

Property 6.2.10 Onset of the Blanking Interval - Atrial Blanking after Atrial [EIS](#) *Each pacing of the atrium or sensing of an atrial [EIS](#) in the atrium is followed by a transition into blanking state for the atrial pacemaker module in the subsequent step.*

Property 6.2.11 Reset of Blanking/ Refractory Clocks - Reset after high Pulse *Each pacing of a heart chamber and the sensing of an [EIS](#) of the [ventricle](#) by the pacemaker is followed by a reset of the clocks controlling the blanking and refractory period to zero in the next step.*

Property 6.2.12 Reset of Blanking/ Refractory Clocks - Atrial Reset after Atrial [EIS](#) *Each pacing of the atrium or sensing of an atrial [EIS](#) in the atrium is followed by a reset of the clocks controlling the blanking and refractory period of the atrium to zero in the subsequent step.*

6.2.3 Conduction Intervals

Should an atrial activity be sensed by the pacemaker, this perception will only occur at a time when the chamber is already advanced in terms of electrical stimulation and contraction. If the **atrium** is stimulated by the pacemaker, both processes will only begin after stimulation by the pacemaker. Consequently, the conduction time between the **atrium** and the **ventricle** must be prolonged after pacing in order to allow the **atrium** sufficient time for the aforementioned processes until the **ventricle** is paced.

Property 6.2.13 Minimal Conducted Pacemaker Stimulation per Minute *The number of pulses transmitted by the pacemaker must not undercut the minimum number of beats per minute in any of the chambers.*

Property 6.2.14 Maximal Conducted Pacemaker Stimulation per Minute *The number of pulses transmitted by the pacemaker must not exceed the maximum number of beats per minute in any of the chambers.*

Property 6.2.15 Conduction Time Adaption - After Sensing *Each pacing of a heart chamber by the pacemaker is followed by the adaption of the conduction time to correspond to the conduction time after stimulation in the atrium.*

Property 6.2.16 Conduction Time Adaption - After Pacing *Each sensing of an **EIS** by the pacemaker is followed by the adaption of the conduction time to correspond to the conduction time after sensing in the atrium.*

Property 6.2.17 Vulnerable Phase Protection Interval Termination due to Conduction *The **vulnerable phase** protection interval must not be terminated by a conduction command.*

6.2.4 Mode Switch

Should the atrial rate be elevated, for instance due to **atrial fibrillation**, not all atrial impulses may be transmitted through the pacemaker into the **ventricle**. In our model, the current atrial frequency is therefore evaluated and compared against the maximum number of stimuli transmitted per minute. Should the rate be too high, the **mode switch** variable is set to true, and it is then determined whether the current beat should be transmitted.

The number of pulses transmitted by the pacemaker must range between the values for minimal and maximal heart rate.

Property 6.2.18 Mode Switch - On and Offset *Whenever the atrial rate exceeds the maximum of pulses to be conducted towards the **ventricle**, the variable that monitors the **mode switch** is true.*

6.3 Summery of the Safety Queries

The following tables provide a succinct overview of the previously defined safety queries, which are organised according to the requisite specifications for the heart and the functional requirements for the pacemakers.

Table 6.1: Overview of the error cases to be tested in the workflow pacemaker characteristics concerning the interaction of the pacemaker and the heart.

Prop.	Short Name	Description
Prop. 6.1.1	Minimal heart rate	The variable quantifying the number of beats per minute per chamber must not fall below the required minimum number of beats per minute for any chamber.
Prop. 6.1.2	Maximal heart rate	The variable quantifying the number of beats per minute per chamber must not exceed the maximum number of beats per minute for any chamber.
Prop. 6.1.4	Vulnerable Phase	The variable monitoring the occurrence of pacing during the vulnerable phase indicates no occurrences of pacing in the vulnerable phase by the pacemaker for any chamber.
Prop. 6.1.3	Coordinated Contractions	The variable quantifying the effective beats per minute must not fall below the minimal required number of effective beats per minute.

Table 6.2: Overview of the error cases to be tested in the workflow pacemaker characteristics concerning the stimulation intervals.

Prop.	Short Name	Description
Prop. 6.2.1	Sensed/ Paced bpm - Minimal	The sum of the variables quantifying the EIS per minute and the paces per minute must not fall below the required minimum number of beats per minute for any chamber.
Prop. 6.2.2	Sensed/ Paced bpm - Maximal	The sum of the variables quantifying the EIS per minute and the paces per minute must not exceed the maximum number of beats per minute for any chamber.
Prop. 6.2.4	Vulnerable Phase Protection Interval Duration	The variable containing the interval until the next stimulation must always exceed the calculated duration of the vulnerable phase for any chamber.
Prop. 6.2.3	Non-Essential Pacemaker Pulses	The ventricular module should be able to enter the systole at the time a pacing pulse from the pacemaker occurs.
Prop. 6.2.5	Termination of the Minimal Interval until Chamber Stimulation	The minimum interval until chamber stimulation must not be terminated by any entity other than the extension of its associated clock for any chamber.
Prop. 6.2.6	Termination of the Maximal Interval until Chamber Stimulation	The sensing of an EIS out of the blanking and refractory period must terminate the stimulation interval.
Prop. 6.2.7	Expiration of the Maximal Interval until Chamber Stimulation	The expiration of the maximal interval until chamber stimulation must be followed by the pacing of the associated chamber.
Prop. 6.2.8	Termination of the Vulnerable Phase Protection Interval	The vulnerable phase protection interval must not be terminated by any entity other than the extension of its associated clock for any chamber.

Table 6.3: Overview of the error cases to be tested in the workflow pacemaker characteristics concerning the onset, the duration and the reset of the blanking and the refractory periods.

Prob.	Short Name	Description
Prop. 6.2.9	Onset of the Blanking Interval - After High Pulse	Each pacing of a heart chamber and the sensing of an EIS of the ventricle by the pacemaker is followed by a transition into blanking state for every pacemaker module in the subsequent step.
Prop. 6.2.10	Onset of the Blanking Interval - Atrial Blanking after Atrial EIS	Each pacing of the atrium or sensing of an atrial EIS in the atrium is followed by a transition into blanking state for the atrial pacemaker module in the subsequent step.
Prop. 6.2.11	Reset of Blanking/ Refractory Clocks - Reset after high Pulse	Each pacing of a heart chamber and the sensing of an EIS of the ventricle by the pacemaker is followed by a reset of the clocks controlling the blanking and refractory period to zero in the next step.
Prop. 6.2.12	Reset of Blanking/ Refractory Clocks - Atrial Reset after Atrial EIS	Each pacing of the atrium or sensing of an atrial EIS in the atrium is followed by a reset of the clocks controlling the blanking and refractory period of the atrium to zero in the subsequent step.

Table 6.4: Overview of the error cases to be tested in the workflow pacemaker characteristics concerning the conduction intervals and the [mode switch](#) properties.

Prob.	Short Name	Description
Prop. 6.2.13	Minimal Conducted Pacemaker Stimulation per Minute	The number of pulses transmitted by the pacemaker must not undercut the minimum number of beats per minute in any of the chambers.
Prop. 6.2.14	Maximal Conducted Pacemaker Stimulation per Minute	The number of pulses transmitted by the pacemaker must not exceed the maximum number of beats per minute in any of the chambers.
Prop. 6.2.15	Conduction Time Adaption - After Sensing	Each pacing of a heart chamber by the pacemaker is followed by the adaption of the conduction time to correspond to the conduction time after stimulation in the atrium.
Prop. 6.2.16	Conduction Time Adaption - After Pacing	Each sensing of an EIS by the pacemaker is followed by the adaption of the conduction time to correspond to the conduction time after sensing in the atrium.
Prop. 6.2.17	Vulnerable Phase Protection Interval Termination due to Conduction	The vulnerable phase protection interval must not be terminated by a conduction command.
Prop. 6.2.18	Mode Switch - On and Off-set	Whenever the atrial rate exceeds the maximum of pulses to be conducted towards the ventricle , the variable that monitors the mode switch is true.

Model of the Human Heart in LabVIEW

This chapter describes the implementation of the system model of the heart in LabVIEW for use as a HIL model. Initially, the implemented architectural design of the model is presented, along with an overview of the communication processes between its constituent modules. Subsequently, the modules of the heart model are described in detail. First, the chamber modules are presented, followed by the modules of the ECSH and the modules representing diseases in the ESCH. Then, the interfaces of the surrounding model to the user and to a real pacemaker are discussed.

7.1 Human Heart Model

As previously discussed, the heart model encompasses a multitude of modules that are capable of receiving and transmitting impulses, thereby replicating the process of electrical impulse conduction and the dynamics of the chambers. The subsequent section will describe the implementation and interaction of these modules within the HIL model.

7.1.1 Architecture and Communication

As previously outlined in Section 2.1.1 (Model Requirements) and in Section 4 (System Model of the Heart), the heart model must comprise disparate parallelized areas that can communicate with each other asynchronously - without impeding each other's operations. In the HIL model, this is accomplished by the utilization of parallelized while loops within the LabVIEW programming environment. These loops are executed pseudo-parallelized.

The asynchronous communication is established by notifier. *Notifier* can be conceptualized as analogous to queues with constrained capacity and discrete content processing, without buffering messages. In the HIL model, the *send* function for the active area is linked to the *wait* function in all subsequent potential areas. Consequently, the active area transmits a signal for activation to the subsequent area(s), initiating a transition to the next state. Upon reception of the signal, the area(s) exposed to the signal will commence the while loop. In areas where the self-activation capability is present, the *timeout* function of the notifier is initiated in the event of an extended delay in message receipt. This implies that the area will activate itself after the specified time has elapsed, unless it has previously received a message via this notification.

7.1.2 Ventricles and Valves

The following sections present the implementation of the atrium and the ventricle for the HIL model. First, the atrium is described, and subsequently, the implementation of the requisite deviations and dilatations for the representation of the ventricle over the atrium is outlined. The implementations of the vulnerable phases and cardiac valves are discussed in the context of the respective chambers.

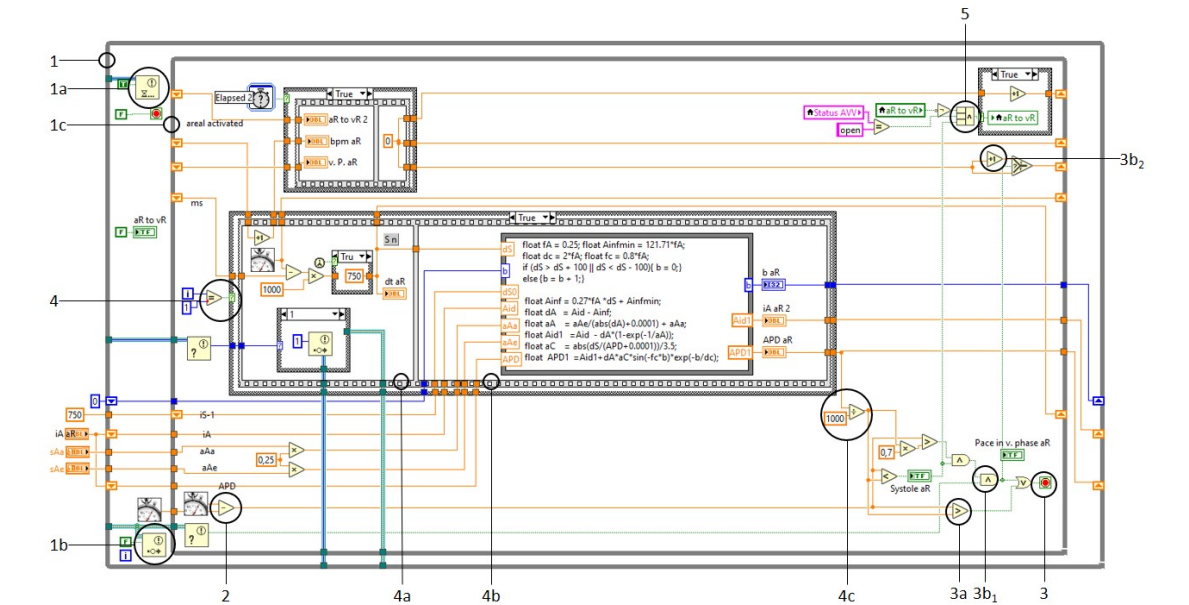


Figure 7.1: Atrial module of the **LabVIEW** model.

The inner while loop (**1c**) is responsible for the execution of numerous concurrent processes. At position (**2**), the area-specific clock is reset. This clock serves as the temporal reference for all events within this module. The box indexed by (**3**) indicates the exit point of the inner while loop. Upon receipt of the input *true* at this point, the area is terminated. It then returns to the **IDLE** state within the outer while-loop. The events that result in the output *true* at this point are

- the exceeding of the current **APD** value by the value of the area-specific clock (**3a**), or
- a stimulation being received on the second notification input (**1b**) in conjunction with the exceeding of the current onset of the **vulnerable phase** value by the value of the area-specific clock (**3b₁**).

The initiation of the **vulnerable phase** is depend upon the newly calculated **APD**. During this phase, a stimulation of the area by the notifier marked with **(1b)** serves to increase a counter, as indicated by the area marked with the assignment number **(3b₂)**. In the second scenario, a reset and restart of the chamber would occur based on the parameters set on the notifier marked with **(1b)**.

The **APD** calculation serves as the basis of all timed events within the chamber. As the **APD** is to be recalculated only once per area activation, at the onset, the recalculation is constrained by an if-statement within the inner while loop, as marked by (4). The execution of the aforementioned if-statement is depend upon the loop execution index being equal to 1. The order of execution of the steps in the following procedure, designated as (4a)

and (4b), is regulated by the sequence structure in which it is built. In the first step, step (4a), the preceding stimulation interval is identified by comparing the current time stamp to that of the previous call to this query. For the initial activation of the area in question, a fixed stimulation interval is designated. The resulting value is subsequently converted to milliseconds. Concurrently, the parameter specifying the stimulations per minute is increased. In accordance with the value of the notification, the pacemaker or a neighboring area of the ECSH is stimulated in the inner if-query.

In the second section, designated as (4b), the APD is calculated. The novel APD is calculated by applying the equations described in Section 4. This includes the user-inputted constants, the data derived from the model for the stimulation interval and the value of the parameter b. The values calculated for b, aid, and APD are then stored for subsequent calculations of APD. Subsequently, the if-statement is exited, and the newly calculated APD value is converted to seconds for subsequent use, as illustrated in the area marked with (4c).

While the inner while loop is executed, the chamber is activated. Consequently, the activation of the chamber prompts the evaluation of the valve status variable, with the objective of determining whether the blood can pass through an open valve. In the event that the valve status is open and the synchronization variable aRtovR is false, the value of aRtovR is set to true. This is indicated by index (5).

Ventricle In the *ventricle* module, the procedure for determination of the new APD is analogous to that for the *atrium*. Figure 7.2 depicts the additional components of the ventricular process in comparison to the atrial process. These relate primarily to the determination of the change in status of the valves.

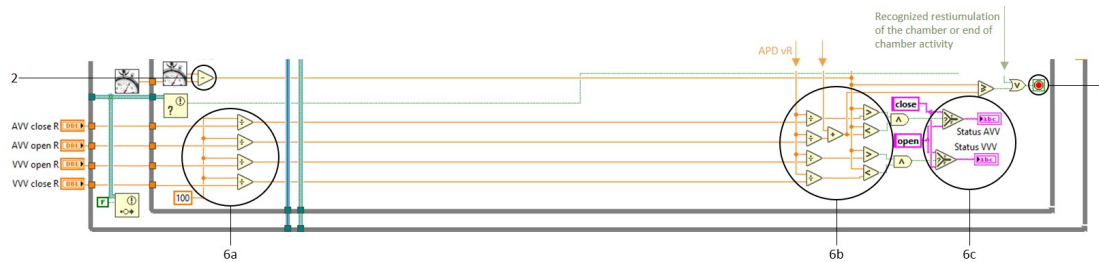


Figure 7.2: Ventricular module of the LabVIEW model.

In (6a), the percentage value entered by the user is converted into the format required for the valve status calculation. The onset of the valve status change is calculated in (6b), based on the equations from Section 4 as functions of the current APD. Subsequently, the resulting intervals are continuously compared with the chamber-specific clock in (2a). The resulting output for the chamber status is represented by the pink-bordered strings in area (6c). The associated *atrium* utilises this string value to ascertain whether the valve is congested. In contrast to the *atrium*, the *ventricle* simulation does not terminate upon the termination of the APD. For the *ventricle*, the process persists until the AV Valve is opened, which occurs after the end of the APD.

7.1.3 Additions to the Heart Chamber Modules for Data Acquisition

To facilitate further analysis of the status changes in the modules over time following the measurement, all status changes in the respective chambers are stored in an array together with a time stamp containing the time in milliseconds during the measurement. In the atria,

the the initiation of contraction, the onset of the **vulnerable phase**, and the conclusion of contraction are documented. In the **ventricles**, the initiation of contraction, the onset of the **vulnerable phase**, the opening of the **AV Valve**, and the conclusion of contraction are recorded as well as the delivery of an impulse by the pacemaker.

7.1.4 Electrical Conduction System of the Heart

Figure 7.3 illustrates the healthy operation of the self-activating AV area within the **LabVIEW** model. The loop structure operates similar to the descriptions of the chambers:

The **IDLE** mode is represented by the outer while loop, marked with (1). This module can be initiated by an activation, received by the notifier (1a). In this instance, however, it is a self-stimulating area. A timeout is therefore set on the notifier. The onset of this timeout is determined by the subsequent if statement. The if statement, marked by (2), is in turn triggered by an activity of the notifier. If a pulse comes in before the timeout, the next self-stimulation is set to the interval length after external-stimulation. In the event that the timeout is elapsed, the interval is set after self-stimulation (3a). This later interval until self-stimulation is shorter, but a probabilistic factor, marked by (3b), is included before the execution of the area's activity, in order to make the reliability of the replacement rhythm variable. If result of the comparison with the probabilistic variable generates the output *true*, the subsequent if statement (4) is executed. In the event of an external-stimulation of the chamber, the value for this if statement is set to *true*.

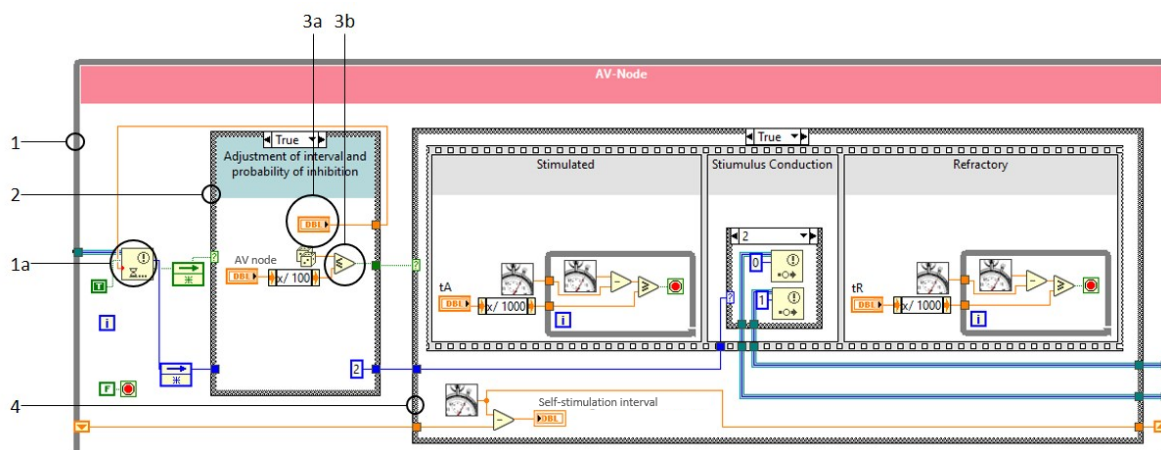


Figure 7.3: Self-stimulating area of the **ECSH** of the **LabVIEW** model.

If the subsequent if statement is activated, the area has been successfully stimulated. In this instance, the sequential structure of the statement is processed, from left to right. The duration of **APBC** can be set by the user-defined input variable *tA*. Subsequently, in the section labeled stimulus conduction, the stimulation direction is determined by retrieving the value area activation message. A value of 0 results in the execution of the case labelled 0, initiating stimulation in the **anterograde** direction. Conversely, a value of 1 signifies stimulation in the **retrograde** direction. Since this is a self-stimulating area a third option, receiving the value 2, is possible. In this case the **anterograde** and **retrograde** neighbouring areas are activated. Thereafter the area transitions to **APAC** and finally to **IDLE**. It is only possible to reactivate the loop and thus the sequence structure by a action of the notifier, once the sequence has been completed.

7.2 Disease Modeling Modules

This section outlines the modules that represent diseases in different areas of the heart, concerning a diseased rate generation, variances in the **QT interval**, and blockages applicable to modules representing different areas of the **ECSH** in the **HIL** model in **LabVIEW**.

7.2.1 Diseased Rate Generation Modules

The following section provides a description of the modules which represent the diseases that affect the pulse rate generated by areas of the **ECSH** for the **HIL** model of the heart in **LabVIEW**.

Bradycardia, Chronotropic Incompetence and Arrest

Figure 7.4 illustrates the section of the **AV node**, which is also part of Figure 7.3. In it the settings for conditions such as **bradycardia**, **chronotropic incompetence** and arrest can be induced. The conditions **bradycardia** and arrest can be emulated for each of the self-stimulating areas of the model.

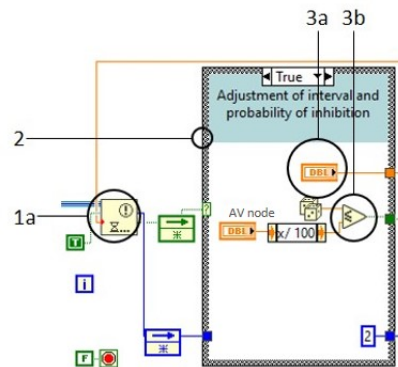


Figure 7.4: Conditions for adjusting the settings for **bradycardia** and arrest (Section of the **ECSH** area from Figure 7.3).

Bradycardia As previously outlined, a **bradycardia** occurs when a self-stimulating region, predominantly the **SA node**, stimulates itself at an insufficient rate. To incorporate **bradycardia** into the **LabVIEW** implementation, the interval until the timeout (**3a**) of the notification (**1a**) of the corresponding area can be extended.

Chronotropic Incompetence As the value for until the timeout (**3a**) of the notification (**1a**) can be controlled in each self-stimulating area, our model is capable of representing the successful adaptation of an area frequency or the absence of the corresponding adaptation (**chronotropic incompetence**) to external factors.

Arrest An arrest is defined as the absence of any self-stimulation of the area in question. This condition is implemented by setting the probability of a successful stroke (**3b**) to zero, thus preventing the generation of further successful strokes by the corresponding area.

Atrial and Ventricular Premature Contractions and Atrial Flutter

Figure 7.5 illustrates the module of the heart model able to mirror the behavior of premature contractions and **atrial flutter** in the **HIL** model. The module is capable of self-stimulation after a time interval defined by **3a**, with a probability determined by **3b**.

Since this module is not part of the **ECSH** configuration, but is instead located within one of the chambers, it does not stimulate one of the modules of the **ECSH**, but rather the chamber to which it is assigned. As the chamber is stimulated from within, the **retrograde ECSH** module is stimulated by a **retrograde** output of the chamber (*Output : chamber_ortho_stimulation*), while the connected pacemaker receives the pulse via the **anterograde** path of the chamber module (*Output : chamber_retro_stimulation*).

Atrial and Ventricular Premature Contractions Premature contractions are initiated by an **ectopic node** spontaneously generating pulses. Given that **PACs** and **PVCs** typically manifest sporadically, the interval preceding self-stimulation (**3a**) is set to a duration greater than a minute, while the probability **3b** is set to 100% to ensure an occurrence.

Atrial Flutter **atrial flutter** is defined as a circulating pulse that stimulates the **atrium** each time it completes its circuit. To mirror the stimulation frequency, due to **atrial flutter**, the module emits a series of pulses mediated by **3a**, reflecting the interval for a single circulation, with a probability of successful self-stimulation, represented by **3b**, of 100%.

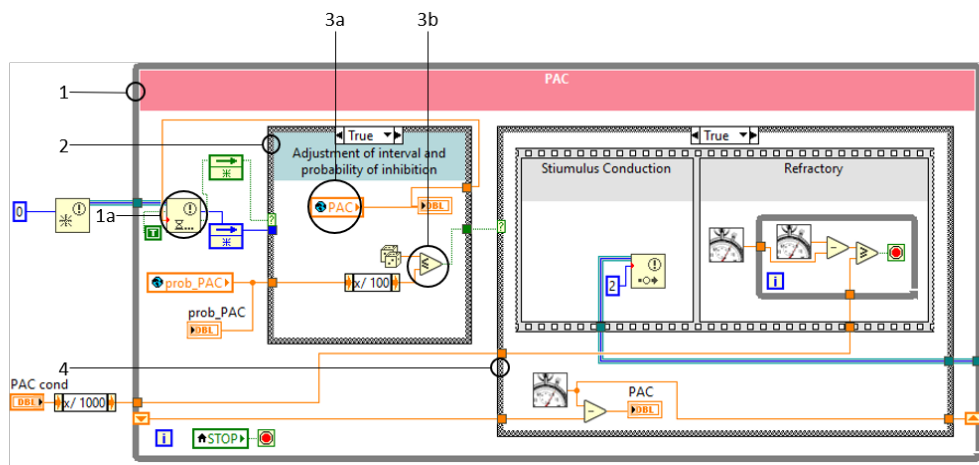


Figure 7.5: Conditions for adjusting the settings for atrial and ventricular premature contractions and **atrial flutter** in the **LabVIEW** model.

7.2.2 Variances in QT

The modeling of fluctuations in the **QT interval** is conducted by modifying the **APD** in relation to the stimulation interval of the corresponding heart chamber. The initial parameter APD_0 is adapted to alter the variable A_{inf} towards which APD_i adjusts over time. This adaption in the recalculation of the **APD** takes place in **4b** of the respective heart chamber module shown exemplarily in Figure 7.1.

Long QT

The **long QT** syndrome is defined by the prolongation of a vulnerable period that follows a stimulation event in the corresponding chamber. This prolonged period increases the likelihood of a subsequent stimulation occurring within that phase.

In order to represent the aforementioned extended chamber activity within our model, the relation between **APD** and the stimulation interval is adapted within the respective chamber module. This is realized by elevating the initial APD_0 until the ratio between APD_0 and S_0 results in a **QTc interval** associated with **long QT** in **4b** of the respective heart chamber module shown exemplary in Figure 7.1.

Menstrual Cycle

The variation in the **QTc interval** in response to the menstrual cycle results from the variances in the duration of the **APD** and stimulation intervals.

The fluctuations of the **QT interval** due to the menstrual cycle are emulated by modifying the **APD** interval in **4b** of the respective heart chamber module shown exemplary in Figure 7.1. Thereby the **APD** and the stimulation interval are either lengthened or shortened in accordance with the parameters for the varying phases. The initial parameter values for APD_0 and S_0 encompass those that result in a **QTc interval** associated with the various phases of the menstrual cycle.

7.2.3 Conduction Disease Modeling Modules

Most of the AV blocks are implemented in the module representing the transition from the **AV node** to the **bundle of his** respectively in the module representing the transition from the **bundle of his** to the **tawara bundles**, represented in Figure 7.6.

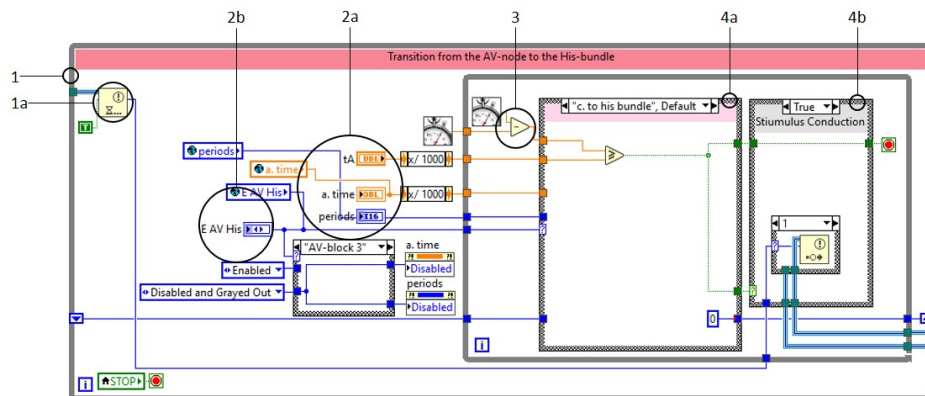


Figure 7.6: Conduction area, with the possibility to embed different disease cases in the conditions marked by 4a, in the LabVIEW model.

To facilitate classification of the individual **Atrioventricular blockage (AV block)**s within the context of the module, an introduction to the module representing the transition from the **AV node** to the **bundle of his**, shown in Figure 7.6, is provided. As previously stated, the while loop (1) commences with the transmission of an input on the notifier (1a). The requisite parameters for determining the duration of the **APBC** are retrieved (2a) and employed to calculate the current **APBC** based on the selected failure scenario (2b).

Upon the start of the inner while loop, the chamber internal clock is reset (3). The if statement in (4a) contains the different failure modes in a stacked register, with each failure mode in a separated register element. The implementation of the individual register elements will be explained in more detail in the following sections. Based on the output of (4a) the following if statement (4b) receives *true* or *false* as an input, after the expiration of the time spent in APBC. In case of *true* as input for the if statement (4b) the neighbouring area in the conduction direction, identified by the value of the notifier which activated this chamber, is activated.

First-degree AV block

The **first-degree AV block** is implemented as a register element of (4a). Therefore the following numbers in Figure 7.7 will be associated to (4a). The **AV Block 1** presents itself with a prolonging in the transition time.

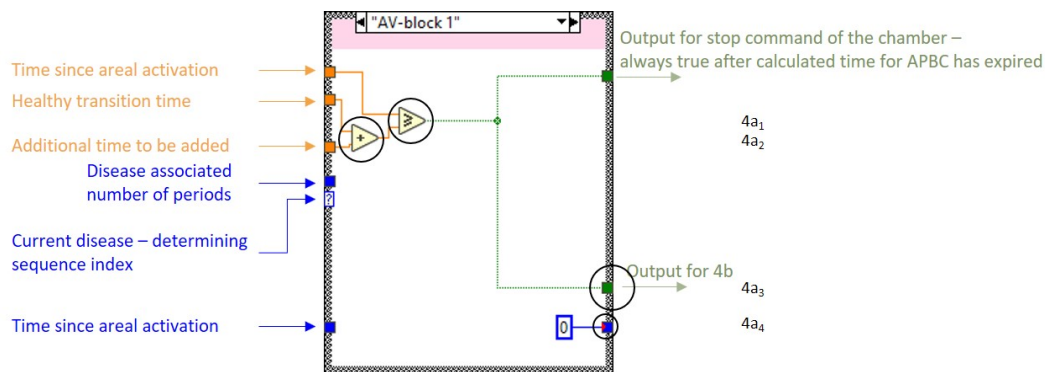


Figure 7.7: Implementation of a **first-degree AV block** from our system model in LabVIEW, which is embedded in the if statement marked 4a in Figure 7.6.

As can be seen in Figure 7.7, the transition period of the module is extended by the variable for additional time to encompass the specific delay (4a₁). The sum is then compared to the area clock (4a₂) to determine the APBC. The output for (4b) will be *true* for each activation. Despite this addition, the module reflecting a **first-degree AV block** corresponds to that of a healthy transition module. The incorporation of specific delays is possible in each constituent area of the ECSH, including the variable t_a .

Second-degree AV block (Type Wenckebach)

As previously outlined, a **second-degree AV block wenckebach** is characterised by the occurrence of a progressive prolongation in the time taken for the electrical impulse to be conducted, until a total conduction blockage occurs within the area of the affected conduction pathway. In the implementation of the LabVIEW module, shown in Figure 7.8, the additional time added with each pulse is multiplied by the current index value (4a₁) and then added to the normal transition time, each time the module is activated. Subsequently, the result of the calculation is compared with the area clock (4a₂) in order to ascertain the APBC. When the time calculated for APBC has elapsed, the area is terminated and returns back to IDLE.

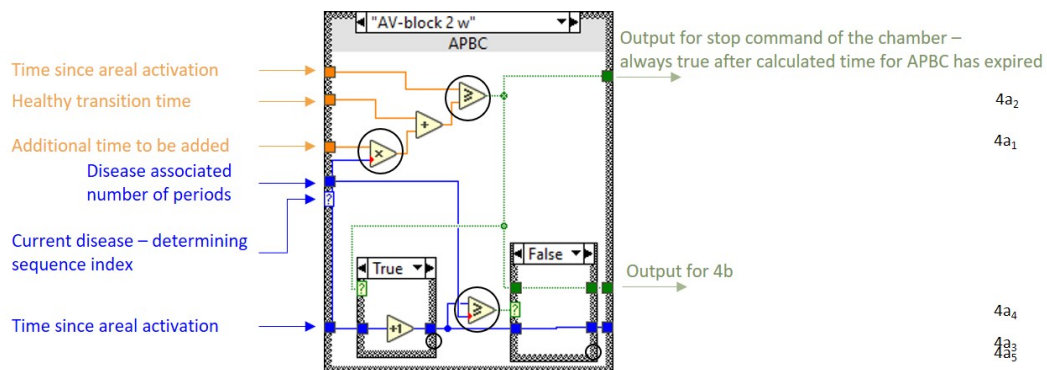


Figure 7.8: Implementation of a [second-degree AV block wenckebach](#) of the system model in LabVIEW, which is embedded in the if statement marked 4a in Figure 7.6.

The outcome transferred to (4b), deciding about the success of the transition, is depend upon the processes running in parallel in the lower part of the if statement. Upon the expiration of the allotted time, an index is incremented by one (4a₃). This index value is then compared with the disease associated number of periods (4a₄). If the two values are identical, the number of beats until blockage has been reached. In this case a value of *false* is passed to the subsequent if statement, inhibiting the execution of a transition. The index is then reset by the if statement in (4a₅). Conversely, if the index value is below the maximum until blockage, a value of *true* is passed, initialising a pulse transition, albeit with a delay.

Second-degree AV block Higher Grade

A [second-degree AV block higher grade](#) blocks a certain number of beats before a single pulse passes. This behavior is emulated for the module of the HIL model, shown in Figure 7.9. The pulse, which is to be conducted, is determined by comparing an index increasing with every chamber activation against the disease associated number of periods (4a₁). In case the values are equal to each other, the output variable for (4b) is set to *true* and the index is reset in the if statement marked by (4a₂). If not, a value of *false* is passed, the neighboring area does not receive a pulse and the index remains unchanged.

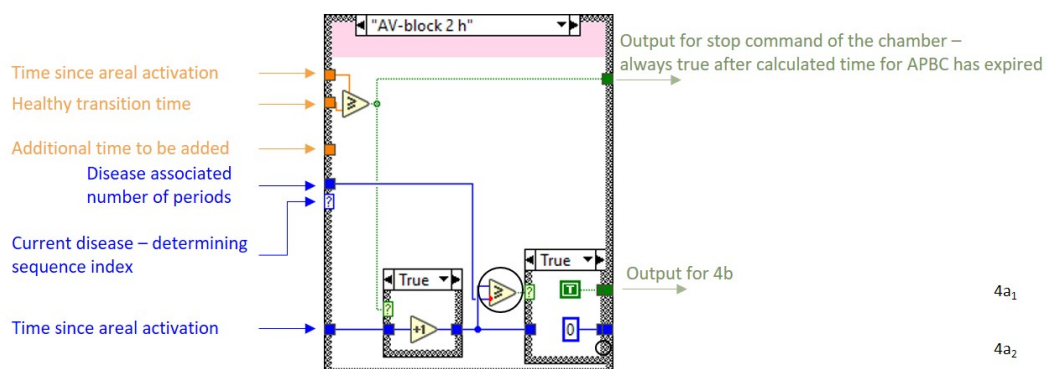


Figure 7.9: Implementation of a [second-degree AV block higher grade](#) in the system model in LabVIEW, which is embedded in the if statement marked 4a in Figure 7.6.

Second-degree AV block Mobitz

The **second-degree AV block mobitz** was implemented between the **bundle of his** and the **tawara bundle**. The fundamental concept of the module is identical to that of the previously presented transition module (**AV node** to **bundle of his**). As no diseases are integrated for this module that require additional parameters, the inputs for the if statement are limited to the transition time and the selection of the disease. This disease randomly blocks incoming pulses.

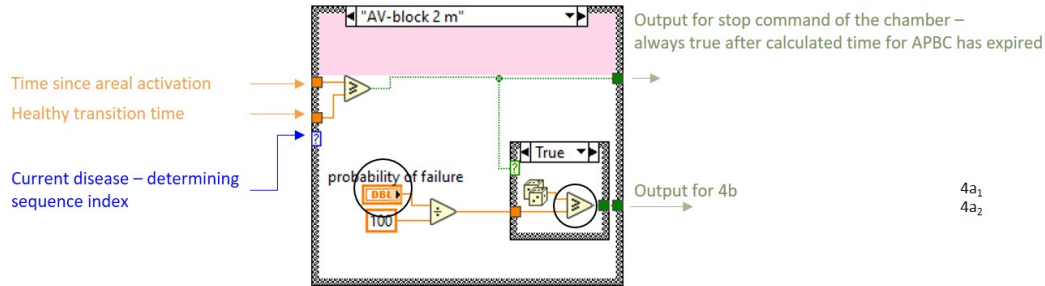


Figure 7.10: Implementation of a **second-degree AV block mobitz** from our system model in **LabVIEW**, which is embedded in the module representing the transition from the **AV node** to the **bundle of his**.

In the implementation of the module, seen in Figure 7.10, the probability for a pulse being blocked by this module can be specified by the user as a percentage value ($4a_1$). Given that the random number generator utilized in this model generates a number between 0 and 1, the value is subsequently divided by 100. If this area is activated, after the transition time has elapsed, a random number between 0 and 1 is generated and compared against the specified threshold value ($4a_2$). If the generated random value is above the threshold the output for (**4b**) is *true*. conversely, if the value is below the threshold, the output is *false*, and the neighboring area is not to be stimulated.

Third-degree AV block

The **third-degree AV block** is implemented as a register element in both transition modules. Given that this blockage represents a complete electrical blockade between the current area and the area below it, the corresponding module of the model must refrain from transmitting any pulses. Consequently, this module can be activated and remains active for the regular transition time, but the subsequent if statement (**4b**) always receives a false value, thereby preventing the transmission of any pulses.

7.3 User Interface

The **HIL** setup allows for the customization of the modeled fault cases occurring in the heart.

Figure 7.11 illustrates exemplary elements of the user interface of the heart model. The illustration on the far left (a) depicts the section for defining the parameters of the **ECSH**, which encompasses the area-specific transfer and refactoring times, as well as the selection of various diseases via drop-down menus. Furthermore, the settings for the probabilities of the self-stimulating areas are incorporated into the central portion on the left side of the figure. Part (b) of the figure on the far right depicts the values set for the initial chamber properties for the heart model.

Figure 7.11b is divided into four different sections, characterized by the fields in a lighter shade of grey, which represent the four heart chambers. For each chamber, an initial action potential duration is defined, marked by the variables APD0 1 to APD0 4. For the two **ventricles**, the values for the status changes of the valves are also inserted in the lower part of the respective areas highlighted in light grey.

a) Parameters for the ECSH.

b) Parameters for the chambers.

Figure 7.11: Exemplary parameter input elements of the user interface of the **HIL** heart model.

Figure 7.12 displays the current output values of the chambers, the **APDs** and the stimulation intervals of the disparate areas of the **ECSH**, depending on the selected panel. Monitoring enables the observation of the parameters and status of each area of the **ECSH** and the heart chambers during operation. Moreover, the output settings for the shape of the heart signal can be adjusted.

b) Output for the current run time.

Figure 7.12: Exemplary parameter output elements of the user interface of the **HIL** heart model.

7.4 Heart Pacemaker Interface

The LabVIEW-generated **Electrical Intrinsic Signal (EIS)** of the heart is transmitted to the poles of the electrode and recorded using a software-hardware interface associated with LabVIEW. As in the human body, the pacemaker in our HIL setup is linked to the external environment through an associated pacemaker electrode. The electrode is connected to the software-hardware interface via its metallic poles via clamps. The analogue input of the software-hardware interface is employed to record both the pacemaker signal and the heart signal, which are then evaluated within LabVIEW.

The triangular signal representing the **EIS**, described in Chapter 3 (Background), is parameterized by partially defined functions for the system model in Section 4 described in Equation 4.11. This allows for the pre-generation an array of voltage values for the **EIS**. The user interface provides access to scaling parameters for the measurement of pulse height and length. In order to facilitate the execution of tests at varying sensitivities, the amplitude level of the **EIS** is adjustable.

Figure 7.13 illustrates the panel for the interaction settings of the heart model with a real heart pacemaker. The values for the output, the generation of the triangular signal, and the formulas can be entered in the upper left-hand section. The subsequent section allows the user to input the threshold values for the incoming signals. The graphs illustrate the perceived pacemaker signal during the measurement (on the left) and the outgoing triangular signal (on the right). The subsequent section contains the output parameters that are generated during the measurement process.

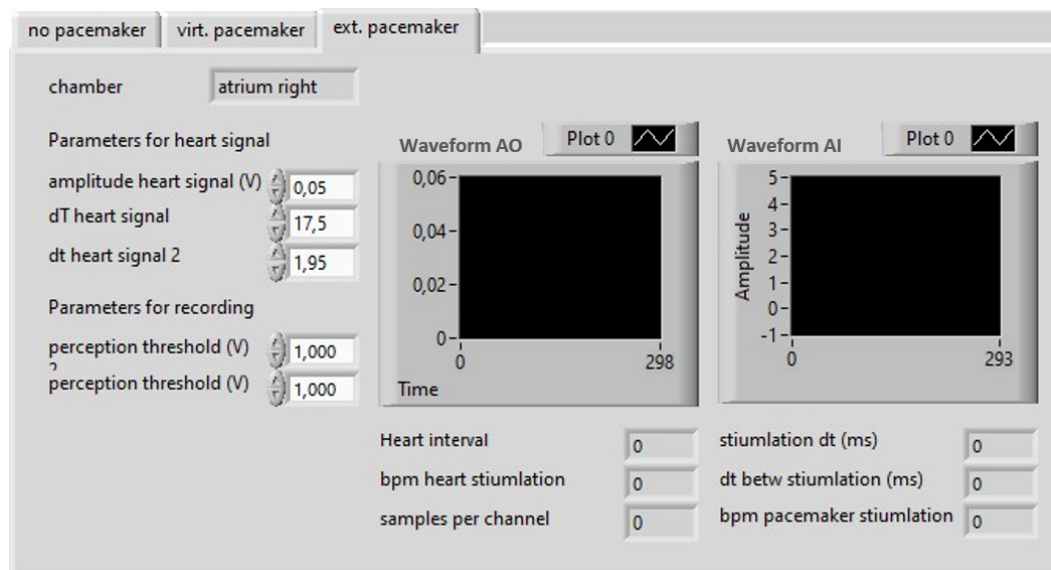


Figure 7.13: Panel for the input and output of parameters for the interaction of the heart model with a real pacemaker.

7.5 Safety Queries in LabVIEW

Table 7.1 summarizes the modeled behavior, which is used to check the safety requirements for LabVIEW defined in Chapter 6.

Table 7.1: Overview of the error cases to be tested for the pacemaker heart interaction.

Prob.	Short Name	Description
Prop. 6.1.1	Minimal heart rate	In our model, the heart rate is measured in beats per minute by counting each successful chamber activation. Successful chamber activation refers to any stimulation that causes the respective chamber module to transition to the state Systole , seen in Figure 4.2 and Figure 4.3.
Prop. 6.1.2	Maximal heart rate	Similar to the monitoring of the minimum heart rate in our model, testing the maximum heart rate involves counting the successful activation of the chambers per minute over a defined period of time. Also, only stimulation that causes the respective chamber module to enter the state Systole , seen in Figure 4.2 and Figure 4.3 is recorded.
Prop. 6.1.3	Coordinated Contractions	In our model, a contraction with respect to this behavior is considered efficient if the atrial module is in a state representing the part of the systole , as seen in Figure 4.2, while the variable monitoring the AV Valve is true, seen in Figure 4.3.
Prop. 6.1.4	Vulnerable Phase	In our model, an occurrence of stimulation during the vulnerable phase is counted when the pacemaker commands stimulation while the chamber to which the pacemaker is connected is in Vulnerable phase .

Human Heart and Pacemaker Models in UPPAAL

This chapter presents the heart model, the pacemaker model, and the modules modeling their interfaces in UPPAAL as models for formal verification. The modeling of the architectural design of the model is presented, accompanied by an overview of the communication processes between its modules. Subsequently, the modules of the heart model are described in detail. Beginning with the *ventricle* modules, which are then followed by the *ECSH* modules and the modules representing diseases in the ESCH. The description of the heart model is followed by the of the modules of the pacemaker model and their interconnections.

8.1 Human Heart Model

The heart model's modular structure enables the model both to transmit and to receive impulses within itself and toward external modules. This allows the model to verify the process of electrical conduction and the dynamics of the *ventricles*. The following section outlines the modeling and interaction of these modules within the verification model.

8.1.1 Architecture and Communication

As mentioned in the Model Requirements section of Chapter 2.1.1 and the System Model in Chapter 4, the heart model must consist of distinct, parallel modules that can communicate asynchronously without interfering with each other. In the context of the formal verification model, this is achieved by representing each area as a separate timed automaton that runs independently and in parallel to the others. The individual modules are connected by broadcast channels. This form of asynchronous communication allows a module to send a synchronization command during a transition, regardless of whether another module is able to receive it. A module can only receive the call by a synchronisation command if it is in a state from where it can perform a transition extended with a matching synchronisation command for reception. Otherwise, the message expires.

8.1.2 Ventricles and Valves

This section outlines the modeling of the *atrium* and *ventricle* within the formal verification model. First the specific characteristics of the *atrium* are described. Subsequently, the requisite modifications and augmentations to the *ventricle* in comparison to the *atrium* are presented. The modelings of the *vulnerable phases* and cardiac valves are discussed in the context of the respective chambers.

Maintenance activities conducted within a committed state are not considered as time steps.

Atrium

Figure 8.1 illustrates the modeling of the right atrium in UPPAAL. As previously outlined for the atrial module within the system model, this module commences in **IDLE** state, awaiting a synchronization command from an external module, which then initiates a transition, eventually leading to **Systole**.

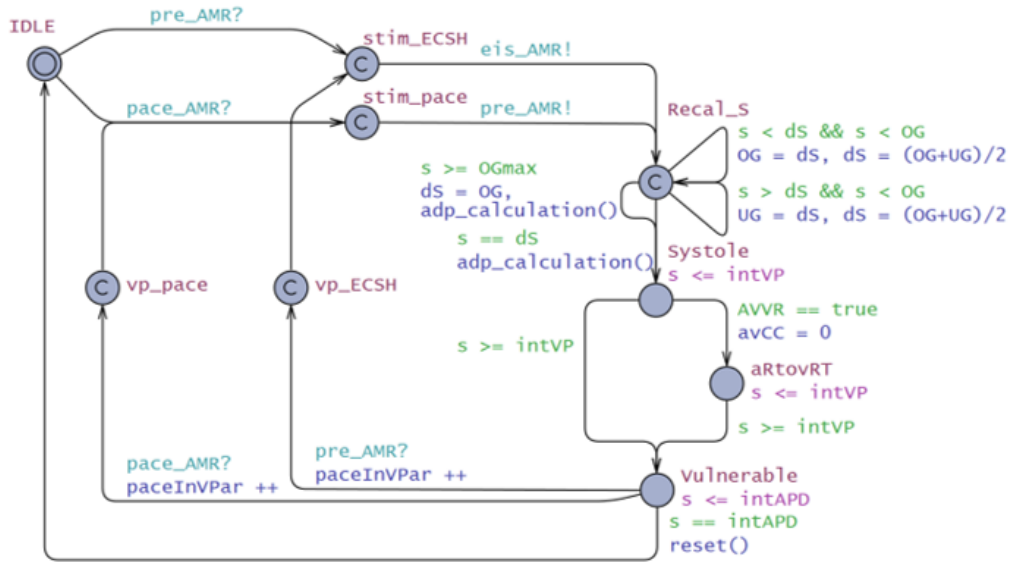


Figure 8.1: Atrial module of the heart model expressed in UPPAAL. Variables are explained in Table 8.1.

The route from **IDLE** to **Systole** has two possible branches:

- one via the committed state **stim_ECSH**, initiated by pulse from the **ECSH** **pre_AMR?**, emitting a pulse for the pacemaker by **eis_AMR!**, and
- the other via the committed state **stim_pace** initiated by a pulse from the pacemaker module **pace_AMR?**, emitting a pulse into the **ECSH** by **preAMR!**.

Both transitions lead to the committed state **Recal_S**, in which the time interval since the last chamber stimulation is determined. As the clocks utilized in Uppaal are symbolic in nature, their values cannot be directly employed as numerical values for the subsequent calculation of the **APD**. Thus, the value of the clock s in milliseconds is repeatedly compared against the integer variable ds in milliseconds until the value of ds equals the value of s . To reduce the required steps for determining the value of s , ds is introduced as a novel upper or lower threshold during the subsequent phase of the search, contingent on the prevailing ratio. In order to restrict the maximum calculated length of the **APD** the variable OG_{max} is introduced. If the actual stimulation interval s in milliseconds exceeds the threshold OG_{max} in milliseconds, the value for the stimulation interval for the following recalculation of the **APD** (ds) is the upper bound (OG) for **APD** adaption ($ds = OG$).

Once the value for s has been identified, namely $s == ds$ or $s >= OG_{max}$ and $ds = OG$, the transition to **Systole** is pursued. Upon transitioning to **systole**, **adp_calculation()** is called and executed. In **adp_calculation()**, the new value for **APD** is calculated based on the formulas from Chapter 4, calculated with $ds = s$. The time interval until the start of the **vulnerable** phase is calculated and s , as well as the upper and lower limits for searching s are reset.

Table 8.1: Overview and descriptions of the variables in Figure 8.1.

Category	Variable	Definition
Locations	IDLE	Initial and waiting status
	Recal_S	Identification of the value of s
	Systole	Representing the interval duration of the systole
	Vulnerable	Representing the interval duration of the vulnerable phase
Locations Indicating a Path	stim_ECSH	Indication of a stimulation of the chamber by the ECSH
	stim_pace	Indication of a stimulation of the chamber by the pacemaker
	aRtovRT	Indication that the AV Valve is open during atrial contraction
	vp_ECSH	Indication of a stimulation in the vulnerable phase by the ECSH
	vp_pace	Indication of a stimulation in the vulnerable phase by the pacemaker
Synchronization commands	eis_AMR	Pulse coming from and going towards the ECSH
	pre_AMR	Pulse coming from and going towards the electrode
	pace_AMR	Pulse coming from and going towards the pacemaker
Clocks	s	Clock containing time since chamber activity
	avCC	Clock containing time since atrial contraction began
Variables	ds	Containing the value of the clock s for further calculations
	AVVR	Boolean containing the value of the AV Valve
	adp_calculation ()	Update in the background to recalculate the APD
	reset ()	Update in the background to reset the values of OG and UG
Interval Thresholds	UG	Lower threshold for determine the next value of ds
	OG	Upper threshold for determine the next value of ds
	OGmax	Maximal upper threshold for ds
Clock Thresholds	intVP	Current interval for the vulnerable phase
	intAPD	Current interval for the APD
Counter	paceInVPar ++	Clock containing time since atrial activity

The module can remain in **Systole** until the **vulnerable phase** has elapsed, as indicated by the invariant $s \leq \text{intVP}$. To exit **Systole** there are two possible pathways both leading to **Vulnerable**:

- The one on the right-hand side leads to **aRtovRT**. It is pursued if the global variable for the status of the A of the associated **ventricle** indicates that the valve currently is open by $\text{AVVR} == \text{true}$. This transition leads to the rest of the variable **caRtovR**, counting the milliseconds since the atrial contraction, necessary to count the contractions of the **atrium** followed by a ventricular contraction, while the valve was open. The module stays in **aRtovRT** until the **vulnerable phase** has elapsed, namely until $s \geq \text{intVP}$. In this case the module transitions to **Vulnerable**.
- In case s reaches **intVP** the module must exit the state **Systole**. In the event that $\text{AVVR} == \text{true}$ has not manifested prior to the occurrence of $s == \text{intVP}$, the module transitions directly from **Systole** to **Vulnerable**.

Should an external pulse, stimulating this chamber (**pre_AMR?** or **pace_AMR?**) be introduced into the model while the model is in **Vulnerable**, the model transitions back to **Systole** via **Recal_S** on one of two paths, depending on the module the pulse was received from:

- one path via the committed state **vp_ECSH**, initiated by pulse from the **ECSH pre_AMR?**, emitting a pulse for the pacemaker by **eis_AMR!**, and
- the other path via the committed state **vp_pace** initiated by a pulse from the pacemaker module **pace_AMR?**, emitting a pulse into the **ECSH** by **preAMR!**.

On both paths the variable for pacing in the **vulnerable phase** is increased during this transition by **paceInVPar++**. In case there is no external pulse received until $s == \text{intAPD}$, the module transitions back to **IDLE** at this point. This transition is accompanied by the execution of **reset()** in which the variables containing the values for the upper and lower bounds of the stimulation interval for this chamber are reset.

Ventricle

The ventricular module follows the realisation of the atrial module. To include the valves, additional states have been incorporated into this module. Exemplary the modeling of the right ventricle is shown in Figure 8.2. The transitions from **IDLE** to **Systole** correspond to those previously described for the atrium, with exception of the adapted nomenclature to initiate one of the transitions:

- The module activation by a pulse from a module of the ECSH by `pre_VMR?`, via the committed state `stim_ECSH` and the emission of a pulse which is recognised by a pacemaker `eis_VMR!`, or
- the activation of the module by the pacemaker with the synchronisation command `pace_VMR?`, via the committed state `stim_pace` and emitting a pulse into the ECSH by `pre_VMR!`.

The execution of `apd_caculation()` for the ventricles not only encompasses the recalculation of the interval until the onset of the vulnerable phase but also the intervals until the congestion changes in the status of the various valves. As in the atrium the clock `s` is reset by entering the state **Systole**.

The following states are divided into **Systole1** and **Systole2**. The module is permitted to remain **Systole** until `s` reaches the calculated time for the closure of the restricted by the guard `s <= AVVRC`. For `s == AVVRC`, the module transitions to **Systole1** and the status of `AVVR` is set to false.

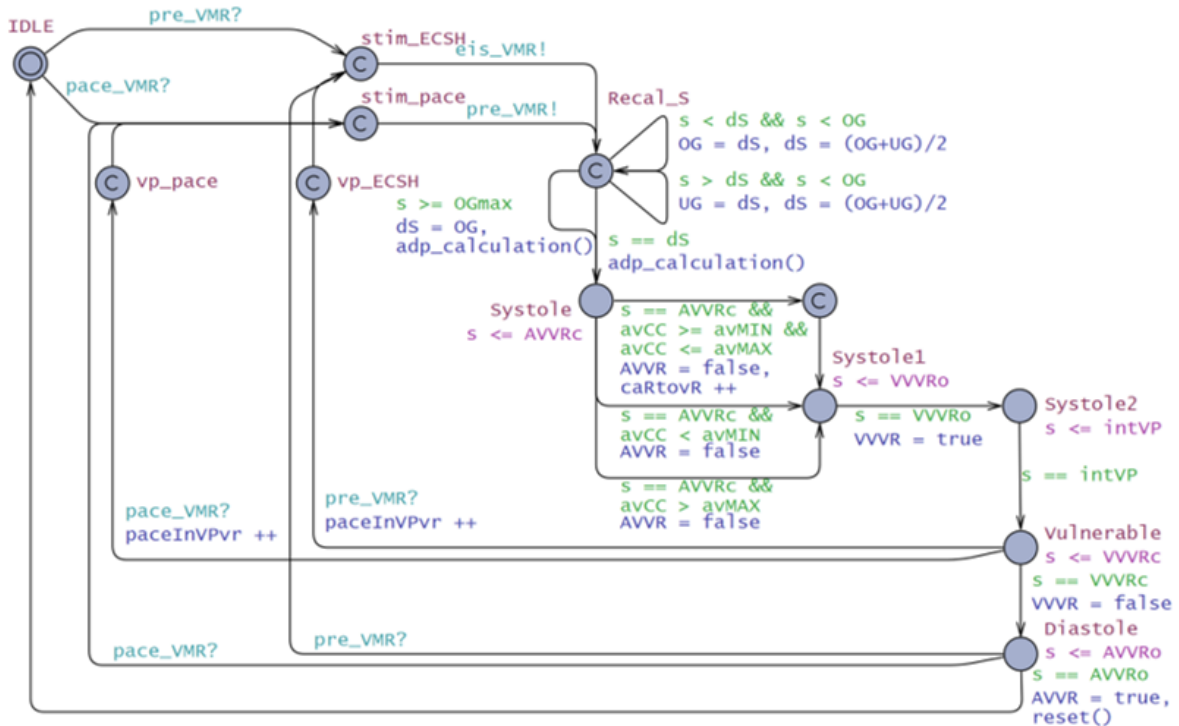


Figure 8.2: Ventricular module of the heart model expressed in UPPAAL. Variables are explained in Table 8.2.

Table 8.2: Overview and descriptions of the variables in Figure 8.2.

Category	Variable	Definition
Locations	<code>IDLE</code>	Initial and waiting status
	<code>ReacaL_s</code>	Identification of the value of <code>s</code>
	<code>Systole</code>	Representing the interval duration of the <code>systole</code>
	<code>Systole1</code>	Representing the interval duration of the <code>systole</code> until the <code>VV Valve</code> opens
	<code>Systole2</code>	Representing the interval duration of the <code>systole</code> until the <code>VV Valve</code> closes
Locations Indicating a Path	<code>Vulnerable</code>	Representing the interval duration of the <code>vulnerable phase</code>
	<code>Diastole</code>	Representing the interval duration of the <code>depolarization</code>
	<code>stim_ECSH</code>	Indication of a stimulation of the chamber by the <code>ECSH</code>
	<code>stim_pace</code>	Indication of a stimulation of the chamber by the pacemaker
	<code>aRtovRT</code>	Indication that the <code>AV Valve</code> is open during atrial contraction
Sync. commands	<code>vp_ECSH</code>	Indication of a stimulation in the <code>vulnerable phase</code> by the <code>ECSH</code>
	<code>vp_pace</code>	Indication of a stimulation in the <code>vulnerable phase</code> by the pacemaker
	<code>eis_VMR</code> <code>pre_VMR</code> <code>pace_VMR</code>	Pulse coming from and going towards the <code>ECSH</code> Pulse coming from and going towards the electrode Pulse coming from and going towards the pacemaker
Clocks	<code>s</code>	Clock containing time since chamber activity
	<code>avCC</code>	Clock containing time since atrial contraction began
Variables	<code>ds</code>	Containing the value of the clock <code>s</code> for further calculations
	<code>AVVR</code>	Boolean containing the value of the <code>AV Valve</code>
	<code>VVVR</code>	Boolean containing the value of the <code>VV Valve</code>
	<code>adp_calculation ()</code> <code>reset ()</code>	Update in the background to recalculate the APD Update in the background to reset the values of <code>OG</code> and <code>UG</code>
Interval Thresholds	<code>UG</code>	Lower threshold for determine the next value of <code>ds</code>
	<code>OG</code>	Upper threshold for determine the next value of <code>ds</code>
	<code>OGmax</code>	Maximal upper threshold for <code>ds</code>
Clock Thresholds	<code>avMIN</code>	Lower interval for the chamber coordination concerning the atrial contraction
	<code>avMAX</code>	Upper interval for the chamber coordination concerning the atrial contraction
	<code>AVVRc</code>	Current interval until the <code>AV Valve</code> closes
	<code>AVVRo</code>	Current interval until the <code>AV Valve</code> opens
	<code>VVVRc</code>	Current interval until the <code>VV Valve</code> closes
	<code>VVVRo</code>	Current interval until the <code>VV Valve</code> opens
	<code>intVP</code> <code>intAPD</code>	Current interval for the <code>vulnerable phase</code> Current interval for the <code>APD</code>
Counter	<code>caRtovR ++</code>	Clock containing time since atrial activity
	<code>paceInVPar ++</code>	Clock containing time since atrial activity

There are three possible paths for the transition from `Systole` to `Systole1` depending on the time since the latest atrial contraction:

- If the timer, initiated at the onset of the atrial contraction `avCC`, is within the range `avMIN` to `avMAX` at the moment of transition, the counter for a ventricular contraction, preceded by an appropriately timed atrial contraction `caRtovR`, is incremented by one.
- Conversely, if the timer is outside the specified range (`avCC < avMIN` or `avCC > avMAX`), the corresponding transition to `Systole1` is executed without the value of `caRtovR` being increased.

It remains in `Systole1` until `s` reaches `s == VVVRo` for the opening of the , which initiates the transition to `Systole2` and the update of `VVVR` to true. Here, the system remains until `s == intVP` and the module transitions to `Vulnerable`.

As described for the `atrium`, the `ventricle` is also capable of reverting to `stim_ECSH` or `stim_pace`, upon receipt of the corresponding impulses (`pre_VMR?` or `pace_VMR?`), while the module remains in `Vulnerable`. In both cases the counter for pacing in the `vulnerable phase` is increased during one of these transitions by `paceInVPar++`.

In the absence of further stimulation until $s == VVVRc$, the module transitions to the state **Diastole**. During the transition, the variable associated with the status of the is updated to *false*. As previously outlined, the relaxation phase for the **ventricles** is distinguished between **IDLE** and **Diastole**, in order to accommodate the alteration in the status of the . At this juncture, a re-stimulation by **pre_VMR?** or **pace_VMR?** is possible, but it no longer signifies stimulation within the **vulnerable phase**. Subsequent to the opening of the at $s == AVVRo$ the variable for the status of the is updated by $AVVR = \text{true}$, the module reverts to **IDLE** and awaits a new activation command.

8.1.3 Electrical Conduction System of the Heart

The exemplary module of the **ECSH** is the self-activating **AV node** module. Figure 8.3 depicts the modeling of the module in **UPPAAL**.

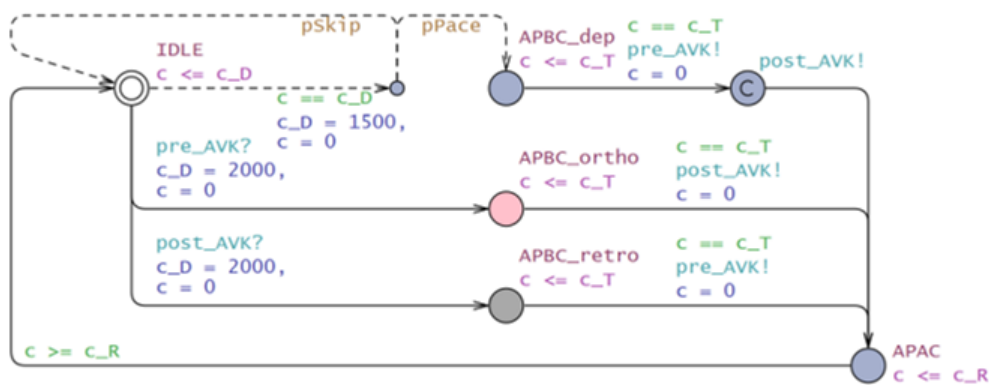


Figure 8.3: Self-stimulating area - **AV node** module of the heart model expressed in **UPPAAL**. Variables are explained in Table 8.3.

Table 8.3: Overview and descriptions of the variables in Figure 8.3.

Category	Variable	Definition
Locations	IDLE	Initial and waiting status
	APBC_dep	Duration until conduction to the next area after self-stimulation
	APBC_ortho	Duration until conduction to the next area after anterograde stimulation
	APBC_retro	Duration until conduction to the next area after retrograde stimulation
	APAC	Duration of the refractory period
Sync. commands	post_AVK	Pulse coming from the anterograde direction of the ECSH
	pre_AVK	Pulse coming from the retrograde direction of the ECSH
Clocks	c	Clock containing time since chamber activity
Probabilistic Values	pSkip	Probability for the return back into IDLE
	pPace	Probability for the successful stimulation of the area
Clock Thresholds	c_D	Interval until self-stimulation
	c_T	Interval until conduction
	c_R	Interval until refractory period ends

Three transitions lead to the three active states (**APBC_ortho**, **APBC_dep** and **APBC_retro**) in this area, depending on the point of origin of the activation: The transitions to **APBC_ortho** and **APBC_retro** may be executed by the synchronisation commands (**pre_AVK?** and **post_AVK?**, respectively) originating from a neighbouring area. As this is a self-activating area, the self-activation time is adjusted in both cases, by **c_D = 2000** and the next self-activation and the clock is reset, by **c = 0**. The model remains in **APBC_ortho** or **APBC_retro** for the specified transit time before the subsequent area is activated by the synchronisation commands (**post_AVK!** and **pre_AVK!**, respectively) and the module specific clock is reset by **c = 0** on the path towards **APAC**, depending on the activation perceived by the synchronisation command. The area remains in **APAC** for the duration designated by the invariant **c ≤ c_R** before reverting to **IDLE** at the conclusion of the specified duration.

Since this is a self-activated area, **IDLE** is assigned a third path and an invariant. This invariant ensures that the module can only remain in this state as long as **c ≤ c_D**. In the event that **c == c_D**, the path at the top that leads to **APBC_dep** is executed. In order for the module to reach **APBC_dep** on this path, the probability factors **pPace** and **pSkip** are incorporated so that the possibility of the absence of self-stimulation can be taken into account.

Upon the execution of the aforementioned transitions, the clock *c* is reset. However, in this instance, the set time until the next stimulation differs from that of the parallel paths, as self-stimulation occurs at a higher frequency following its commencement. Subsequently, the two neighboring areas are activated by **pre_AVK!** and **post_AVK!** following the transition period in **APBC_dep**. The intermediate state between the two states is designated as a committed state in order to prevent a temporal gap. It is necessary to split the synchronisation commands for both paths, as only one synchronisation command per path is set in **UPPAAL**.

8.2 Disease Modeling Modules

The sections below outline a summary of the modeling of **bradycardia** and arrests in modules representing diverse areas of the **ECSH**. Subsequently, the modules for the first to third-degree atrioventricular blocks for the verification in **UPPAAL** are presented.

8.2.1 Diseased Rate Generation Modules

The following sections provide an overview of the modules which represent the diseases that affect the pulse rate generated by areas of the heart for the formal verification model in **UPPAAL**.

Bradycardia and Arrest

The parameters for conditions such as **bradycardia**, **chronotropic incompetence** and arrest can be induced in the self-stimulating areas of the **ECSH**. The conditions **bradycardia** and arrest can be emulated for each of the self-stimulating areas of the model. Figure 8.4 shows the parts of a self-stimulating module of the **ECSH** which should be concerned in modeling **bradycardia**, **chronotropic incompetence** and arrest.

Bradycardia As previously outlined, a **bradycardia** occurs when a self-stimulating region, predominantly the **SA node**, stimulates itself at an insufficient rate. To incorporate **bradycardia** into the implementation, variable until self-stimulation, in the invariant **c ≤ c_D** and in the guard of the corresponding transition **c == c_D**, is extended.

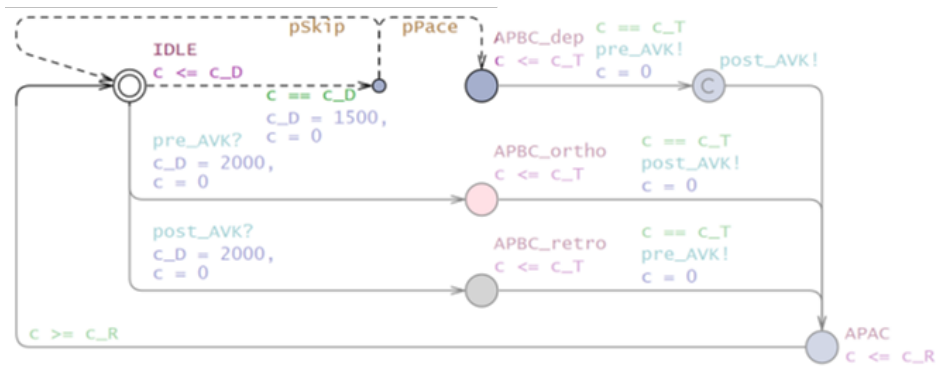


Figure 8.4: Conditions for adjusting the settings for atrial and ventricular premature contractions and [atrial flutter](#) in the formal verification model. Variables are explained in Table 8.4.

Table 8.4: Overview and descriptions of the variables in Figure 8.4.

Category	Variable	Definition
Locations	IDLE	Initial and waiting status
	APBC_dep	Duration until conduction to the next area after self-stimulation
	APBC_ortho	Duration until conduction to the next area after anterograde stimulation
	APBC_retro	Duration until conduction to the next area after retrograde stimulation
	APAC	Duration of the refractory period
Sync. commands	post_AVK	Pulse coming from the anterograde direction of the ECSH
	pre_AVK	Pulse coming from the retrograde direction of the ECSH
Clocks	c	Clock containing time since chamber activity
Probabilistic Values	pSkip	Probability for the return back into IDLE
	pPace	Probability for the successful stimulation of the area
Clock Thresholds	c_D	Interval until self-stimulation
	c_T	Interval until conduction
	c_R	Interval until refractory period ends

Chronotropic Incompetence As the variable until self-stimulation can be controlled by the [invariant](#) $c \leq c_D$ and in the guard of the corresponding transition $c == c_D$ in each self-stimulating area, our model is capable of representing the successful adaptation of an area frequency or the absence of the corresponding adaptation ([chronotropic incompetence](#)) to external factors.

Arrest An arrest is defined as the absence of any self-stimulation of the area in question. This condition is implemented by setting the probability of a successful pulse generation (**pPace**) to zero and the probability for retiring into [IDLE](#) (**pSkip**) to 100%, thus preventing the generation of further successful strokes by the corresponding area.

Atrial and Ventricular Premature Contractions and Atrial Flutter

The module of the heart model able to mirror the behavior of premature contractions and [atrial flutter](#) in the formal verification model in [UPPAAL](#) is capable of self-stimulation after a time interval defined by the [invariant](#) $c \leq c_D$ and in the guard of the corresponding transition $c == c_D$, with a probability determined by **pPace** and **pSkip**.

Since this module is not part of the **ECSH** configuration, but is instead located within one of the chambers, it does not stimulate one of the modules of the **ECSH**, but rather the chamber to which it is assigned. As the chamber is stimulated from within, the **retrograde ECSH** module is stimulated by a **retrograde** output of the chamber (**pre_VMR!**), while the connected pacemaker receives the pulse via the **anterograde** path of the chamber module (**eis_VMR!**).

Atrial and Ventricular Premature Contractions Premature contractions are initiated by an **ectopic node** spontaneously generating pulses. Given that **PACs** and **PVCs** typically manifest sporadically, c_D controlling the interval until self-stimulation is set to a value up to greater than a minute. The probability **pPace** is set to 100%, while **pSkip** is set to zero, to ensure an occurrence.

Atrial Flutter **atrial flutter** is defined as a circulating pulse that stimulates the **atrium** each time it completes its circuit. To mirror the stimulation frequency, due to **atrial flutter**, the module emits a series of pulses mediated by c_D , reflecting the interval for a single circulation, with a probability of successful self-stimulation, represented by **pPace** and **pSkip**, with the values of 100% and 0%.

8.2.2 Variances in QT

The modeling of fluctuations in the **QT interval** is conducted by modifying the **APD** in relation to the stimulation interval of the corresponding heart chamber. Therefore, the initial parameter APD_0 is adapted to alter the variable A_{inf} towards which APD_i adjusts over time. This adaption in the recalculation of the **APD** takes place in the update **apd_calculation()** of the respective heart chamber module.

Long QT Long QT, is characterized by a prolonged period of activity following a stimulation event in the respective chamber. This prolongation of the **vulnerable phase** of the corresponding chamber increases the probability of stimulation occurring within that phase.

In order to represent the aforementioned extended chamber activity within our model, the relation between **APD** and the stimulation interval is adapted within the respective chamber module. This is realized by elevating the initial APD_0 until the ratio between APD_0 and S_0 results in a **QTc interval** associated with **long QT** in the update **apd_calculation()**.

Menstrual Cycle The fluctuation of the **QT interval** due to the menstrual cycle lengthen or shorten the ratio of the **APD** interval and the stimulation interval and the **QTc interval**.

The fluctuation of the **QT interval** due to the menstrual cycle are emulated by modifying the **APD** interval (in the update **apd_calculation()**) and the stimulation interval in accordance with the parameters for the varying phases, either lengthened or shortened, in our model. The initial parameter values for APD_0 and S_0 encompass those that result in a **QTc interval** associated with the various phases of the menstrual cycle.

8.2.3 AV blockages

The AV blocks are modeled for the transition from the **AV node** to the **bundle of his**. The healthy module, seen in Figure 8.5 is comprised of three states: **IDLE** and the two transition states **retro** and **ortho**. In the event that the area receives a pulse, it transitions to the corresponding state, dependent on the direction of the incoming synchronisation command, and resets the area clock.

An incoming **anterograde** impulse, triggered by **post_AVK?** leads to a synchronisation command of the area below, by **pre_His!**, after passing **ortho**. Consersly, an incoming **retrograde** impulse, triggered by **pre_His?** leads to a synchronisation command of the area above, by **post_AVK!**, after passing **retro**. The module stays in **ortho** respectively **retro** until $c == c_T$. Subsequently, the module transitions back to **IDLE**. It is possible for the area to remain in **IDLE** indefinitely, provided that it has not been activated externally by a synchronisation command.

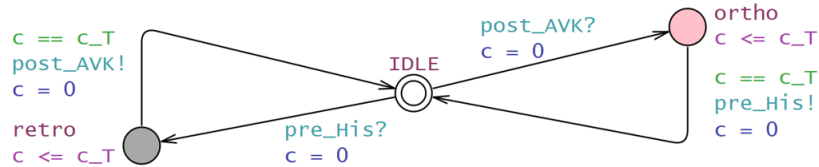


Figure 8.5: Transition Module from **AV node** to **bundle of his** module of the heart model expressed in UPPAAL. Variables are explained in Table 8.5.

Table 8.5: Overview and descriptions of the variables in Figure 8.5.

Category	Variable	Definition
Locations	IDLE	Initial and waiting status
	retro	Duration until conduction to the next area after retrograde stimulation
	ortho	Duration until conduction to the next area after anterograde stimulation
Sync. commands	post_AVK	Pulse coming from the anterograde direction of the ECSH
	pre_His	Pulse coming from the retrograde direction of the ECSH
Clocks	c	Clock containing time since chamber activity
Clock Thresholds	c_T	Interval until conduction

First-degree AV block To represent a **first-degree AV block**, the transition time of a specific module (c_t) is extended. Apart from this, the module is identical to that of the healthy transition module, shown in Figure 8.5. This delay is included in each area of the **ECSH** in our model, by extending the value for c_T . The subsequent modelings of second-degree AV blocks are more complex.

Second-degree AV block Wenckebach As previously described, a **second-degree AV block wenckebach** is defined by a repeating progressive prolongation of the conduction time until a complete conduction blockage occurs within the affected area. Figure 8.6 shows the modeling of module in UPPAAL.

The **anterograde** and **retrograde** transitions in this module exhibit a mirrored relationship. In addition to the healthy transition module shown in Figure 8.5, there are two further possible transitions and a guard in this module. If an incoming pulse is received (**post_AVK?** respectively **pre_His?**), the guard, $i < dtp$, must be checked before a pulse is transmitted. In the guard the status of the index is compared to the number of beats conducted prior to the blockage. If the index is less than the number until blockage ($i < dtp$), the transition towards the transition state **ortho** respectively **retro** is executed. Subsequently, the index is updated by $i = i + 1$. In the event that the number of the index and the number of beats until blockage are equal ($i \geq dtp$), the respective path without a state is selected and the index is reset.

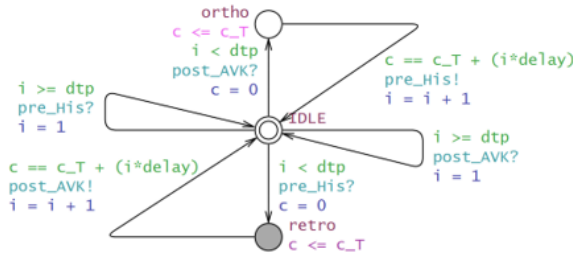


Figure 8.6: AV Block 2 w replacing the transition from AV node to bundle of his. Variables are explained in Table 8.6.

Table 8.6: Overview and descriptions of the variables in Figure 8.6 and in Figure 8.7.

Category	Variable	Definition
Locations	IDLE	Initial and waiting status
	retro	Duration until conduction to the next area after retrograde stimulation
	ortho	Duration until conduction to the next area after anterograde stimulation
Sync. commands	post_AVK	Pulse coming from the anterograde direction of the ECSH
	pre_His	Pulse coming from the retrograde direction of the ECSH
Variables	i	Counter, containing the pulses since the latest blockage
	dtp	Threshold, for the pulses until the next blockage
	delay	Additional delay for each pulse
Clocks	c	Clock containing time since chamber activity
Clock Thresholds	c_T	Interval until conduction

Second-degree AV block Higher Grade The **second-degree AV block higher grade**, is modeled in **UPPAAL** by the module shown in Figure 8.7. Upon each activation of a chamber by **post_AVK?** respectively **pre_His?**, the current index value i is compared with the value relevant for the transition dtp . In case a pulse is received while $i == dtp$ the transition to the subsequent area and the transition back to **IDLE** is proceeded. Upon returning to **IDLE**, the index value is reset by $i = 1$. In the event that the equality condition is not met, the index value is increased by $i = i + 1$, via the respective transitions.

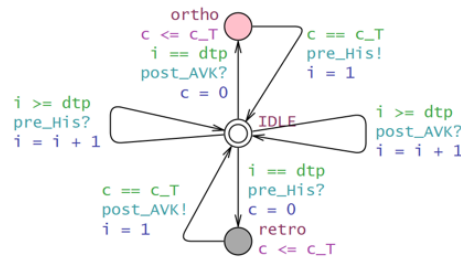


Figure 8.7: AV Block 2 h replacing the transition from AV node to bundle of his. Variables are explained in Table 8.6.

Second-degree AV block Mobitz As previously described the transition of pulses is randomly blocked in case of a module representing a **second-degree AV block mobitz**. The module representing this disorder is modeled in the **UPPAAL** model as a replacement for the transition module connecting the **bundle of his** and the **tawara bundles**. Figure 8.8 shows the modeling of the module for the formal verification. This area serves as a connection between three distinct regions of the **ECSH**. In terms of orthography, it links the **bundle of his** to both of the underlying **tawara bundles**.

An incoming pulse from the orthograd direction (**post_His**), or one of the two incoming pulses from retrograd direction (**pre_TSL?** or **pre_TSR?**), starts the transition process for the module, by leaving **IDLE**. For any transition leaving **IDLE** **prob()** is executed during the transition. By every call of **prob()** a random number is generated, which is then compared against a threshold value. In case the random number extends the threshold the variable **tran** is set to *true*. Conversely, a generated random number below the threshold sets the variable to *false*. Depending on the status of the variable **tran** the module returns back to **IDLE** for **tran == false**, or it transitions to **ortho_TsR** respectively **retro_His**, to emit the pulse to the neighboring areas. In case of the **retrograde** transition, via **retro_His**, the area transitions via **ortho_TsR** and **ortho_TsL** back to **IDLE**, thereby emitting stimulation pulses for the **bundle of his** (**post_His?**) and both of the **tawara bundles** (**pre_TsR** and **pre_TsL**). For the orthograd direction the module transitions directly towards **ortho_TsR**. From here it follows the described path, emitting pulses for both of the underlying **tawara bundles**.

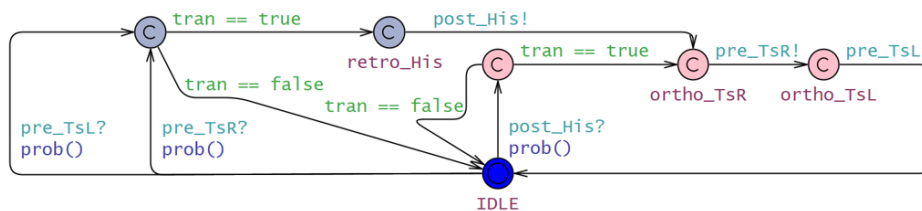


Figure 8.8: **second-degree AV block mobitz** replacing the transition from **bundle of his** to **tawara bundle**. Variables are explained in Table 8.7.

Table 8.7: Overview and descriptions of the variables in Figure 8.8.

Category	Variable	Definition
Locations	IDLE	Initial and waiting status
	retro_His	Indicating retrograde stimulation
	ortho_TsR	Indicating anterograde stimulation
	ortho_TsL	Indicating anterograde stimulation
Sync. commands	post_His	Pulse coming from the anterograde direction of the ECSH
	pre_TsR	Pulse coming from the retrograde direction of the ECSH (from the right side)
	pre_TsL	Pulse coming from the retrograde direction of the ECSH (from the left side)
Variables	trans	Variable determining if the pulse is conducted
Update	prob ()	Update determining the value of trans
Clocks	c	Clock containing time since chamber activity
Clock Thresholds	c_T	Interval until conduction

Third-degree AV block To model a third-degree AV block, which blocks the incoming impulses completely and at all times, a module receiving the incoming impulse, but does not emit any further impulses is modeled in the UPPAAL model. This blockage is modeled for the pulse transition from the **AV node** towards the **bundle of his** and for the pulse transition from the **bundle of his** to the **tawara bundles**. The incoming pulses trigger a transition from the initial state **IDLE** right back into **IDLE**, blocking any pulse in orthograd and in **retrograde** direction.

8.3 Pacemaker Model

The pacemaker model, like the heart model, is composed of interlocking modules that are adjusted over programmable periods of time in analogy to the bioelectronic system. The atrial module is responsible for sensing and delivering electrical activity to the [atrium](#), while the ventricular module performs the same function for the [ventricle](#). These modules are interconnected by a conduction module and interact with the heart model by lead modules.

8.3.1 Atrial Module

The atrial module is represented in Figure 8.9. As schematically represented in the description of the system model in Chapter 5, the atrial module commences in **IDLE**. Upon departure from this state, four potential transitions are possible, all of which ultimately lead to **Blanking**:

- In order to ensure that a ventricular signal is not identified as an atrial signal on the atrial lead, the [atrium](#) immediately transitions to blanking following the occurrence of an electrical signal received at the ventricular module of the pacemaker via the synchronization commands `pmp_VM?` or `pms_VM?` (ventricular pacing or sensing). Both transitions are accompanied by updates of the clocks and variables containing the duration for the stay in **Blanking** and **Refractory** in `vtr_pace()` respectively `vtr_sense()`.
- In the event of an activity being sensed on the atrial electrode (`pms_AM?`), the module transitions from **IDLE** to **Sense** while updating the clocks and variables containing the duration for the stay in **Blanking** and **Refractory** associated with atrial sensing in `atr_sense()`. As **Sense** is a committed state, the model transitions immediately to the subsequent committed state **Recal_S** while the conduction module's synchronization command (`av_CA!`) is being executed.
- Furthermore, the module can enter **Recal_S** state via **pace**. The initiation of the transition along this pathway follows the elapse of the specified pacing duration ($t \geq ssA$) and the knowledge of the time since the last chamber activity by the pacemaker, which must exceed the time range for the [vulnerable phase](#) by $s > intVP$. During the transition from **IDLE** to **Recal_S**, the synchronization commands for the stimulation of the atrial chamber and the conduction module, namely `pmp_AM!` and `av_CA!`, are executed. The clocks and variables coordinating the blanking and refractory periods are updated in `atr_pace()`.

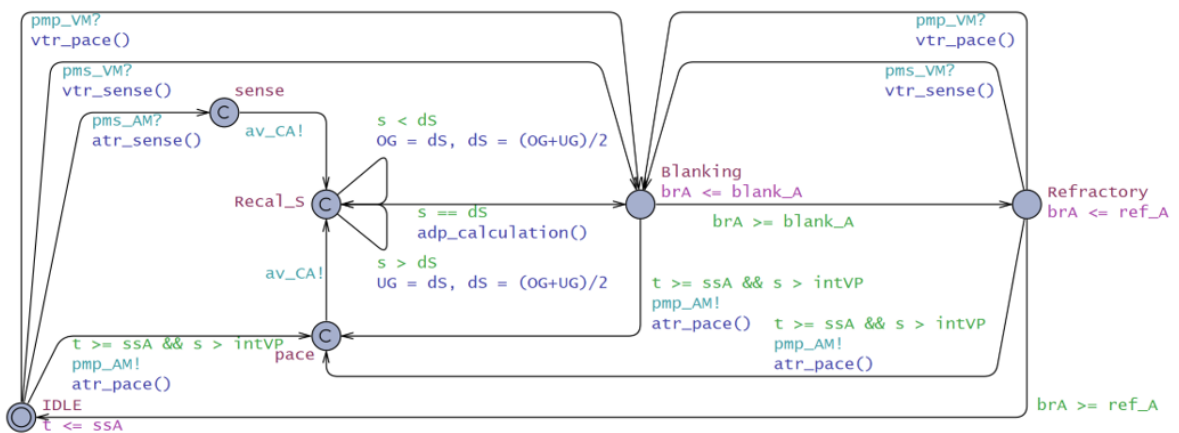


Figure 8.9: Atrial module of the pacemaker model. Variables are explained in Table 8.8.

`atr_pace()` = $br_A = 0$; $blank_A = PAABP$; $ref_A = PAARP$; $av_{dt} = avc_P$; $pmp_A ++$;
`atr_sense()` = $br_A = 0$; $blank_A = PAABS$; $ref_A = PAARS$; $av_{dt} = avc_S$; $pms_A ++$;
`vtr_pace()` = $br_A = 0$; $blank_A = PVABP$; $ref_A = PVARP$;
`vtr_sense()` = $br_A = 0$; $blank_A = PVABS$; $ref_A = PVARS$;

Table 8.8: Overview and descriptions of the variables in Figure 8.9.

Category	Variable	Definition
Locations	IDLE	Initial and waiting status
	sense	Indicating a pulse sensed by the module
	pace	Indicating a the pacing of the module
	Recal_S	Identification of the value of s
	Blanking	Duration of the blanking interval
Sync. commands	Refractory	Duration of the refractory interval
	pmp_AM	Pulse pacing the atrium
	pms_AM	Pulse coming from the atrium
	pmp_VM	Pulse pacing the ventricle
	pms_VM	Pulse coming from the ventricle
Variables	av_CA	Pulse activating the conduction module
	ds	Variable determining s
Interval Thresholds	UG	Lower threshold for determine the next value of ds
	OG	Upper threshold for determine the next value of ds
Update	atr_sense ()	Update after sensing in the atrium
	vtr_sense ()	Update after sensing in the ventricle
	atr_pace ()	Update after pacing in the atrium
	vtr_pace ()	Update after pacing in the ventricle
Clocks	t	Clock containing time since module activation
	s	Clock containing time since module activation to ensure that the intVP expired
	brA	Clock containing time since pacemaker activation
Clock Thresholds	ssA	Duration until pacing of the heart
	intVP	Duration of the calculated vulnerable phase
	blank_A	Duration of the blanking interval
	ref_A	Duration of the refractory interval

Since the latter two transition paths necessitate the recalculation of the duration of the **vulnerable phase**, the requisite value of the time interval since the most recent heart chamber activity s is designated by the transitions that reenter **Recal_S**. This is similar to the recalculation of the time since the last chamber activity in the chamber modules of the heart model in Section 8.1.2. Incorporating s , the presumed **vulnerable phase** of the corresponding **ventricle** is calculated during the subsequent transition in **adp_calculation()** based on the formulas presented in Section 4.2.5.

Eventually, the module reaches **Blanking**, wherein it remains until the clock containing the time since the last instance of cardiac activity relevant for the **atrium** bra (including atrial and ventricular activity) reaches the value that corresponds to the length of the current blanking interval ($brA \geq blank_A$). At this stage, the module must exit the current state, as its duration within this state is determined by the invariant $brA \leq blank_A$.

Subsequently, the module transitions to **Refractory**. In this state, the module can remain until the clock that indicates the time since the last instance of heart activity reaches the value corresponding to the current refractory interval ($brA \geq ref_A$). For $brA \geq ref_A$ the module transitions back to **IDLE**.

From **Blanking** and **Refractory**, the module can transition back to **Blanking**. One such transition occurs

- when the ventricular module of the pacemaker emits the synchronisation command (**pmp_VM?** or **pms_VM?**) to announce an electrical pulse in the **ventricle** or
- when $t \geq ssA$ and $s > intVP$, which means the allotted stimulation time has elapsed and the calculated time for the **vulnerable phase** has expired.

The former leads the module to transition directly back into **Blanking**, since this update only affects the sensing of the **atrium**. The latter necessitates an indirect route via **pace** and **Recal_S**, to incorporate the activation of the atrial chamber of the heart by **pmp_AM!**, the update of the variables coordinating the blanking and refractory intervals in **atr_pace()**, the activation of the conduction module by **av_CA!**, and the recalculation of the **vulnerable phase** in **adp_calculation()**.

8.3.2 Conduction Module

Figure 8.10 displays the modeling of both the conduction module of the pacemaker (a) and the linked monitor module (b). The conduction module shown in (a) is situated between the atrial and the ventricular module of the pacemaker. It is modeled in a three-state configuration. In **IDLE**, the module remains inactive until a pulse, emitted from the **atrium**, is received. Concurrent with the reception of the pulse, specifically the command **av_CV!**, the quantity of atrial pulses is compared to the maximum number of pulses that are to be transmitted.

- In the event that the number of atrial contractions per minute is below the programmable maximum, ($\text{bpm_pm_A} < \text{bpm_max}$) the module will transition directly to **Conduction**.
- For $\text{bpm_pm_A} \geq \text{bpm_max}$, the module will determine the number of pulses that must occur until a pulse is permitted to pass by determining i_pmp . As described in Chapter 5, i_pmp is calculated by $i_pmp = \text{pmp_bpmA} / (60000 / \text{bpm_max})$. The following comparison of the number of inhibited beats i leads to **Conduction** and a reset of i , if $i == i_pmp$, or back into **IDLE** with an increase of i by $i++$, in case $i < i_pmp$.

If the module has reached **IDLE**, it remains in this state for a time period determined by the invariant $t \leq \text{av_dt}$. This is essential to maintain the aforementioned coordination and delay between the **atrium** and the **ventricle** via the pacemaker. If the module reaches $t \geq \text{av_dt}$ it transitions back to **IDLE**. This transition emits the synchronisation command **av_CV!** potentially initialising transitions in the ventricular module of the pacemaker.

Additionally, the module represented by Figure 8.10 (b) is modeled to update the required parameter for the calculation of i_pmp . The recursive transition from **timer** occurs once per minute, coordinated by the invariant $c \leq 60000$ and the guard $c \geq 60000$. With each transition, the values for pmp_bpmA and pmp_bpmV are updated by $\text{pmp_bpmA} = \text{pmp_A}$ and $\text{pmp_bpmV} = \text{pmp_V}$ before the values for pmp_A and pmp_V are reset. The values of pmp_bpmA and pmp_bpmV are required for the calculation of i_pmp in the conduction module and for the evaluation of the safety queries regarding the pacemaker activity.

Table 8.9: Overview and descriptions of the variables in Figure 8.10.

Category	Variable	Definition
Locations	IDLE	Initial and waiting status
	supr	Decision between blockage and transmission
	Conduction	State in which the module stays for the time until conduction is executed
Sync. commands	av_CA	Pulse activating the conduction module
Variables	mSwitch	Contains the status of the mode switch
	bpm_pm_A	Contains the stimulations in the atrium in bpm
	bpm_max	Contains maximum number of pulses to be conducted
	i	Counter, counting the transmitted pulses since the last blockage
	i_pmp	Threshold, for the number of beats until a pulse is blocked
Clock Thresholds	av_dt	Duration of the conduction interval
Clocks	t	Clock containing time since module activation

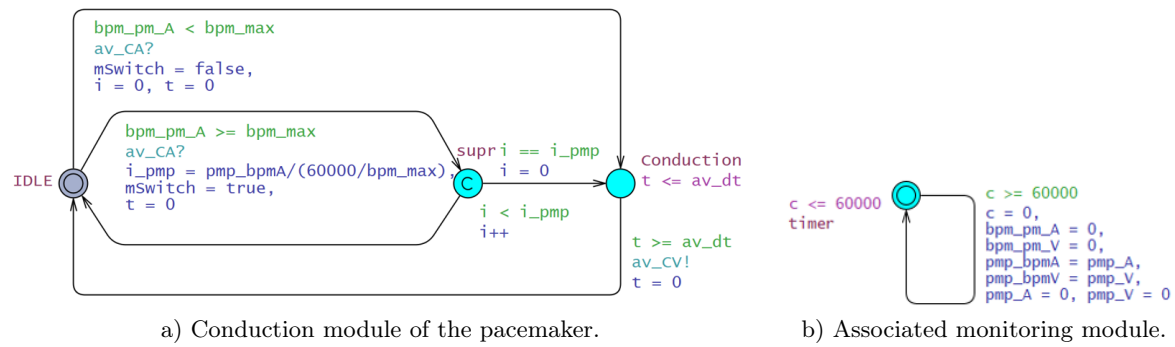


Figure 8.10: Conduction module of the pacemaker - responsible for connecting the atrial and ventricular components of the device and determining which pulses should be conducted to the ventricular module (a) and associated monitoring module (b) - resetting and updating the variables acquired for the conduction module. Variables are explained in Table 8.9.

8.3.3 Ventricular Module

The ventricular module, illustrated in Figure 8.11, represents, for the most parts, the same pathways as those previously described for the modeling of the atrial module, with chamber-adapted synchronization commands. There are important differences: To initiate a transition from **IDLE** in the ventricular module three potential synchronization commands are employed.

- The transition for sensing the intrinsic ventricular activity is modeled by the synchronisation command `pms_VM?`, waiting for a pulse from the associated electrode. On the following path towards `Recal_S` the variables and clocks, necessary for the blanking and the refractory periods, are adapted in `vtr_sense()`.
- The pathways utilized for pacing the chamber after a designated interval has elapsed, are substituted with pathways that are triggered by a pulse emanating from the conduction module of the pacemaker (`av_CV?`). To prevent stimulations during the `vulnerable phase`, the condition `s > intVP` has to be *true* to enable the transition leading to the pacing of the chamber, as described for the atrial module. The following command for the stimulation of the connected chamber is changed to `pmp_VM?` for the ventricular module and the variables and clocks coordinating the execution of the blanking and the refractory periods are adapted in `vtr_pace()`.
- Subsequently, the recognition of a pacing impulse of the `atrium` is included. The transitions provided with the synchronisation command `pmp_AM?` lead directly into **Blanking**. The variables for the blanking and refractory intervals are thereby adapted in `atr_pace()`.

The ventricular pacemaker section is not equipped with a pathway that would enable the detection of intrinsic chamber activity originating from the `atrium`. As previously stated, the intrinsic impulse emitted by the atrial chamber lacks the required intensity to be effectively recognized in the `ventricle`.

8.4 Heart Pacemaker Interface

To connect the modules of the pacemaker to the corresponding heart modules two further connection modules are modeled. Figure 8.12 illustrates the modules for the connection between the right `atrium` and the atrial module of the pacemaker (a) and the connection between the right `ventricle` and the `ventricle` module of the pacemaker (b).

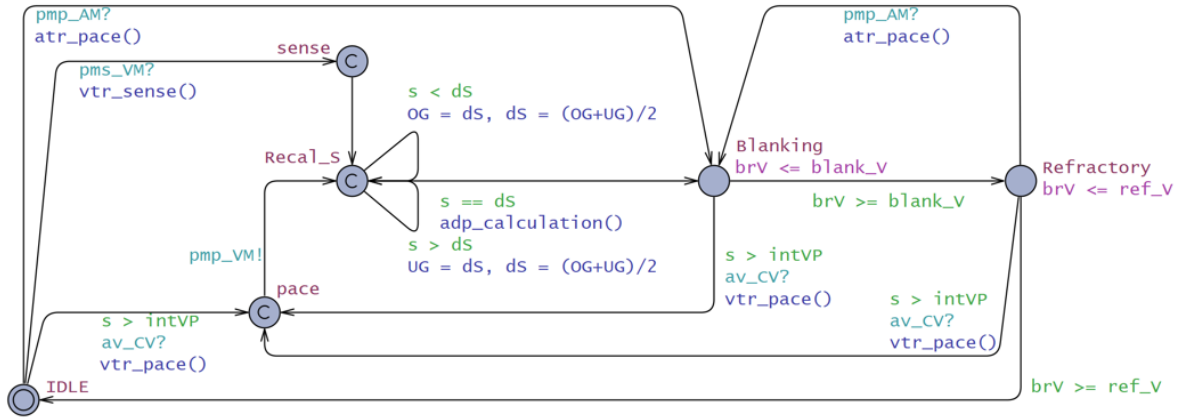


Figure 8.11: Ventricular module of the pacemaker model. Variables are explained in Table 8.10.

`vtr_pace()` = $brV = 0$; $blank_V = PVVBP$; $ref_V = PVVRP$; $pmp_V ++$;

`vtr_sense()` = $brV = 0$; $blank_V = PVVBS$; $ref_V = PVVRS$; $pms_V ++$;

`atr_pace()` = $brV = 0$; $blank_V = PAVBP$; $ref_V = PAVRP$;

Table 8.10: Overview and descriptions of the variables in Figure 8.11.

Category	Variable	Definition
Locations	IDLE	Initial and waiting status
	sense	Indicating a pulse sensed by the module
	pace	Indicating a the pacing of the module
	Recal_S	Identification of the value of s
	Blanking	Duration of the blanking interval
Sync. commands	Refractory	Duration of the refractory interval
	<code>pmp_AM</code>	Pulse pacing the atrium
	<code>pms_AM</code>	Pulse coming from the atrium
	<code>pmp_VM</code> <code>pms_VM</code>	Pulse pacing the ventricle Pulse coming from the ventricle
Variables	dS	Variable determining s
Interval Thresholds	UG	Lower threshold for determine the next value of ds
	OG	Upper threshold for determine the next value of ds
Update	<code>atr_sense ()</code>	Update after sensing in the atrium
	<code>vtr_sense ()</code>	Update after sensing in the ventricle
	<code>atr_pace ()</code>	Update after pacing in the atrium
	<code>vtr_pace ()</code>	Update after pacing in the ventricle
Clocks	t	Clock containing time since module activation
	s	Clock containing time since module activation to ensure that the intVP expired
	brA	Clock containing time since pacemaker activation
Clock Thresholds	ssA	Duration until pacing of the heart
	intVP	Duration of the calculated vulnerable phase
	blank_A	Duration of the blanking interval
	ref_A	Duration of the refractory interval

Both modules can receive EIS pulses from their associated chamber (`eis_AM?`/ `eis_VM?`), an interfering signal (`pms_interA?`/ `pms_interV?`) or a pulse from the stimulation of another chamber (`pmp_AM?`/ `pmp_VM?`). These synchronization commands lead to a transition of the model to the committed state `hm_pm`. The designated following transition back into `IDLE` emits a pulse (`pms_AM!` and `pms_VM!`) that has the capacity to initiate the transitions designated for sensing in the modules of the pacemaker.

The opposite direction is modeled in the path via **pm_hm**. To reach this state the module must receive a synchronisation command, representing the emission of the pacing pulse by the pacemaker. These commands are **pmp_AM?** respectively **pmp_VM?**. The following transition emits a pulse (**pace_AM!** and **pace_VM!**) that has the capacity to initiate the transitions in the chamber modules of the heart.

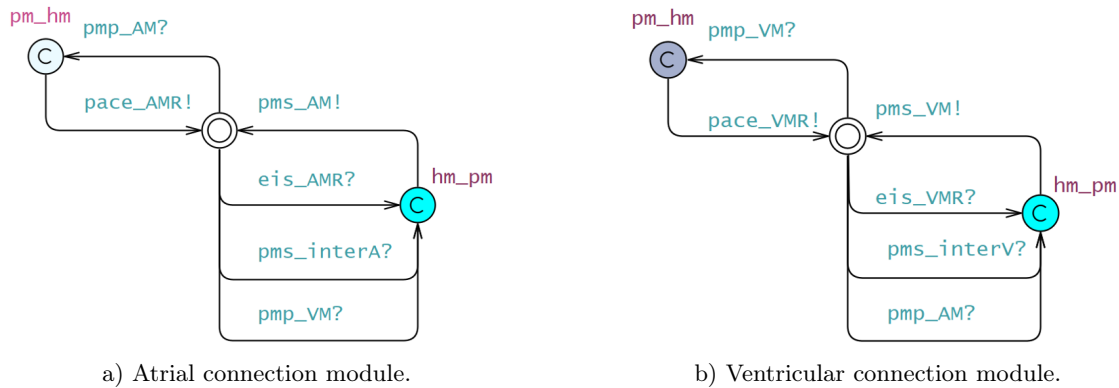


Figure 8.12: Connection module between atrial (a) respectively ventricular (b) part of the pacemaker and the associated atrial respectively ventricular module of the cardiac model- representing pacemaker electrodes. Variables are explained in Table 8.11.

Table 8.11: Overview and descriptions of the variables in Figure 8.12.

Category	Variable	Definition
Locations	pm_hm	Pulse transition from pacemaker to heart
	hm_pm	Pulse transition from heart to pacemaker
Sync. commands	pmp_AM	Incoming pulse from the atrial module of the pacemaker due to pacing
	pace_AM	Pulse emitted to stimulate the atrial module of the heart
	pms_AM	Incoming pulse from the atrial module of the pacemaker due to sensing
	eis_AM	Incoming pulse from the atrial module of the pacemaker
	pms_interA	Interfering pulse on the atrial module
	pmp_VM	Incoming pulse from the ventricular module of the pacemaker due to pacing
	pace_VM	Pulse emitted to stimulate the ventricular module of the heart
	pms_VM	Incoming pulse from the ventricular module of the pacemaker due to sensing
	eis_VM	Incoming pulse from the ventricular module of the pacemaker
	pms_interV	Interfering pulse on the ventricular module

8.5 Safety Queries in UPPAAL

The following tables show the modeling of the safety queries defined in Chapter 6 in the query language for UPPAAL. Table 8.12 lists the variables in the subsequent safety queries.

Table 8.12: Variables used in the following safety queries.

Category	Variable	Description
Heart Modules	Counters	bpm_.bpm_AMR atrial contractions per minute bpm_.bpm_VMR ventricular contractions per minute bpm_n_eis_VMR atrial stimulations by the ECSH per minute paceInVPar stimulations into the vulnerable phase in the atrial module paceInVPvr stimulations into the vulnerable phase in the ventricular module bpm_caRtovR ventricular stimulations following an atrial contraction per minute
	Boundaries per Minute	bpm_min required minimal beats per minute to keep a patient symptom free bpm_max limit of maximal beats per minute to keep a patient symptom free
Pacemaker Modules	Values per Minute	bpm_pms_A atrial EIS sensed and counted by the atrial pacemaker module bpm_pmp_A atrial pulses paced and counted by the atrial pacemaker module bpm_pms_V ventricular EIS sensed and counted by the ventricular pacemaker module bpm_pmp_V ventricular pulses paced and counted by the ventricular pacemaker module
	Atrial States	DDD_A.sense marking the path for sensing in the atrial module DDD_A.pace marking the path for pacing in the atrial module DDD_A.Recal_S re-calculation of the APD after sensing and pacing in the atrial module DDD_A.Blanking blanking period in the atrial module
	Ventricular States	DDD_V.sense marking the path for sensing in the ventricular module DDD_V.pace marking the path for pacing in the ventricular module DDD_V.Recal_S re-calculation of the APD after sensing and pacing in the ventricular module DDD_V.Blanking blanking period in the ventricular module
	Overall Intervals	ssA interval until the stimulation of the heart module by the pacemaker
	Atrial Intervals	DDD_A.intVP vulnerable phase for the atrium calculated by the pacemaker
	Conduction Intervals	av_dt current duration of the conduction interval avc_S interval duration to which the conduction interval is updated after sensing avc_P interval duration to which the conduction interval is updated after pacing
	Ventricular Intervals	DDD_V.intVP vulnerable phase for the ventricle calculated by the pacemaker
	Atrial Clocks	DDD_A.t reset by atrial activity for interval until the stimulation DDD_A.s reset by atrial activity to prevent stimulation in the vulnerable phase brA reset by a cardiac activity
	Ventricular Clocks	DDD_V.t reset by ventricular activity for interval until the stimulation DDD_V.s reset by ventricular activity to prevent stimulation in the vulnerable phase brV reset by a cardiac activity
	Atrial Counters	pmp_A counting the pulses emitted by the atrial module of the pacemaker
	Ventricular Counters	pms_A counting the EIS sensed by the atrial module of the pacemaker pmp_V counting the pulses emitted by the atrial module of the pacemaker pms_V counting the EIS sensed by the atrial module of the pacemaker
	Conduction Variable	DDD_C.mSwitch monitoring the occurrences of mode switches in the pacemaker

Table 8.13: Overview of the error cases to be tested for the pacemaker heart interaction.

Prob.	Short Name	Description
Prop. 6.1.1	Minimal heart rate	$\text{Pr}[\leq b](\square \text{ bpm_bpm_AMR} > \text{bpm_min} \ \&\& \ \text{bpm_bpm_VMR} > \text{bpm_min})$
Prop. 6.1.2	Maximal heart rate	$\text{Pr}[\leq b](\square \text{ bpm_bpm_AMR} < \text{bpm_max} \ \&\& \ \text{bpm_bpm_VMR} < \text{bpm_max})$
Prop. 6.1.4	Vulnerable Phase	$\text{Pr}[\leq b](\square \text{ paceInVPar} == 0 \ \&\& \ \text{paceInVPvr} == 0)$
Prop. 6.1.3	Coordinated Contractions	$\text{Pr}[\leq b](\square \text{ bpm_caRtovR} > \text{bpm_min})$

Table 8.14: Overview of the error cases to be tested in the workflow pacemaker characteristics.

Prob.	Short Name	Description
Prop. 6.2.1	Sensed/ Paced bpm - Minimal	$\text{Pr}[\leq b]([] \text{ bpm_pmp_A} + \text{ bpm_pms_A} > \text{ bpm_min})$ $\text{Pr}[\leq b]([] \text{ bpm_pmp_V} + \text{ bpm_pms_V} > \text{ bpm_min})$
Prop. 6.2.2	Sensed/ Paced bpm - Maximal	$\text{Pr}[\leq b]([] \text{ bpm_pmp_A} + \text{ bpm_pms_A} < \text{ bpm_max})$ $\text{Pr}[\leq b]([] \text{ bpm_pmp_V} + \text{ bpm_pms_V} < \text{ bpm_max})$
Prop. 6.2.4	Vulnerable Phase Protection Interval Duration	$\text{Pr}[\leq b]([] \text{ ssA} > \text{ DDD_A.intVP})$
Prop. 6.2.3	Non-Essential Pacemaker Pulses	$\text{Pr}[\leq b](\langle \rangle \text{ bpm_pmp_V} + \text{ bpm_n_eis_VMR} - \text{ bpm_bpm_VMR}) > 15)$
Prop. 6.2.5	Termination of the Minimal Interval until Chamber Stimulation	$\text{Pr}[\leq b](\langle \rangle \text{ DDD_A.pace} \ \&\& \ \text{ DDD_A.t} < \text{ ssA})$
Prop. 6.2.6	Termination of the Maximal Interval until Chamber Stimulation	$\text{Pr}[\leq b](\langle \rangle \text{ DDD_A.Recal_S} \ \&\& \ \text{ DDD_A.t} > 0)$
Prop. 6.2.7	Expiration of the Maximal Interval until Chamber Stimulation	$\text{Pr}[\leq b]([] \text{ DDD_A.t} \geq \text{ ssA} \ \text{ imply } \text{ DDD_A.pace})$
Prop. 6.2.8	Termination of the Vulnerable Phase Protection Interval	$\text{Pr}[\leq b]([] \text{ DDD_A.pace} \ \text{ imply } \text{ DDD_A.s} > \text{ DDD_A.intVP})$ $\text{Pr}[\leq b]([] \text{ DDD_V.pace} \ \text{ imply } \text{ DDD_V.s} > \text{ DDD_V.intVP})$

Table 8.15: Overview of the error cases to be tested in the workflow pacemaker characteristics.

Prob.	Short Name	Description
Prop. 6.2.9	Onset of the Blanking Interval - After High Pulse	$\text{Pr}[\leq b](\langle \rangle \text{ DDD_A.pace} \ \&\& \ \text{ not } \text{ DDD_V.Blanking})$ $\text{Pr}[\leq b](\langle \rangle \text{ DDD_V.Recal_S} \ \&\& \ \text{ not } \text{ DDD_A.Blanking})$
Prop. 6.2.10	Onset of the Blanking Interval - Atrial Blanking after Atrial EIS	$\text{Pr}[\leq b]([] \text{ DDD_A.sense} \ \text{ imply } \text{ DDD_A.Blanking})$
Prop. 6.2.11	Reset of Blanking/ Refractory Clocks - Reset after high Pulse	$\text{Pr}[\leq b](\langle \rangle \text{ DDD_V.pace} \ \&\& \ \text{ DDD_A.t} > 0 \ \&\& \ \text{ brA} > 0 \ \&\& \ \text{ brV} > 0)$ $\text{Pr}[\leq b](\langle \rangle \text{ DDD_V.pace} \ \&\& \ \text{ DDD_A.t} > 0 \ \&\& \ \text{ brA} > 0 \ \&\& \ \text{ brV} > 0)$ $\text{Pr}[\leq b](\langle \rangle \text{ DDD_V.pace} \ \&\& \ \text{ DDD_A.t} > 0 \ \&\& \ \text{ brA} > 0 \ \&\& \ \text{ brV} > 0))$
Prop. 6.2.12	Reset of Blanking/ Refractory Clocks - Atrial Reset after Atrial EIS	$\text{Pr}[\leq b](\langle \rangle \text{ DDD_A.sense} \ \&\& \ \text{ DDD_A.t} > 0 \ \&\& \ \text{ brA} > 0)$

Table 8.16: Overview of the error cases to be tested in the workflow pacemaker characteristics.

Prob.	Short Name	Description
Prop. 6.2.13	Minimal Conducted Pacemaker Stimulation per Minute	$\text{Pr}[\leq b]([] \text{ pmp_V} + \text{ pms_V} > \text{ bpm_min})$
Prop. 6.2.14	Maximal Conducted Pacemaker Stimulation per Minute	$\text{Pr}[\leq b]([] \text{ pmp_V} + \text{ pms_V} < \text{ bpm_max})$
Prop. 6.2.15	Conduction Time Adaption - After Sensing	$\text{Pr}[\leq b]([] \text{ DDD_A.sense} \ \text{ imply } (\text{ av_dt} == \text{ avc_S}))$
Prop. 6.2.16	Conduction Time Adaption - After Pacing	$\text{Pr}[\leq b]([] \text{ DDD_A.pace} \ \text{ imply } (\text{ av_dt} == \text{ avc_P}))$
Prop. 6.2.17	Vulnerable Phase Protection Interval Termination due to Conduction	$\text{Pr}[\leq b]([] \text{ DDD_V.pace} \ \text{ imply } \text{ DDD_V.s} \geq \text{ DDD_V.intVP})$
Prop. 6.2.18	Mode Switch - On and Offset	$\text{Pr}[\leq b]([] (\text{ bpm_bpm_AMR} > \text{ bpm_max})$ $\text{ imply } \text{ DDD_C.mSwitch} == \text{ true})$

Evaluation and Results

This chapter presents the evaluation of the models and discusses their capabilities and limitations. It commences with a comparison of the [APD](#) calculation employed by the model with physiologically measured data, in order to confirm the validity of the calculation method used. Subsequently, the safety queries defined in Chapter 6 are evaluated for the [HIL](#) heart model in [LabVIEW](#) in interaction with a physical pacemaker. This is followed by an evaluation of the safety queries for the interaction of the formal verification model of the heart in [UPPAAL](#), against the pacemaker model described in Chapter 5. The chapter concludes with an evaluation of the test results and an assessment of the limitations of the model.

9.1 Generated Action Potential Duration

The [APD](#) prediction by the formulas proposed in Section 4.2.3 is evaluated by a comparison of the results obtained from our model with physiological data. Figure 9.1 visualises the progression of the [APD](#) in this model (lines) and the physiological data measured in [123] (data points). The parameters the model is initialised with are provided in Table 9.1.

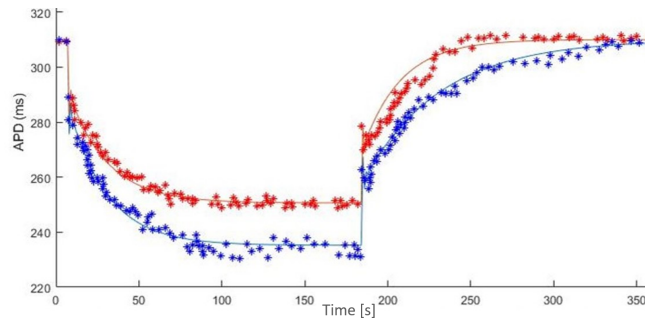


Figure 9.1: Comparison of the physiological data measured by [123] with the [APD](#) adaption in the model.

Table 9.1: List of model parameters used for the evaluation of the [APD](#) for the settings employed.

Parameter	Value	Parameter	Value
α	0.25	APD_0	320 [ms]
ω	2.5	S_{max}	280 [ms]
ψ	0.22	S_0	750 [ms]
β_0, γ_1	0.03	aid_0	APD_0
γ_2	0.06		

The data points in red (and subsequently in blue) illustrate the outcomes for a steady state stimulation interval of 750 ms, which is reduced to a steady state of 480 ms (410 ms) and subsequently elevated to a steady-state of 750 ms again, derived from measurements of the cardiac response in patients undergoing cardiac stimulation in [123]. As illustrated in Figure 9.1, the adaptive response of the [APD](#) to alterations in the stimulation interval is comparable between our model and the the physiological data presented in [123].

9.1.1 Effect of APD Calculation Parameters on APD Progression

Figure 9.2 illustrates the impact of alterations in the steady-state stimulation interval on the progression of the APD for varying steady-state intervals. The figure illustrates the results of the progression of the APD for a change from three different steady-state intervals over a period of 350 seconds to a steady-state stimulation interval of 750 milliseconds for the following 350 ms. The colours correspond to the steady-state intervals employed during the initial phase of the experiment:

- 1000 ms (blue), 2000 ms (green) and 3000 ms (red).

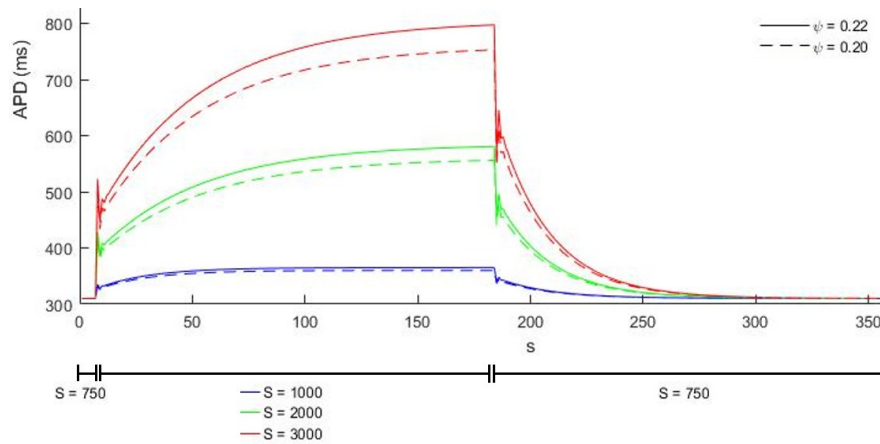


Figure 9.2: Progression of the APD with the parameters listed in in Table 9.1 a and Table 9.1 b and variances in the parameters S and ψ .

The dashed lines in Figure 9.2 demonstrate the influence of ψ , the effect of an altering stimulation interval relative to the initial parameters in calculating the value of A_{inf} towards which APD_i adjusts over time, on the subsequent APD calculation. The linear relationship between the APD and stimulation interval, which has been observed to occur around a value of 23 ms for a change of 100 ms in the stimulation interval, has previously been described by [123].

We calculated the range for the value ψ based on the ratio between the first and last APD, divided by the distance between the initial and final stimulation intervals. The values for the stimulation intervals and the resulting APD are retrieved from reference [123]. Figure 9.3 illustrates the distribution we found for the ratio between the first and last APD, divided by the distance between the initial and final stimulation interval. Accordingly, the distribution for the ratio ψ in our model falls within the range 0.17 to 0.28.

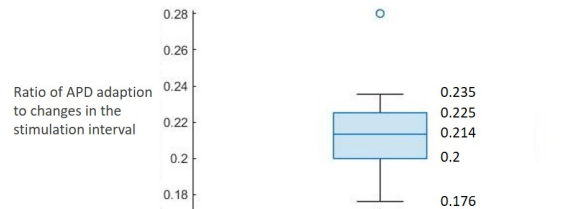


Figure 9.3: Distribution of the ratios by dividing the distance between the action potential durations at the beginning and the final action potential duration by the distance between the start and end stimulation intervals from Table 9.1 in [123].

9.2 Application of the HIL Model

The **HIL** setup is illustrated in Figure 9.4. It incorporates a software-based cardiac model developed in **LabVIEW**, executed on a computer, a software-hardware interface associated with **LabVIEW**, a circuit incorporating a tissue resistor and a commercial pacemaker. The electrical activity of the heart chamber, which the pacemaker is designed to interact with, is transmitted to the pacemaker via the software-hardware interface, as the triangular **EIS** proposed in Section 4.7. The software-hardware interface also records the pacemaker's responses and feeds them back to the heart model, thereby establishing a closed loop between the software-based heart model on the computer and the commercial pacemaker.

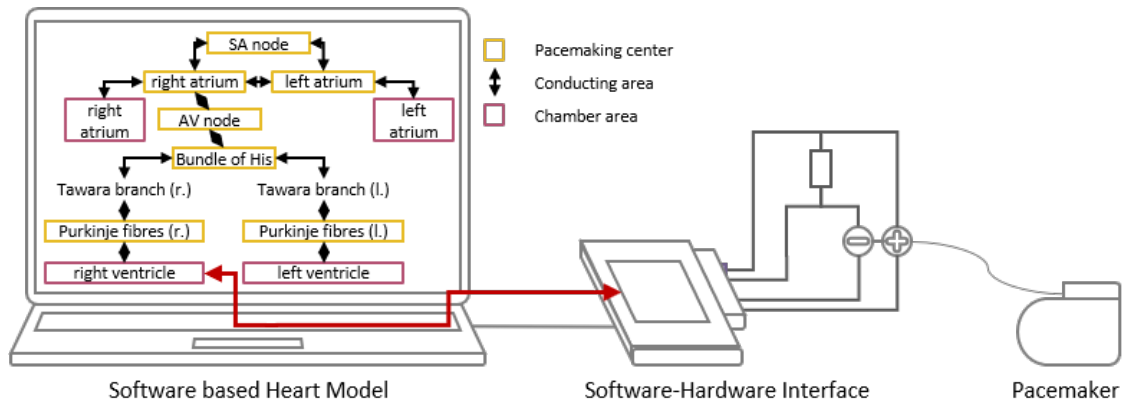


Figure 9.4: Schematic representation of the **HIL** setup.

The heart model is implemented in **LabVIEW** 2022 Q3, extended by the application software for the software-hardware interface, DAQExpress, version 5.1.0. The measurements were performed on an Intel® Core™ i9-10900K CPU 3.70GHz with 32 GB of main memory. The analog inputs and outputs of the BNC-2110 (a **LabVIEW**-associated software-hardware interface) serve as the conduit between the software and the hardware. To transmit the **EIS** generated within the heart model to the poles of the electrode and to record the pacemaker activity, the software-hardware interface and the pacemaker are connected via the two metallic poles of an associated single bipolar pacemaker electrode, as illustrated in Figure 9.5. The pacemaker integrated in the **HIL** setup is the single-chamber pacemaker Effecta S(R)TM, which is employed in the treatment of **bradycardia** [125]. The device is programmed to 60 bpm, which is a common rate set for an average patient.

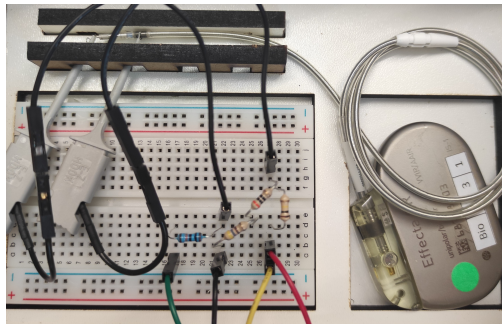


Figure 9.5: **HIL** setup for connecting the **LabVIEW** heart model software-hardware interface of the real-time to the pacemaker (Effecta S(R)TM) via the pacemaker associated electrode.

Data Example

To provide an overview of the output generated by the HIL setup, Figure 9.6 depicts the recorded behavior for the **atrium** (blue), **ventricle** (red) and pacemaker (black) within a limited time frame. The progression of the **atrium**, represented by the blue line can exist in either

- state 2, representing the contracted state in which the **atrium** is unable to be stimulated,
- state 1, in which the **atrium** is undergoing relaxation and can be stimulated, but a stimulation may result in the onset of **tachyarrhythmias**, regarded as the **vulnerable phase** and
- state 0, in which the **atrium** is relaxed and awaiting an incoming stimulation to reenter state 2.

Similarly to the **atrium**, the **ventricle**, depicted in red, exhibits distinct phases, including

- state 3, the non-stimulatable contraction phase, followed by
- state 2, representing the aforementioned **vulnerable phase** described for the **atrium**,
- state 1, in which the **ventricle** is in a further relaxed phase during which stimulation is possible without the onset of **tachyarrhythmias**, but the **AV Valve** is not yet opened ultimately and
- state 0, which is signifying complete relaxation.

Each black line represents an incoming pacemaker stimulation.

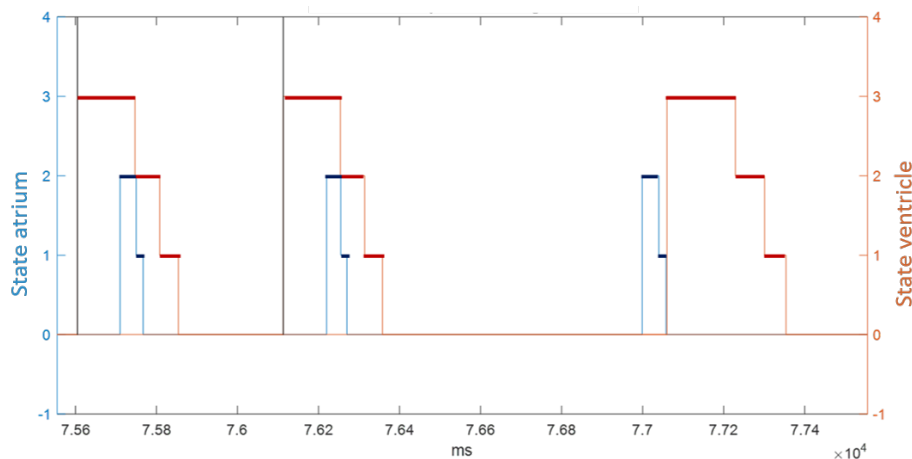


Figure 9.6: Interaction between the LabVIEW heart model and a commercial pacemaker, showing the changes in state over time. Pacemaker pulses are represented in black. The states of the right **atrium** respectively **ventricle** are depicted in blue respectively red.

Figure 9.6 illustrates the sequence of events that occur in the development of **pacemaker syndrome**. Here a pacemaker stimulus pacing the **ventricle** results in a parallel contraction of the **atrium** and **ventricle**. In consequence an atrial contraction pumps blood against a closed **AV Valve** and back into the correlated blood vessel, instead of into the **ventricle**. Such an inadequate timing of the pacemaker due to a lack of adaptability to the heart's activity can result from a number of factors, including interference, inadequate programming, or low battery power.

Additionally, the figure illustrates the anticipated outcome of an extended simulation interval. The duration of the third ventricular activity is consistently longer than that of the preceding two, emphasizing the necessity for a comprehensive representation of the time-dependent progression of the action potential.

9.2.1 Parameter Initialization for Continuous Tests with the HIL Model

In the process of data acquisition, the heart model is controlled by a [Virtual Instrument \(VI\)](#) in [LabVIEW](#) that has been specifically designed for the parameter initialisation and data acquisition of the heart model. The interaction between the data acquisition module and the heart model is illustrated in Figure 9.7.

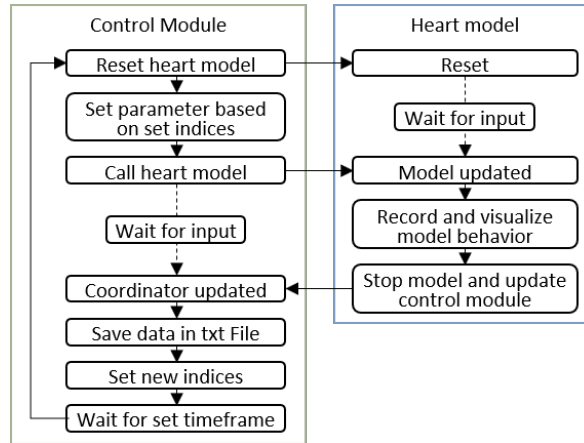


Figure 9.7: Procedure of the measurement.

At the onset of a sequence, the aforementioned data acquisition module initiates a reset of all parameters associated with the heart model, returning them to their initial conditions. Subsequently, a series of parameters are configured for the forthcoming measurement, including the chamber paced by the pacemaker, the rate of the [SA node](#), the conditions of the [ECSH](#), and the reliability of the replacement rhythms. The initial properties are displayed in Figure 9.8. The measurements are conducted with a single property per category, which was maintained throughout the duration of the measurement. Subsequently, each property within each category was combined with each property within the other categories.

During the measurement the status of the individual cardiac chambers is recorded throughout the entire runtime period. Upon completion of the designated run time, the heart model is terminated and the acquisition module is updated. This involves the saving of the data in a text file and the setting of the indices for the new measurement setup. The subsequent waiting period serves to ensure that the pacemaker initiates the next measurement under identical conditions. This process is then repeated iteratively.

The [APD](#) calculation was performed with the formulas presented in Section 4.2, initialized by employing the parameters listed in Table 9.1, Table 9.2 a and Table 9.2 b.

Table 9.2: List of model parameters used for the evaluation of the [APD](#) for the settings employed.

Table 9.2 a: Atrial connection module.

Parameter	Value	Unit
AVV_{close}	1	[%]
VVV_{open}	11	[%]
VVV_{close}	100	[%]
AVV_{open}	22	[%]

Table 9.2 b: Atrial connection module.

Parameter	Value	Unit
n_0	0	
A	0.05	[V]
t	1.95	[ms]
T	17.5	[ms]

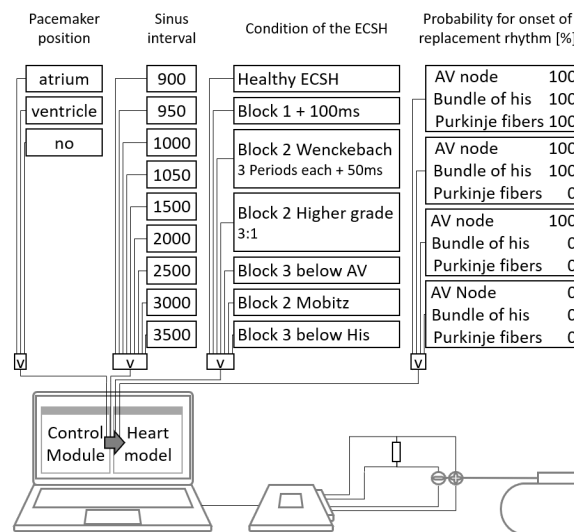


Figure 9.8: The set of parameters for the interaction between the heart and the pacemaker includes variances in the position of the pacemaker electrodes, the length of the SA node interval, the properties of the ECSH, and the reliability of the different replacement rhythms in the heart model.

Two distinct timed measurement sequences were employed: one to investigate the continuous interaction between the heart and the pacemaker, and one to investigate the changes surrounding the onset of the pacemaker.

Test Sequence 1: Heart Pacemaker Interaction over 11 Minutes

In this measurement sequence, the interactions between the heart and the pacemaker are documented over a total duration of 11 minutes. The aforementioned sequence is followed by the measurement process and initialisation of the parameters. The detailed sequence is as follows:

- Initialisation of the heart model (2 minutes) and
- Interaction between the heart and the pacemaker (2 - 9 minutes).

Following each sequence a two minute rest of the heart model was maintained before the next sequence was initiated.

Test Sequence 2: Heart Pacemaker Interaction with Delayed Pacemaker Onset

In this measurement sequence, the interactions between the heart and the pacemaker, both before and after the insertion of a pacemaker, are documented over a total duration of 16 minutes. The measurement process and the initialisation of the parameters are conducted in accordance with the aforementioned sequence. The detailed sequence is as follows:

- Initialisation of the heart model (2 minutes),
- Heart monitored without the pacemaker (5 minutes)
- Connection to the pacemaker
- Interaction between the heart and the pacemaker (9 minutes).

Also for this sequence each interaction was followed by a two-minute pause before the start of the next measurement.

9.2.2 Comparison Model Data and Medical Data

The data for this comparison has been recorded as a continuous measurement of the interaction between the heart and the pacemaker over 11 minutes, as detailed in Section 9.2.1. To validate the temporal intervals derived from our heart model against those of a real heart, an [ElectroCardioGram \(ECG\)](#) annotated by a physician was evaluated in conjunction with the temporal changes observed in a dataset generated by our model. Figure 9.9 presents the results. The initial [P wave](#) of the [ECG](#) and each atrial activation within the dataset from the model are designated to $x = 0$. These are employed as reference points to evaluate the temporal differences in the occurrence of the following five atrial and ventricular activations between the model generated data and the annotated [ECG](#).

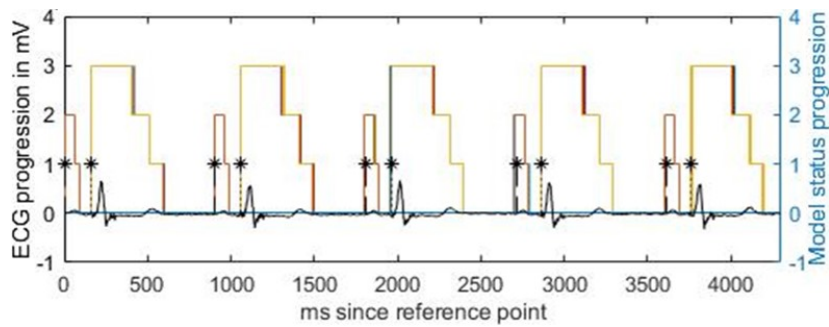


Figure 9.9: Superimposition of the model data set in comparison with an [ElectroCardioGram \(ECG\)](#) data set, annotated by a physician [126]. The reference points of the datasets (first annotated [P wave](#) in [ECG](#) and each atrial activation in the model) were set to zero.

Figure 9.10 depicts the temporal distance between the annotated time intervals in relation to the initial annotation of the initial [P wave](#) derived from the [ECG](#), in comparison to the time intervals derived from the model in relation to each [P wave](#) identified in the model data. The discrepancies in milliseconds are illustrated for all five beats following the initial annotated [P wave](#) of the [ECG](#) in relation to the five beats following each modeled [P wave](#). As can be seen, there is a high degree of correlation between the model data and the intervals observed in the [ECG](#).

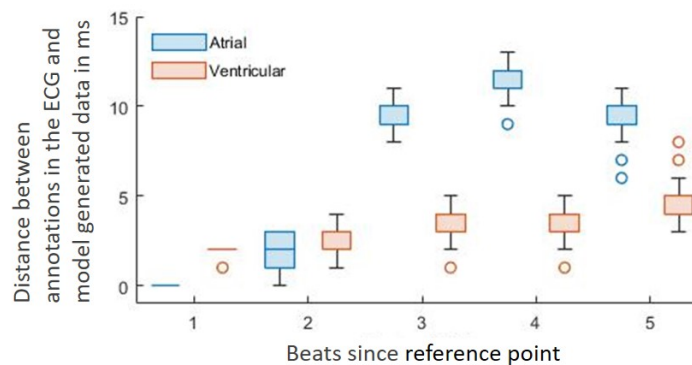


Figure 9.10: Temporal discrepancies between the annotations by a physician on an [ECG](#) and the data set generated by the model. The discrepancies in milliseconds are illustrated for all five beats following the initial annotated [P wave](#) of the [ECG](#) in relation to the five beats following each modeled [P wave](#).

9.2.3 Heart Rate Boundaries and Coordinated Contractions

Figure 9.11, Figure 9.12 and Figure 9.13 present the results for the interaction of our heart model with a physical pacemaker. These figures illustrate the bpm for distinct cardiac chambers in comparison to the [SA node](#) interval and under the influence of varying [ECSH](#) conditions performed with Test Sequence 1 (the continuous heart pacemaker interaction over 11 minutes) for the properties displayed in Section 9.2.1. The first row in each figure depicts the bpm in the [atrium](#), the second row depicts the bpm in the [ventricle](#), and the third row shows the ventricular contraction was preceded by an atrial contraction per minute ([coordinated contractions](#)).

Heart without a Pacemaker The data in Figure 9.11 is obtained in the absence of a pacemaker. It shows a proportional relationship between the atrial rate in relation to [SA node](#) rate. For the interaction of the heart model with a healthy [ECSH](#) (dark blue) or only minor defected [ECSH](#), such as an [AV Block 1](#) and a stimulation frequency of the [SA node](#) extending the frequency of the replacement rates (Sinus stimulation interval ≤ 2000), the numbers of ventricular and effective contractions align with those of the [atrium](#). In instances where the [SA node](#) stimulation interval exceeds 2000 ms, the dark blue and orange bars demonstrate a heart rate that extends the anticipated rate of the [SA node](#). As the replacement rhythms, generating this rate, originate from the middle to lower regions of the [ECSH](#), the orientation of stimulus conduction results in a decline in the number of [coordinated contractions](#).

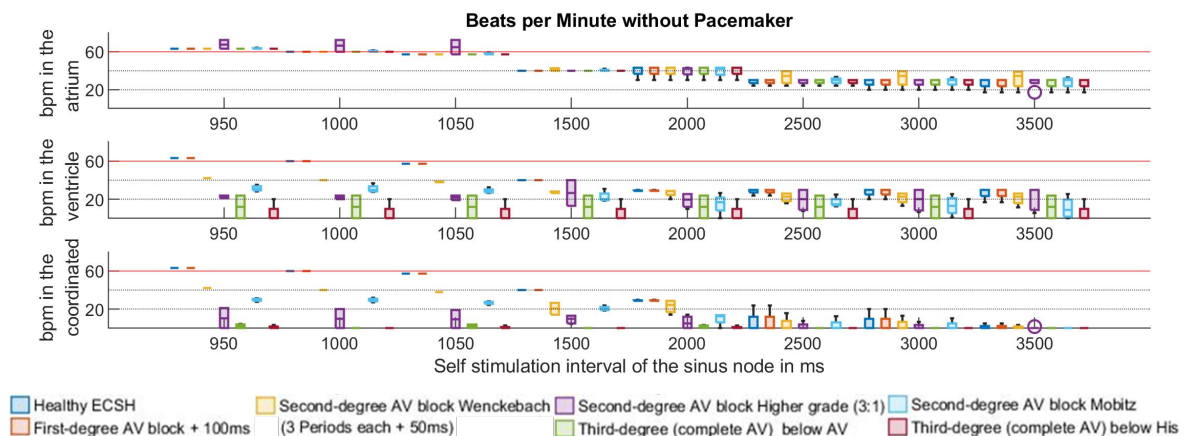


Figure 9.11: Generated bpm of the heart model for the parameters named in Figure 9.8, recorded without a pacemaker.

In cases of second-degree atrioventricular blocks, a similar correlation between [SA node](#) and ventricular frequencies, as well as effective stimulations, can be observed for [SA node](#) self-stimulation intervals exceeding 2000 ms. However, for intervals of 2000 ms and below, the differences between the various [SA node](#) self-stimulation intervals are minimal. A similar trend is observed in the number of effective beats per minute, with minimal differences between the different diseases. In cases of [AV Block 3](#), the frequency of atrial stimulation has no impact on ventricular activity, which remains below 30 beats per minute. This value is frequently observed to be below 20 bpm. The number of [coordinated contractions](#) of the impulses is reduced for all [SA node](#) rates.

The figure also shows the relevance of the replacement rhythms. It demonstrates, the enhanced ventricular activities for [AV Block 3i](#) under the [AV node](#) (green) in comparison to those for [AV Block 3s](#) under the [bundle of his](#) (red). Furthermore, the replacement rhythms have a notable impact on the generated beats for the [AV Block 2 h](#) and [AV Block 2 m](#).

Pacemaker connected to the Atrium The data in Figure 9.12 illustrate the results of the heart pacemaker interaction with the pacemaker connected to the [atrium](#). The pacemaker successfully increased the atrial rate. Moreover, the data obtained for healthy conduction and [first-degree AV block](#) indicate a successful increase in both ventricular and [coordinated contractions](#). Also, the second-degree AV blockages demonstrate an increase in the number of the ventricular beats and the number of [coordinated contractions](#) at low [SA node](#) rates, in comparison with the absence of a pacemaker. The values recorded for ventricular activity and [coordinated contractions](#) in the case of the [third-degree AV block](#) are consistent with those recorded in the absence of a pacemaker.

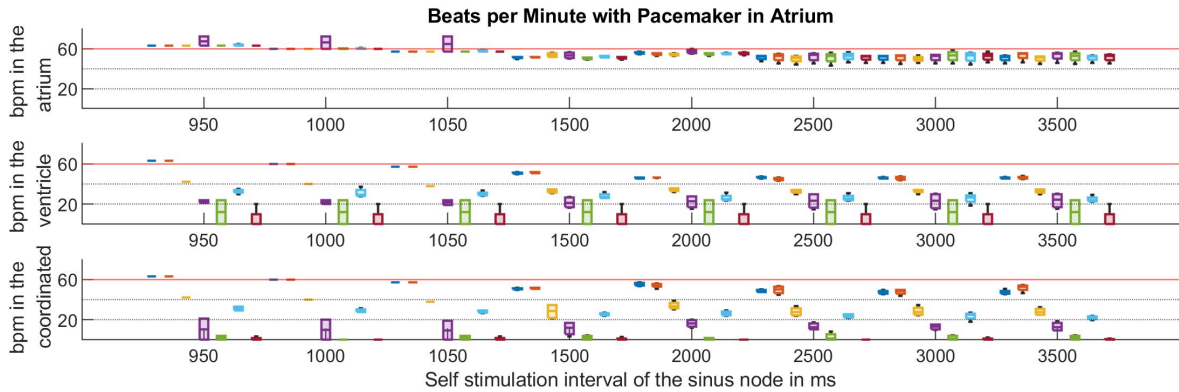


Figure 9.12: Generated bpm of the heart model for the parameters named in Figure 9.8, recorded with a pacemaker connected to the [atrium](#). The color coding corresponds to the legend of Figure 9.11.

Pacemaker connected to the Ventricle Figure 9.13 illustrates the data for the heart pacemaker interaction with a pacemaker connected to the [ventricle](#). The figure demonstrates a stable rate of over 50 bpm in the [ventricle](#) for all conditions of the [ECSH](#). Also the number of atrial contractions can be elevated, especially for healthy conduction and first- and second-degree atrioventricular block. However, the number of [coordinated contractions](#) declines for the healthy conduction and first- and second-degree atrioventricular block as soon as the pacemaker rate extends the [SA node](#) rate. Conversely, the third-degree AV blocks demonstrate enhanced [coordinated contractions](#) at higher [SA node](#) rates in comparison to measurements without or an atrial pacemaker. The number of [coordinated contractions](#) for [SA node](#) intervals below 1050 ms is inferior to that observed without a pacemaker.

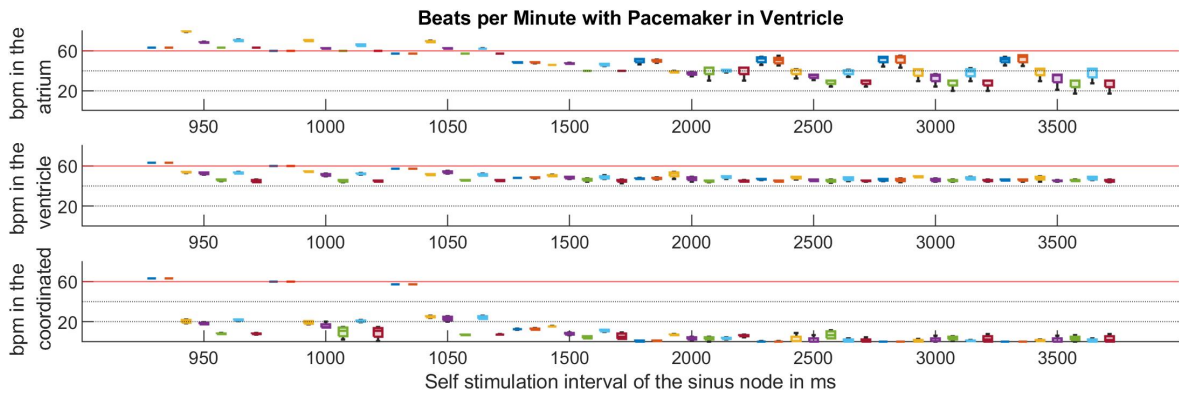


Figure 9.13: Generated bpm of the heart model for the parameters named in Figure 9.8, recorded with a pacemaker connected to the [ventricle](#). The colour coding corresponds to the legend of Figure 9.11.

Figure 9.14 shows the number of beats per chamber for the healthy ECSH and the AV Block 1 presented in Figure 9.11, Figure 9.12, Figure 9.13. The illustration demonstrates how an incorrectly programmed pacemaker can reduce the number coordinated contractions. While the atrial and ventricular stimulations are increased in the atrium and ventricle when the pacemaker is applied in comparison to the measurement without the pacemaker, the number of coordinated contractions falls below that without a pacemaker for a pacemaker connected in the ventricle at a low SA node rate.

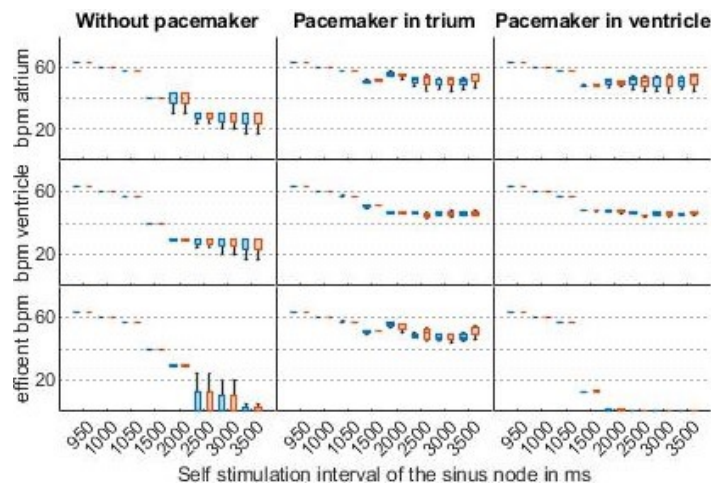


Figure 9.14: Comparison of the bpm generated by the heart model for the parameters named in Figure 9.8 for a healthy ECSH (blue) and a first-degree AV block (orange).

9.2.4 Vulnerable Phase

Figure 9.15 illustrates the data generated by the HIL heart model in interaction with a physical pacemaker. For the first 3 minutes the heart model is monitored without a pacemaker connected. The pacemaker is connected to the HIL heart model in minute 4. The initial parameters for the HIL heart model are depicted in Figure 9.8. APD and valve status prediction is performed based on the formulas from Section 4.2.3, with the parameters proposed in Table 9.1 and Table 9.2. The figure illustrates the number of stimulations for the entire data set across all measurement runs, categorized by minute intervals. The underlying corresponding boxplots, differentiated according to the SA node stimulation intervals during the measurement, are provided in Chapter D of the Appendix.

The potential for stimulation in the vulnerable phase is enhanced with the insertion of the pacemaker for all diseases, as illustrated by the data in Figure 9.15. However, the quartiles for the respective stimulations are approximately zero for the overall average of all measurements for all diseases. It can be ascertained that the impact of second-degree atrioventricular blocks on the ECSH appears to influence the probability of pacing into the vulnerable phase. Given their irregular nature, AV Block 2 h and AV Block 2 m seem to increase the probability for the occurrence of isolated stimulations into the vulnerable phase for both the atrium and the ventricle, even in the absence of a pacemaker. For the AV Block 2 h, this phenomenon is amplified for the atrium by atrial pacing by the pacemaker and mitigated for the ventricle by ventricular pacing by the pacemaker. In the case of the arbitrarily transmitting AV Block 2 m, the number of stimulations into the vulnerable phase for both the atrium with and without stimulation seems to be approximately equal.

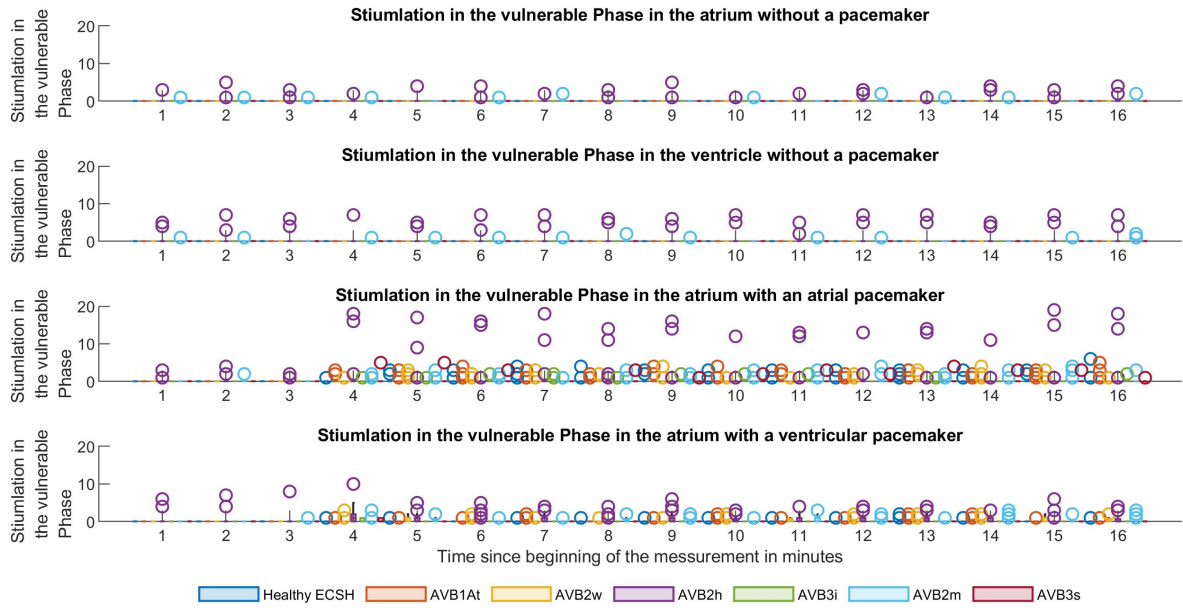


Figure 9.15: Stimulations in the vulnerable phase in bpm over 16 minutes.

In all other disease cases, atrial pacing by the pacemaker, with the selected parameters, appears to increase the probability of pacing into the vulnerable phase. In ventricular pacing, isolated stimulations into the vulnerable phase occur for the AV Block 2 w in addition to those expected for AV Block 2 h and AV Block 2 m, as well as a single isolated stimulation in the vulnerable phase recorded for the healthy conduction.

Figure 9.16 shows the data for a SA node interval of 1500 ms, which indicates fewer stimulations into the vulnerable phase occurring during stimulation with a ventricular pacemaker for a AV Block 2 h than without a pacemaker.

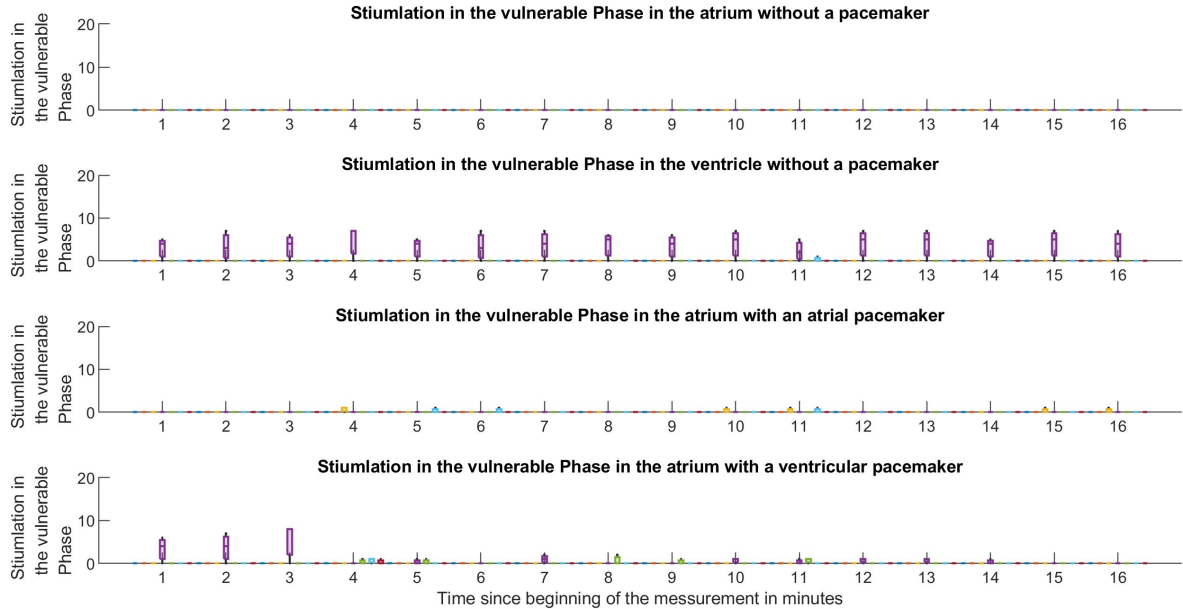


Figure 9.16: Stimulation in the vulnerable phase of the HIL heart model for the pacemaker onset after 4 minutes for a SA node interval of 1500.

9.2.5 Non-Essential Pacing Pulses Delivered by the Pacemaker

In order to evaluate the number of non-essential pacing pulses delivered by the pacemaker, under the conditions to prioritize the activity of the heart, under the condition that activities by the heart are prioritized, the discrepancy between the stimulations delivered compared to the number of contractions observed in the corresponding chamber is evaluated by

$$n_{\text{non-essential}} = n_e + n_p - n_c \quad (9.1)$$

with n_e and n_p as the total number of chamber stimulations by the ECSH and the pacemaker, respectively, while n_c represents the total number of contractions of the respective chamber.

Figure 9.17 presents the results for the interaction of our heart model with a physical pacemaker. The figure illustrates the number of non-essential pacing pulses delivered by the pacemaker in bpm for the atrium and the ventricle in comparison to the SA node interval and under the influence of varying ECSH conditions. The data are generated by the previously described Test Sequence 1 (the continuous heart pacemaker interaction over 11 minutes) for the properties displayed in Section 9.2.1. The first row depicts the bpm in the atrium and the second row depicts the bpm in the ventricle.

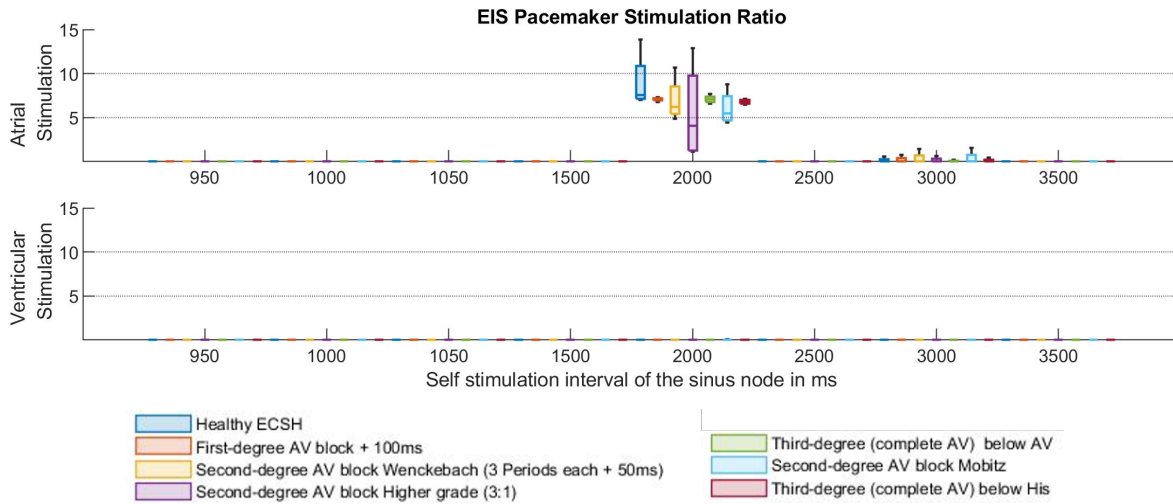


Figure 9.17: Non-efficient beats generated by the interaction between the pacemaker and the heart model for the parameters named in Figure 9.8.

Figure 9.17 illustrates in most cases at most a very slight discrepancy between the stimulations delivered compared to the number of contractions observed for the interaction of the heart model with the pacemaker connected to the atrium. However, this is not the case for the SA node intervals of 2000 ms and 3000 ms, where additional stimulations were recorded. In the runs with an SA node interval of 2000 ms, supplementary stimulations were observed across all measurement runs, with two conditions of the ECSH even exhibiting up to 15 additional stimulations per minute. For the measurement runs with a stimulation interval of 3000 ms, the number of additional stimulations is considerably lower, yet they still occur for each measurement run.

The discrepancy between the stimulations delivered compared to the number of contractions observed for the interaction of the heart model with the pacemaker connected to the ventricle is zero for all measurement runs independent of the conditions of the ECSH and the SA node self-stimulation intervals.

9.2.6 Variances in QT - Long QT and Menstrual Cycle

In considering the data related to alterations in the [QT interval](#), the actual beats per minute, the changes in the number of stimulations into the [vulnerable phase](#), and the number of non-essential pacing pulses collectively represent a subject of interest. As prolonging the [QT interval](#) results in a chamber taking longer to gain back the ability to be successfully stimulated, the prolonging of the [QT interval](#) could lead to a reduction in the number of ventricular contractions and an increase in the number of pacemaker stimulations, while the cardiac model was not able to be stimulated, which would be counted as non-essential pacing pulses. The prolonged [vulnerable phase](#) could result in an increased number of stimulation into the [vulnerable phase](#).

Figure 9.24, Figure 9.19 and Figure 9.21 present the results for the interaction of our heart model with a physical pacemaker for varying [SA node](#) intervals and under the influence of varying [ECSH](#) conditions. The data are generated by a scaled down version the previously described Test Sequence 1 and a runtime of 5 minutes. The properties displayed in Section 9.2.1 are reduced in the number of diseases and the number of [SA node](#) self-stimulation intervals.

Stimulations in the Vulnerable Phase Figure 9.18 and Figure 9.19 show the number of stimulations in the [vulnerable phase](#) for two different [QT interval](#) lengths. There is only a small discrepancy between the number of stimulations in the [vulnerable phase](#) for the [QT interval](#) considered to be within the normal range (Figure 9.18) and the [QT interval](#) regarded as prolonged (Figure 9.19).

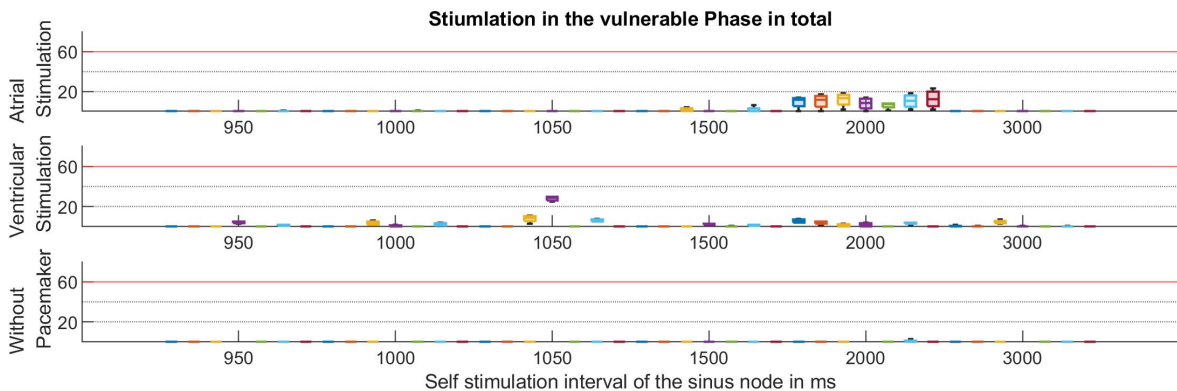


Figure 9.18: Stimulation in the [vulnerable phase](#) for a [QT interval](#) of 380 ms.

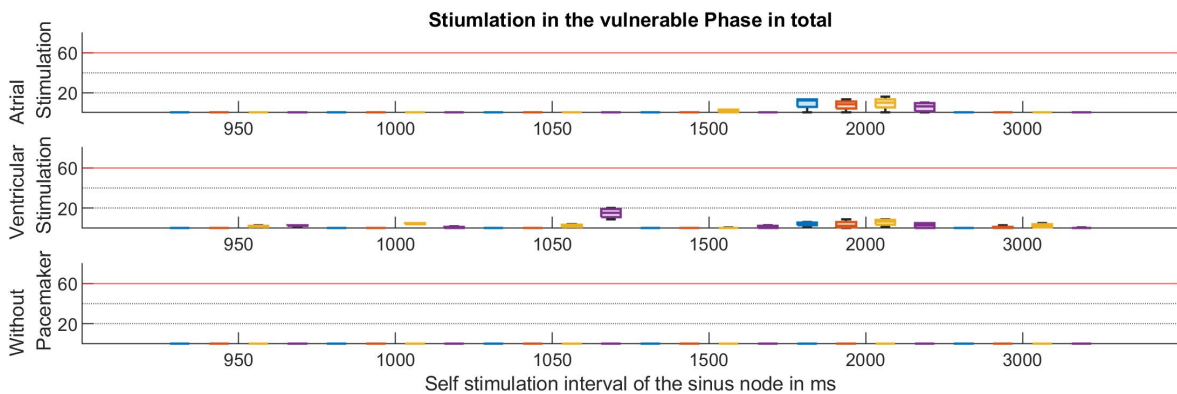


Figure 9.19: Stimulation in the [vulnerable phase](#) for a [QT interval](#) of 420 ms.

Non-Essential Pacemaker Pulses Figure 9.18 and Figure 9.19 show the number of non-essential stimulations for two different **QT interval** lengths. There is only a small discrepancy between the number of stimulations in the **vulnerable phase** for the **QT interval** considered to be within the normal range (Figure 9.20) and the **QT interval** regarded as prolonged (Figure 9.19).

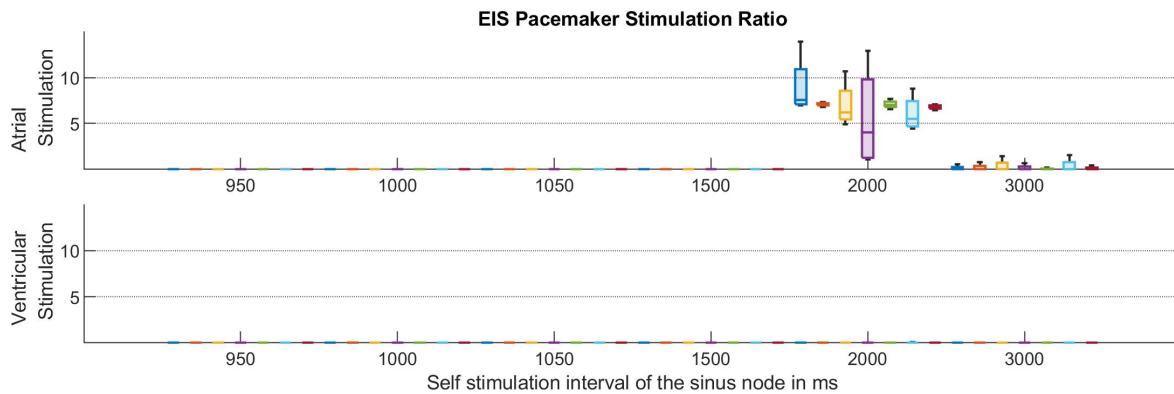


Figure 9.20: Non-essential stimulations for a **QT interval** of 380 ms.

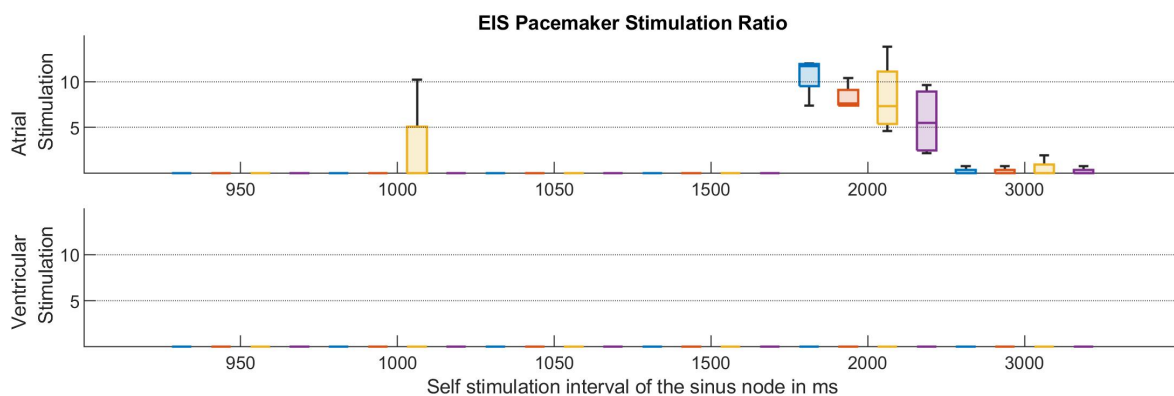
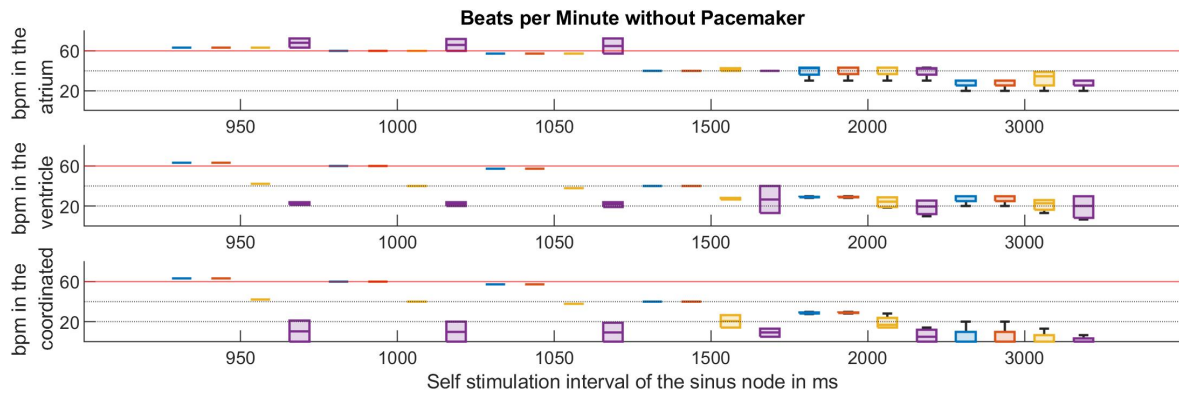
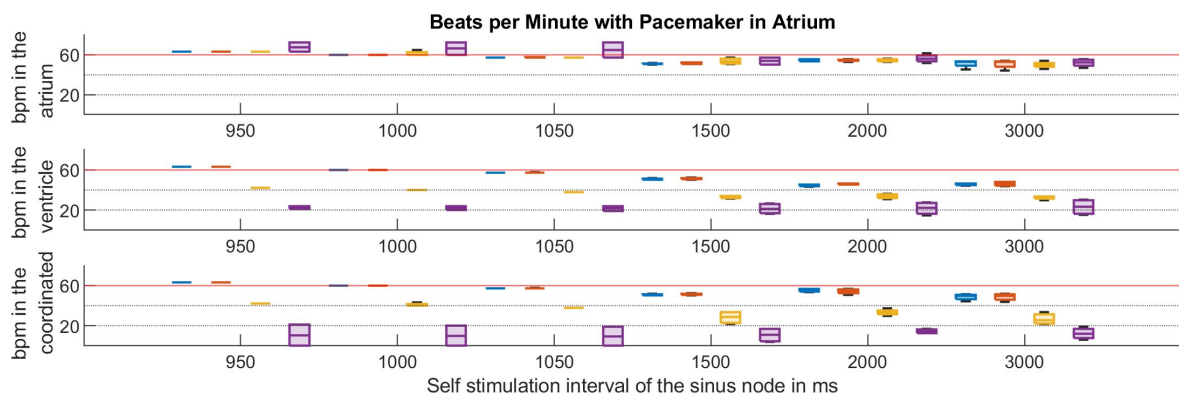
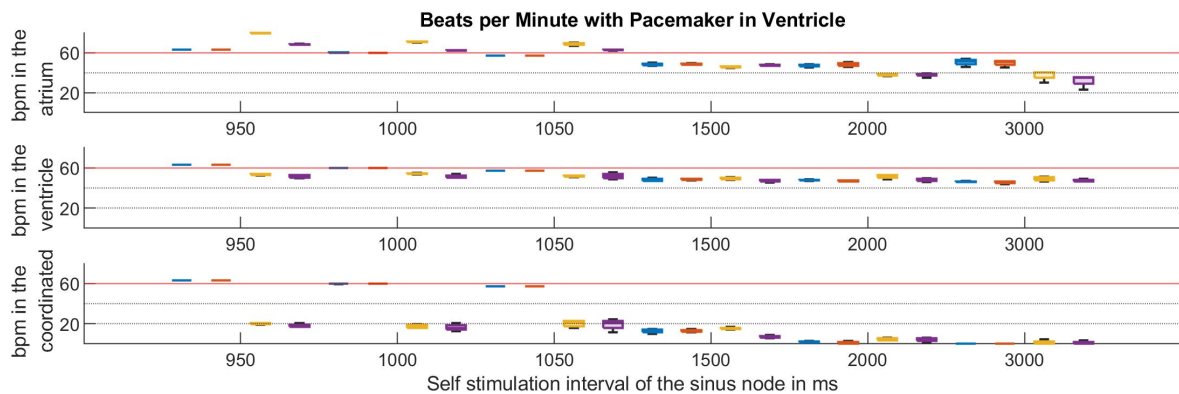


Figure 9.21: Non-essential stimulations for a **QT interval** of 420 ms.

Generated Beats per Minute The number of contractions per minute based on the conditions of the **ECSH**, the self-stimulation interval of the **SA node** and the chamber the pacemaker is connected to, represented in Figure 9.22, Figure 9.23, Figure 9.24 for the conditions of **long QT**. The figures are comparable to the figures generated with a shorter **QT interval** in Figure 9.11, Figure 9.12, Figure 9.13. This indicates that the longer **QT interval** has no impact on the number of atrial and ventricular contractions under the conditions of the measurements.

Figure 9.22: Stimulations in bpm for a [QT interval](#) of 420 ms without a pacemaker.Figure 9.23: Stimulations in bpm for a [QT interval](#) of 420 ms with a pacemaker in the [atrium](#).Figure 9.24: Stimulations in bpm for a [QT interval](#) of 420 ms with a pacemaker in the [ventricle](#).

9.2.7 Diseased Rate Generation Modules

The following section presents a summary of the results obtained from the [HIL](#) measurements, which were conducted with the incorporation of the modules of the heart model that emulate the behavior of [PAC](#), [PVC](#), as well as atrial and ventricular [flutter](#) for varying [SA node](#) intervals and under the influence of varying [ECSH](#) conditions. The data is generated by a scaled down version the previously described Test Sequence 1. The runtime 5 minutes per run and the properties displayed in Section 9.2.1 are reduced in the number of diseases and the number of [SA node](#) self-stimulation intervals.

Premature Atrial and Ventricular Contractions

In order to ascertain the impact of the **PAC** and **PVC**, the timer for the occurrence of an additional impulse was configured to deliver a supplementary impulse at minute 4 of the 5-minute measurement, as outlined in Chapter 4. The consequences on the **vulnerable phase** and on the non-essential pacemaker stimulations were then examined.

Stimulation in the Vulnerable Phase The data indicate that there is no significant alteration in the data with premature contractions in the **atrium** (Figure 9.25a) or in the **ventricle** (Figure 9.25b).

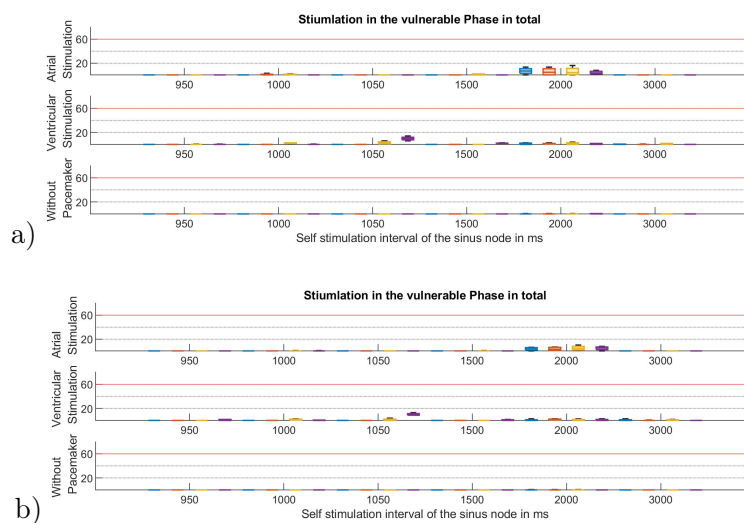


Figure 9.25: Stimulations in the **vulnerable phase** for a **QT interval** of 380 ms (a) and 420 ms (b).

Non-Essential Pacemaker Pacing Pulses The data analysis indicates an increase in non-essential pacing for the **SA node** self-stimulation intervals of 1000 ms and 3000 ms in the data sets exhibiting **PAC** with a pacemaker connected to the **atrium** (Figure 9.26a) and a pacemaker connected to the **ventricle** (Figure 9.26b).

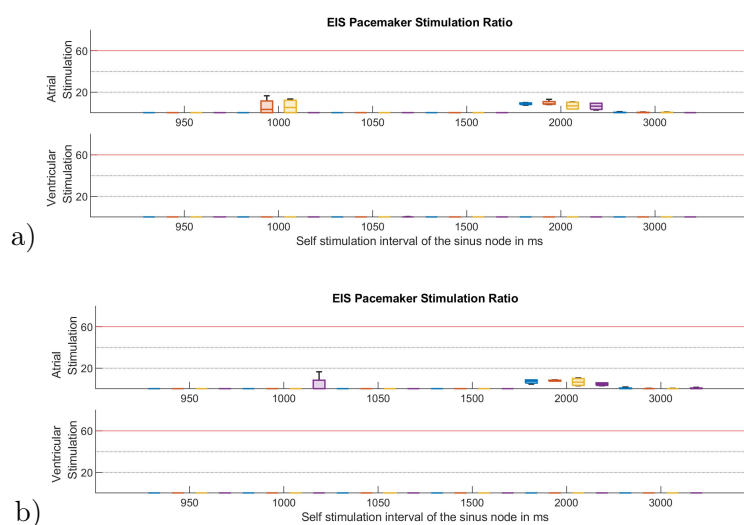


Figure 9.26: Non-essential pacing pulses for a **QT interval** of 380 ms (a) and 420 ms (b).

Atrial Flutter

Irrespective of the self-stimulating frequency of the [SA node](#), the characteristics of the [ECSH](#) and the chamber to which the pacemaker is connected, the number of contractions per minute in the [atrium](#) is above 180 bpm. The number of beats transferred to the [ventricle](#) per minute varies contingent on the characteristics of the [ECSH](#). It is, however, consistent for all [SA node](#) self-pacing frequencies and is always above 60 bpm.

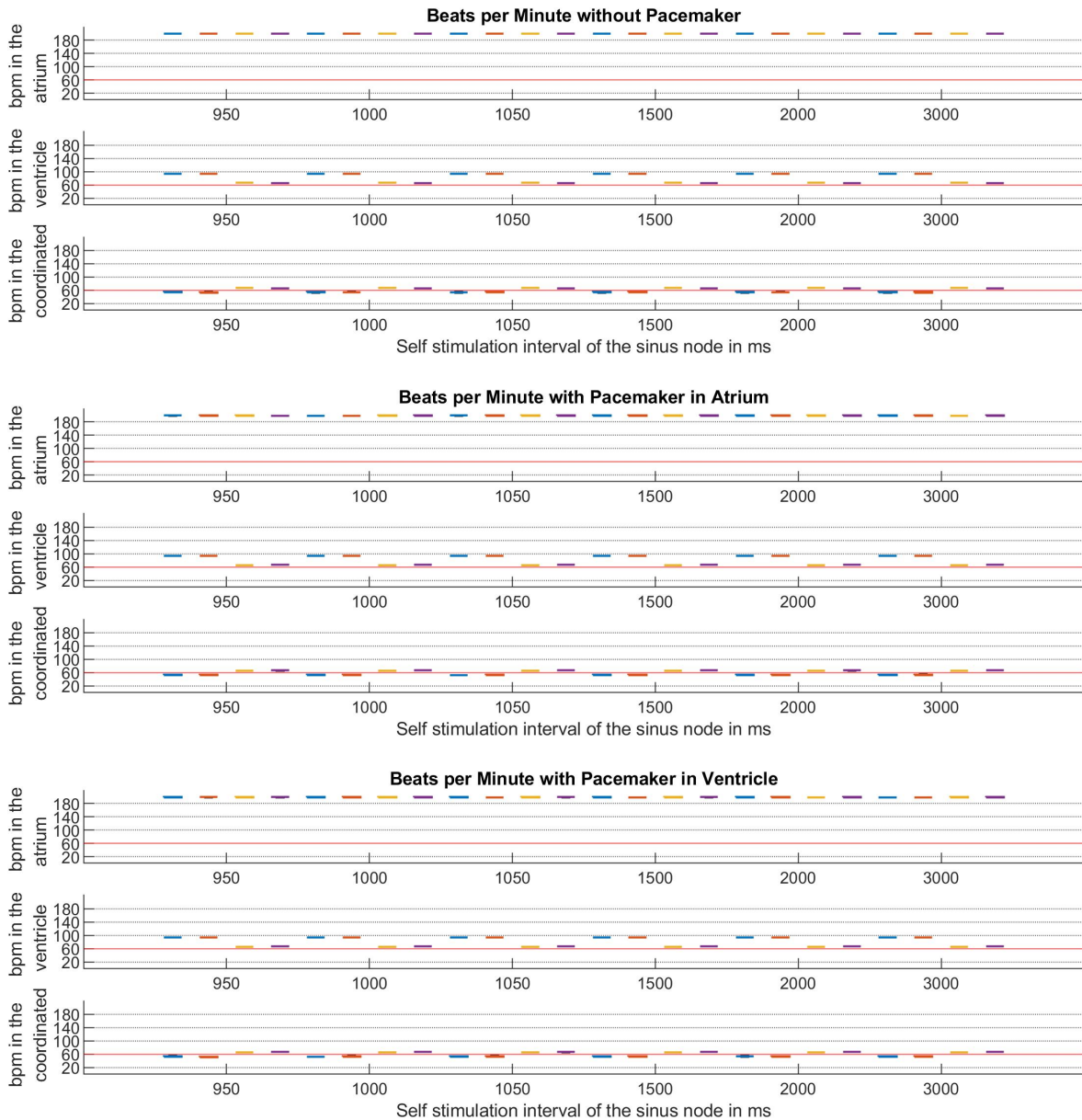


Figure 9.27: Contractions in bpm for [atrial flutter](#).

Stimulation in the Vulnerable Phase and Non-Essential Pacemaker Pacing Pulses

The data show that no stimulations were observed during the [vulnerable phase](#), and that no non-essential stimulations were detected when our heart model interacted with a pacemaker in the presence of an [atrial flutter](#).

Ventricular Flutter

Figure 9.28 shows the interaction between the heart model and the pacemaker for different properties of the **ECSH**, different diseases and different chambers, when the pacemaker is connected to the heart model, including **ventricular flutter**.

Irrespective of the self-stimulating frequency of the **SA node**, the characteristics of the **ECSH** and the chamber to which the pacemaker is connected, the number of contractions per minute in the **ventricle** is above 180 bpm. The number of beats transferred to the **atrium** per minute varies contingent on the characteristics of the **ECSH**. It is, however, consistent for all **SA node** self-pacing frequencies and is always above 60 bpm.

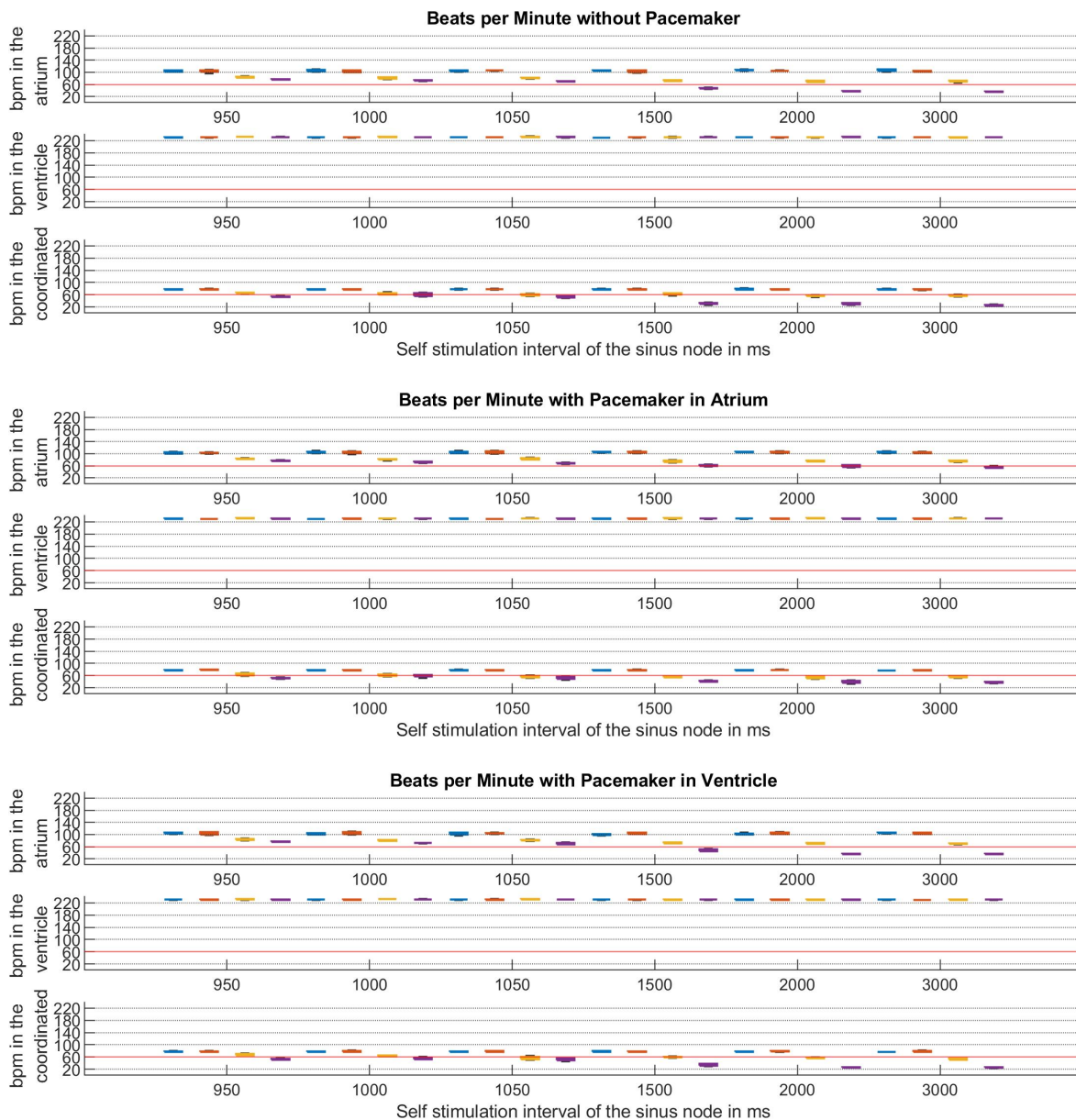


Figure 9.28: Contractions in bpm for **ventricular flutter**.

Stimulation in the Vulnerable Phase Figure 9.29 shows a few stimulations into the **vulnerable phase** for the measurements including **ventricular flutter**. The stimulations in the **vulnerable phase** were evenly increased and distributed for all runs during which the pacemaker was connected to the **ventricle** of the heart model.

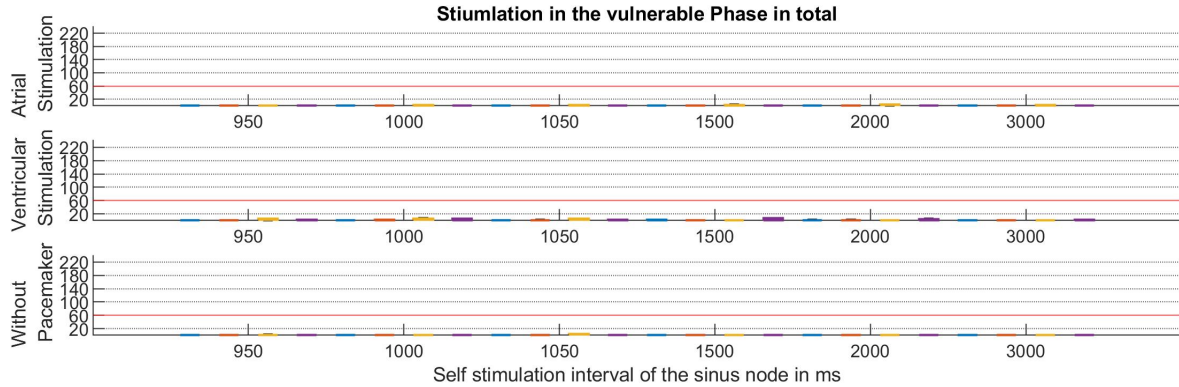


Figure 9.29: Stimulations into the **vulnerable phase** for **ventricular flutter**.

Non-Essential Pacemaker Pacing Pulses As Figure 9.30 indicates, only one non-essential stimulation per minute was detected, when our heart model interacted with a pacemaker in the presence of a **ventricular flutter**. This stimulation occurred for **AV Block 2 h**.

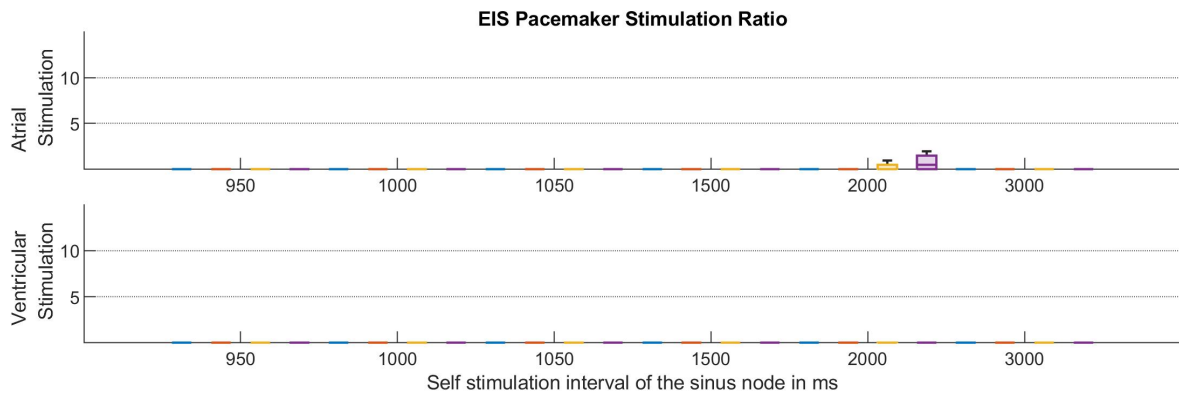


Figure 9.30: Non-essential pacing pulses by the pacemaker into the **vulnerable phase** for **ventricular flutter**.

9.2.8 Summary and Discussion of the HIL Model

The heart model facilitates the realistic, real-time simulation of a range of diseases and failures affecting the ECSH of the human heart. The HIL setup in LabVIEW is capable of interacting with a commercial pacemaker in real time, while including a representation of the ECSH and the chamber activity. The results presented in Figure 9.9 and Figure 9.10 demonstrate that the time intervals generated by our heart model are comparable to those of a physician-annotated ECG. The aforementioned model enables the drawing of conclusions regarding the safety of patients with regard to the chamber activity. The model allows for the visualisation and analysis of malfunctions within various areas of the conduction system, either concurrently or independently. Furthermore, the model can be employed to examine borderline cases.

Incorporating a dynamic APD as a function of the pacing interval enables more precise prediction of the timing of status changes in the chamber, as illustrated in Figure 9.6. This is important to

- monitor the effectiveness of heart contractions due to the chamber coordination,
- monitor stimulation in the vulnerable phase and
- monitor the effectiveness of pacing pulses by the pacemaker.

The model is able to monitor both, the occurrence and duration of vulnerable phases and the synchronisation of the chamber activity in real time. Testing with the model revealed specific disease states and at particular stimulation intervals, in which the patient is at risk of adverse outcomes. These include

- life-threatening reduction in heart rate, as illustrated in Figure 9.11 - Figure 9.14,
- incoordinated contractions due to the chamber coordination which, shown in Figure 9.11 - Figure 9.14,
- stimulation in the vulnerable phase as demonstrated in Figure 9.15 and
- non-essential pacing pulses by the pacemaker shown in Figure 9.17.

The use of a HIL setup has enabled the identification of a number of critical scenarios that can occur in the interaction between the two entities. These scenarios were previously identified during pacemaker implantation in patients and subsequently documented in the medical literature. However, they can be investigated in greater detail on the basis of the generated data differentiated with regard to the different properties of the system.

9.3 Evaluation using the Formal Verification Model

The setup in UPPAAL incorporates the software-based heart model and the cardiac pacemaker model that has been described in Chapter 5 and Section 8.3. The electrical activity of the heart chamber, which the pacemaker is designed to interact with, is transmitted to the pacemaker via the corresponding broadcast channels of the electrodes. These broadcast channels are integrated for both directions, also recording the pacemaker's actions and feeding them back to the heart model, thereby establishing a closed loop between the two software-based models.

The UPPAAL framework is version 5.0.0, 2023-06-21, which involved the Java Development Kit 17, executed on a 2.90GHz Intel(R) Xeon(R) CPU E3-1535M v5 with 32 GB of memory.

9.3.1 Parameter Initialisation in the UPPAAL Model

In the process of data acquisition, the heart model and the pacemaker model are verified against the defined queries in order to ensure their accuracy and reliability in fulfilling the safety properties. The workflow of the aforementioned components in UPPAAL are illustrated in Figure 9.31.

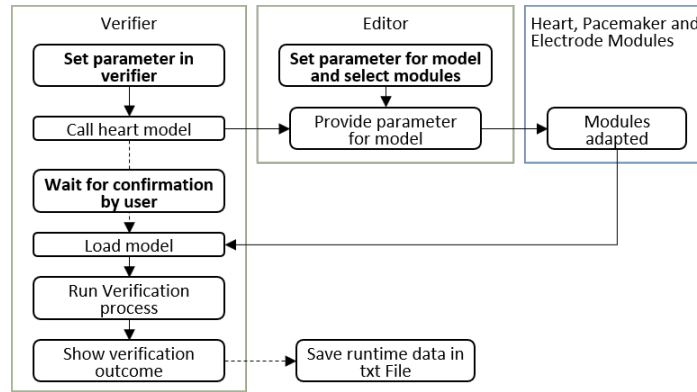


Figure 9.31: Procedure of the measurement.

The initial stage of the measurement procedure is to define the queries that will be employed in the verification process. The queries address the previously outlined safety concerns, detailed in Chapter 6 and implemented in Section 8.5 for UPPAAL. All heart and pacemaker parameters are loaded for the forthcoming measurement, as defined in the editor. The position of the pacemaker, SA node rhythm, abnormalities within the ECHS, and the reliability of replacement rhythms, as well as all pacing, conduction, blanking and refractory for the pacemaker, are all taken into consideration. Upon receiving confirmation from the user, the verification process is initiated. Verification involves the generation of a deterministic or probabilistic response, indicating whether the query was satisfied on the currently loaded heart, pacemaker and electrode modules and their current set of properties. Fluctuations in value during runtime can be represented graphically for subsequent analyses.

The initial parameters for the heart are presented in Figure 9.8. APD progression is achieved by the application of the formulas presented in Section 4.2, utilizing the parameters listed in Table 9.1a and Table 9.2b for all performed measurements. The setting for the intervals and rate boundaries of the pacemaker are summarised in Table 9.3a and Table 9.3b.

Table 9.3: List of model parameters used for the evaluation of the APD for the settings employed.

Table 9.3 a: Atrial connection module.

Category	Parameter	Wert
Interval until pacing	ssA	1050 ms
	ssV	1050 ms
Rate Boundaries	bpm_max	140 bpm
	bpm_min	50 bpm
Conduction Interval	av_dt	145 ms
Blanking Intervals	blank_A	35 ms
	blank_V	7 ms
Refractory Intervals	ref_A	300 ms
	ref_V	250 ms

Table 9.3 b: Atrial connection module.

Category	Parameter	Wert
Blanking Intervals	PVABP, PVABS	35 ms
	PAABP	125 ms
	PAVBP	7 ms
	PVVBP	11 ms
	PAABS	125 ms
	PVVBS	100 ms
Refractory Intervals	PAARP, PAARS, PVARs, PVARP	300 ms
	PAVRP, PVVRS, PVVRP	250 ms
Conduction interval	avc_P	300 ms
	avc_S	270 ms

9.3.2 Heart Rate Boundaries and Coordinated Contractions

The results of the verification queries, defined in Chapter 6 and implemented for UPPAAL in Section 8.5, regarding the heart rate boundaries and [coordinated contractions](#) are presented in Table 9.4. Within the table the characteristics of the heart model are structured in the columns, while the queries are displayed in the rows. The appendix provides a detailed account of the runtime and memory consumption for each individual query.

Table 9.4: Overview of the queries tested for the interaction of the heart and the pacemaker. The cells highlighted in green indicate that the query property has been met with a probability of ≥ 0.95 (95% CI), while the cells marked in red represent instances where the property has been fulfilled with a probability of ≤ 0.05 (95% CI).

Prob.	Short Name	Sinus Interval 950						Sinus Interval 1500						Sinus Interval 2500									
		healthy conduction	AV Block 1	AV Block 2 h	AV Block 2 w	AV Block 2 m	AV Block 3i	AV Block 3s	healthy conduction	AV Block 1	AV Block 2 h	AV Block 2 w	AV Block 2 m	AV Block 3i	AV Block 3s	healthy conduction	AV Block 1	AV Block 2 h	AV Block 2 w	AV Block 2 m	AV Block 3i	AV Block 3s	
		Without Pacemaker																					
Prop. 6.1.1	Minimal heart rate																						
Prop. 6.1.2	Maximal heart rate																						
Prop. 6.1.3	Coordinated Contractions																						
		With Double Chamber Pacemaker																					
Prop. 6.1.1	Minimal heart rate																						
Prop. 6.1.2	Maximal heart rate																						
Prop. 6.1.3	Coordinated Contractions																						
		With Single Chamber Pacemaker in the Atrium																					
Prop. 6.1.1	Minimal heart rate																						
Prop. 6.1.2	Maximal heart rate																						
Prop. 6.1.3	Coordinated Contractions																						
		With Single Chamber Pacemaker in the Ventricle																					
Prop. 6.1.1	Minimal heart rate																						
Prop. 6.1.2	Maximal heart rate																						
Prop. 6.1.3	Coordinated Contractions																						

The results presented in Table 9.4 demonstrate that the safety series for exceeding the maximum heart rate was successfully satisfied by each pacemaker at all states. Furthermore, the dual-chamber pacemaker heart interaction was able to satisfy all three safety requirements. The heart model on it's own was unable to achieve the minimum required heart rate for the [atrium](#) and [ventricle](#) in the absence of a pacemaker. Even our single-chamber pacemakers are only capable of generating the necessary heart rate in both chambers for a healthy conduction or an [first-degree AV block](#). In cases of more severe conduction blockages, from second-degree AV blocks onwards, the property is satisfied for both chambers.

In the absence of the requisite contractions in one of the chambers, our single-chamber pacemakers are unable to maintain the optimal beats per minute. However, there is a distinction between the pacemaker positioning: Atrial stimulation by the pacemaker in combination with a low [SA node](#) rate allows for the maintenance of both atrial and ventricular rates, as well as the number of [coordinated contractions](#) for a healthy conduction system. Conversely, ventricular stimulation by the pacemaker in combination with a low [SA node](#) rate enables the maintenance of the chambers rates, but lacks [coordinated contractions](#).

9.3.3 Sensing and Pacing by the Pacemaker

Table 9.5 shows the evaluation of the safety requirements, defined in Chapter 6 and adapted for UPPAAL in Section 8.5.

Table 9.5: Overview of the queries tested for the interaction of the heart and the pacemaker regarding the sensed and paced stimulations by the pacemaker. The cells highlighted in green indicate that the query property has been met with a probability of ≥ 0.95 (95% CI). Cells marked in light green represent instances where the property has been fulfilled with a probability of ≤ 0.05 (95% CI) and the occurrence of the property is to be excluded. The values indicated in white do not correspond to a definitive answer.

Prob.	Short Name	Sinus Interval 950 healthy conduction AV Block 1 AV Block 2 h AV Block 2 w AV Block 2 m AV Block 3i AV Block 3s	Sinus Interval 1500 healthy conduction AV Block 1 AV Block 2 h AV Block 2 w AV Block 2 m AV Block 3i AV Block 3s	Sinus Interval 2500 healthy conduction AV Block 1 AV Block 2 h AV Block 2 w AV Block 2 m AV Block 3i AV Block 3s
Without a Pacemaker				
Prop. 6.1.4	Vulnerable Phase			
With Double Chamber Pacemaker				
Prop. 6.1.4	Vulnerable Phase			
Prop. 6.2.1	Sensed/ Paced bpm - Minimal			
Prop. 6.2.2	Sensed/ Paced bpm - Maximal			
Prop. 6.2.3	Non-Essential Pacemaker Pulses			
With Single Chamber Pacemaker in the Atrium				
Prop. 6.1.4	Vulnerable Phase			
Prop. 6.2.1	Sensed/ Paced bpm - Minimal			
Prop. 6.2.2	Sensed/ Paced bpm - Maximal			
Prop. 6.2.3	Non-Essential Pacemaker Pulses			
With Single Chamber Pacemaker in the Ventricle				
Prop. 6.1.4	Vulnerable Phase			
Prop. 6.2.1	Sensed/ Paced bpm - Minimal			
Prop. 6.2.2	Sensed/ Paced bpm - Maximal			
Prop. 6.2.3	Non-Essential Pacemaker Pulses			

The safety requirements pertaining to the minimum and maximum values recorded by the pacemaker module were met in each instance. However, this is not the case with regard to the safety test for stimulation in the **vulnerable phase**. It is important to note that the probability of stimulation in the **vulnerable phase** is already present even in the absence of a pacemaker. Nevertheless, the probability of stimulation during the **vulnerable phase** is greater when the atrial pacing model is included than when it is absent.

9.3.4 Variances in QT

Table 9.6 contains the results of the verification queries, defined in Chapter 6 and implemented for UPPAAL in Section 8.5, regarding the heart rate boundaries and **coordinated contractions**, in conjunction with the prolonged **QT interval**. Within the table the characteristics of the heart model are structured in the columns, while the queries are displayed in the rows. The appendix provides a detailed account of the runtime and memory consumption for each individual query.

The evaluation of the safety queries with the inclusion of an extended **QT interval** yields the same results as those observed for the shortened **QT interval**.

Table 9.6: Overview of the queries tested for the interaction of the heart and the pacemaker regarding the sensed and paced stimulations by the pacemaker. The cells highlighted in green indicate that the query property has been met with a probability of ≥ 0.95 (95% CI), while the cells marked in red represent instances where the property has been fulfilled with a probability of ≤ 0.05 (95% CI). Cells marked in light green represent instances where the property has been fulfilled with a probability of ≤ 0.05 (95% CI) and the occurrence of the property is to be excluded. The values indicated in white do not correspond to a definitive answer.

Prob.	Short Name	Sinus Interval 950						Sinus Interval 1500						Sinus Interval 2500								
		healthy conduction	AV Block 1	AV Block 2 h	AV Block 2 w	AV Block 2 m	AV Block 3i	AV Block 3s	healthy conduction	AV Block 1	AV Block 2 h	AV Block 2 w	AV Block 2 m	AV Block 3i	AV Block 3s	healthy conduction	AV Block 1	AV Block 2 h	AV Block 2 w	AV Block 2 m	AV Block 3i	AV Block 3s
		Without Pacemaker																				
Prop. 6.1.1	Minimal heart rate																					
Prop. 6.1.2	Maximal heart rate																					
Prop. 6.1.3	Coordinated Contractions																					
		With Double Chamber Pacemaker																				
Prop. 6.1.1	Minimal heart rate																					
Prop. 6.1.2	Maximal heart rate																					
Prop. 6.1.3	Coordinated Contractions																					
		With Single Chamber Pacemaker in the Atrium																				
Prop. 6.1.1	Minimal heart rate																					
Prop. 6.1.2	Maximal heart rate																					
Prop. 6.1.3	Coordinated Contractions																					
		With Single Chamber Pacemaker in the Ventricle																				
Prop. 6.1.1	Minimal heart rate																					
Prop. 6.1.2	Maximal heart rate																					
Prop. 6.1.3	Coordinated Contractions																					
		Without a Pacemaker																				
Prop. 6.1.4	Vulnerable Phase																					
		With Double Chamber Pacemaker																				
Prop. 6.1.4	Vulnerable Phase																					
Prop. 6.2.1	Sensed/ Paced bpm - Minimal																					
Prop. 6.2.2	Sensed/ Paced bpm - Maximal																					
Prop. 6.2.3	Non-Essential Pacemaker Pulses																					
		With Single Chamber Pacemaker in the Atrium																				
Prop. 6.1.4	Vulnerable Phase																					
Prop. 6.2.1	Sensed/ Paced bpm - Minimal																					
Prop. 6.2.2	Sensed/ Paced bpm - Maximal																					
Prop. 6.2.3	Non-Essential Pacemaker Pulses																					
		With Single Chamber Pacemaker in the Ventricle																				
Prop. 6.1.4	Vulnerable Phase																					
Prop. 6.2.1	Sensed/ Paced bpm - Minimal																					
Prop. 6.2.2	Sensed/ Paced bpm - Maximal																					
Prop. 6.2.3	Non-Essential Pacemaker Pulses																					

9.3.5 Diseased Rate Generation Modules

Table 9.7 presents a summary of the results pertaining to the pacemaker side of the pacemaker heart interaction for the safety queries, including [PAC](#), [PVC](#), atrial and ventricular [flutter](#) within the heart model.

Table 9.7: Overview of the queries tested for the interaction of the heart and the pacemaker regarding the sensed and paced stimulations by the pacemaker. The cells highlighted in green indicate that the query property has been met with a probability of ≥ 0.95 (95% CI). Cells marked in light green represent instances where the property has been fulfilled with a probability of ≤ 0.05 (95% CI) and the occurrence of the property is to be excluded. The values indicated in white do not correspond to a definitive answer.

Prob.	Short Name	Sinus Interval 950 healthy conduction AV Block 1 AV Block 2 h AV Block 2 w AV Block 2 m AV Block 3i AV Block 3s	Sinus Interval 1500 healthy conduction AV Block 1 AV Block 2 h AV Block 2 w AV Block 2 m AV Block 3i AV Block 3s	Sinus Interval 2500 healthy conduction AV Block 1 AV Block 2 h AV Block 2 w AV Block 2 m AV Block 3i AV Block 3s
Without a Pacemaker				
Prop. 6.1.4	Vulnerable Phase			
With Double Chamber Pacemaker				
Prop. 6.1.4	Vulnerable Phase			
Prop. 6.2.1	Sensed/ Paced bpm - Minimal			
Prop. 6.2.2	Sensed/ Paced bpm - Maximal			
Prop. 6.2.3	Non-Essential Pacemaker Pulses			
With Single Chamber Pacemaker in the Atrium				
Prop. 6.1.4	Vulnerable Phase			
Prop. 6.2.1	Sensed/ Paced bpm - Minimal			
Prop. 6.2.2	Sensed/ Paced bpm - Maximal			
Prop. 6.2.3	Non-Essential Pacemaker Pulses			
With Single Chamber Pacemaker in the Ventricle				
Prop. 6.1.4	Vulnerable Phase			
Prop. 6.2.1	Sensed/ Paced bpm - Minimal			
Prop. 6.2.2	Sensed/ Paced bpm - Maximal			
Prop. 6.2.3	Non-Essential Pacemaker Pulses			

The data presented in the table demonstrate that the pacemaker in question meets the set of criteria demanded in the safety queries. The only exception is the safety query regarding the [vulnerable phase](#) for the [AV Block 2 m](#). The corresponding query could not be formally verified due to the occurrence of a [state explosion](#).

Premature Atrial Contractions and Premature Ventricular Contractions

Table 9.8 shows the results of the [PAC](#) and [PVC](#) integration within the pacemaker model, applied to the safety queries delineated in Chapter 6 and implemented for [UPPAAL](#) in Section 8.5, regarding the heart rate boundaries and [coordinated contractions](#).

Table 9.8: Overview of the queries tested for the interaction of the heart and the pacemaker. The cells highlighted in green indicate that the query property has been met with a probability of ≥ 0.95 (95% CI), while the cells marked in red represent instances where the property has been fulfilled with a probability of ≤ 0.05 (95% CI).

Prob.	Short Name	Sinus Interval 950	Sinus Interval 1500	Sinus Interval 2500
		healthy conduction AV Block 1 AV Block 2 h AV Block 2 w AV Block 2 m AV Block 3i AV Block 3s	healthy conduction AV Block 1 AV Block 2 h AV Block 2 w AV Block 2 m AV Block 3i AV Block 3s	healthy conduction AV Block 1 AV Block 2 h AV Block 2 w AV Block 2 m AV Block 3i AV Block 3s
Without Pacemaker				
Prop. 6.1.1	Minimal heart rate			
Prop. 6.1.2	Maximal heart rate			
Prop. 6.1.3	Coordinated Contractions			
With Double Chamber Pacemaker				
Prop. 6.1.1	Minimal heart rate			
Prop. 6.1.2	Maximal heart rate			
Prop. 6.1.3	Coordinated Contractions			
With Single Chamber Pacemaker in the Atrium				
Prop. 6.1.1	Minimal heart rate			
Prop. 6.1.2	Maximal heart rate			
Prop. 6.1.3	Coordinated Contractions			
With Single Chamber Pacemaker in the Ventricle				
Prop. 6.1.1	Minimal heart rate			
Prop. 6.1.2	Maximal heart rate			
Prop. 6.1.3	Coordinated Contractions			

The results demonstrate that there is no difference in the interaction between heart and pacemaker with and without the presence of PACs and PVCs. This indicates that the interaction between the cardiac pacemaker and the heart model remains unaffected by the [PAC](#) and the [PVC](#).

Atrial and Ventricular Flutter

Table 9.9 demonstrates the results of atrial and ventricular **flutter** integrated within the pacemaker model, applied to the safety queries delineated in Chapter 6 and implemented for UPPAAL in Section 8.5, regarding the heart rate boundaries and **coordinated contractions**.

The results for atrial and ventricular **flutter** differ from those described above. Due to the high number of beats, the respective chamber stimulated by **flutter** is contracted independently of the frequency of the **SA node** node and the signals, throttled by the **AV node**, are transmitted to the other chamber. Accordingly, the number of maximum stimulations is fulfilled for all chambers. It can be observed that the minimum stimulation number is not fulfilled for each chamber, as the flooding of the chamber resulting from the **ECSH** already exceeds the minimum stimulation number.

Table 9.9: Overview of the queries tested for the interaction of the heart and the pacemaker. The cells highlighted in green indicate that the query property has been met with a probability of ≥ 0.95 (95% CI), while the cells marked in red represent instances where the property has been fulfilled with a probability of ≤ 0.05 (95% CI).

Prob.	Short Name	Sinus Interval 950						Sinus Interval 1500						Sinus Interval 2500									
		healthy conduction	AV Block 1	AV Block 2 h	AV Block 2 w	AV Block 2 m	AV Block 3i	AV Block 3s	healthy conduction	AV Block 1	AV Block 2 h	AV Block 2 w	AV Block 2 m	AV Block 3i	AV Block 3s	healthy conduction	AV Block 1	AV Block 2 h	AV Block 2 w	AV Block 2 m	AV Block 3i	AV Block 3s	
		Without Pacemaker																					
Prop. 6.1.1	Minimal heart rate																						
Prop. 6.1.2	Maximal heart rate																						
Prop. 6.1.3	Coordinated Contractions																						
		With Double Chamber Pacemaker																					
Prop. 6.1.1	Minimal heart rate																						
Prop. 6.1.2	Maximal heart rate																						
Prop. 6.1.3	Coordinated Contractions																						
		With Single Chamber Pacemaker in the Atrium																					
Prop. 6.1.1	Minimal heart rate																						
Prop. 6.1.2	Maximal heart rate																						
Prop. 6.1.3	Coordinated Contractions																						
		With Single Chamber Pacemaker in the Ventricle																					
Prop. 6.1.1	Minimal heart rate																						
Prop. 6.1.2	Maximal heart rate																						
Prop. 6.1.3	Coordinated Contractions																						

9.3.6 Pacemaker Characteristics

Table 9.10 contains the results that show successful fulfillment of the safety requirements (Chapter 6 and 8.5) concerning the internal pacemaker procedure. The results presented in Table 9.10 can be classified into two categories: events that are required to occur in every case and events that should be avoided under any circumstances. The latter are indicated by the annotation 'must not be satisfied'. As single-chamber pacemaker models are modules of dual-chamber pacemaker models, with the specific configuration that the other pacemaker modules are deactivated and only the module with the appropriate electrode is utilized, the criteria for single-chamber pacemakers have not been verified separately. This is because the fulfillment of the criteria for dual-chamber pacemakers inherently encompasses the fulfillment of the criteria for single-chamber pacemakers.

Table 9.10: Overview of the queries tested for the pacemaker workflow. The cells highlighted in green indicate that the query property has been met with a probability of ≥ 0.95 (95% CI). Cells marked in light green represent instances where the property has been fulfilled with a probability of ≤ 0.05 (95% CI) and the occurrence of the property is to be excluded.

Prob.	Short Name	Results
Prop. 6.2.4	Vulnerable Phase Protection Interval Duration	
Prop. 6.2.5	Termination of the Minimal Interval until Chamber Stimulation	must not be satisfied
Prop. 6.2.6	Termination of the Maximal Interval until Chamber Stimulation	must not be satisfied
Prop. 6.2.7	Expiration of the Maximal Interval until Chamber Stimulation	
Prop. 6.2.8	Termination of the Vulnerable Phase Protection Interval	
Prop. 6.2.9	Onset of the Blanking Interval - After High Pulse	must not be satisfied
Prop. 6.2.10	Onset of the Blanking Interval - Atrial Blanking after Atrial EIS	
Prop. 6.2.11	Reset of Blanking/ Refractory Clocks - Reset after high Pulse	must not be satisfied
Prop. 6.2.12	Reset of Blanking/ Refractory Clocks - Atrial Reset after Atrial EIS	must not be satisfied
Prop. 6.2.13	Minimal Conducted Pacemaker Stimulation per Minute	
Prop. 6.2.14	Maximal Conducted Pacemaker Stimulation per Minute	
Prop. 6.2.15	Conduction Time Adaption - After Sensing	
Prop. 6.2.16	Conduction Time Adaption - After Pacing	
Prop. 6.2.17	Vulnerable Phase Protection Interval Termination due to Conduction	
Prop. 6.2.18	Mode Switch - On and Offset	

As indicted by Table 9.10, our dual-chamber pacemaker meets the previously established safety criteria pertaining to scheduling, resetting, and adjusting of intervals. The queries for the events that have to occur with a probability of ≥ 0.95 (95% CI), as indicated by their green marking in the table. Furthermore, all events that must not occur have a probability of occurrence of ≤ 0.05 (95% CI).

9.3.7 Summary and Discussion of the Formal Verification Model

The results of the formal verification indicate promising outcomes for the pacemaker model including the calculation of the **vulnerable phase** based on the formulas presented in Section 4.2.3. The results for **AV Block 2 m** indicate an increased probability of pacing into the **vulnerable phase**. However, it should be noted that **AV Block 2 m** tends to stimulate into the **vulnerable phase** even in the absence of a pacemaker, due to the spontaneous, erratic conduction of stimuli, as exemplified by the results presented in Table 9.5.

Moreover, the pacemaker model developed for the dual-chamber pacemaker demonstrates satisfying results with regard to the minimum and maximum frequency of the **atrium** and **ventricle**, as well as the coordination of cardiac contractions. The single-chamber pacemakers, components of a dual-chamber pacemaker, demonstrate limitations with regard to both the minimum heart rate and the coordination of ventricular contractions. With regard to the coordination of contractions, the atrial pacemaker is superior to the ventricular pacemaker for a healthy **ECSH** or an **AV Block 1**.

The safety queries for the pacemaker workflow were satisfied without any objections. The probability of events that had to occur was fulfilled, while the probability of events that were not allowed to occur was very unlikely. The single-chamber pacemaker models are modules of the dual-chamber pacemaker model. In this configuration, the other pacemaker modules are deactivated, and only the module with the appropriate electrode is utilized. The criteria for single-chamber pacemakers have not been developed because the fulfillment of the criteria for dual-chamber pacemakers inherently encompasses the fulfillment of the criteria for single-chamber pacemakers.

The pacemaker models developed have been found to be suitable for use as single-chamber atrial pacemakers for the treatment of low [SA node](#) rates in combination with healthy or slightly slower [ECSH](#) such as the [AV Block 1](#). The dual-chamber pacemaker has been shown to fulfil the criteria for all diseases except of the [AV Block 2 m](#), in which the pacemaker has been found to have difficulty in predicting the [vulnerable phase](#).

9.4 Comparison of the HIL and the Formal Verification Model

The results obtained from the test model and the verification model differ in their nature. This dissimilarity in the types of results is discussed in the following section, along with an investigation into the limitations of the heart model and the limitations of our heart models in [LabVIEW](#) and [UPPAAL](#).

Results for the Hardware-in-the-Loop Approach

The tests conducted with the [HIL](#) model have presented certain risks, particularly in relation to the stimulation of [vulnerable phases](#) and the occurrence of incoordinated contractions. The results are based on run time data collected at defined time intervals in real time. Hereby,

- the dataset includes the data for a fixed number of measurements conducted over a defined period of time and
- the measured values are averaged over specific time intervals or documented individually. Consequently, the results are concrete and physically tangible.

The [HIL](#) model is particularly suited to the testing of defined test phases and the detailed observation of the pacemaker's behaviour over different periods of time. Furthermore, the results can be visualised, thereby facilitating the comprehension of the observed behaviour.

Results for the Formal Verification

The outcome of statistical model checking concerns the probability of specific occurrences across a range of potential scenarios or pathways that would exceed the number of test runs conducted in real time within the [HIL](#) mode, for the aforementioned risks. Hereby,

- the results are generated across a range of potential scenarios or pathways that would exceed the number of test runs conducted in real time within the [HIL](#) model and
- a binary output, indicates whether a specific requirement is satisfied or not.

Formal verification is particularly well-suited for an analysis of entire time periods, thereby enabling the assessment of whether safety requirements are met under all possible conditions. The model does not focus on the consideration of individual values or intervals; rather, it assesses the overall correctness over a longer period of time.

Comparison of the Generated Results

In conclusion, the [HIL](#) heart model provides valuable insights into the physical behaviour of the heart, enabling detailed observations of individual phases and outcomes of the interaction. Formal verification ensures that the individual systems of the heart and the pacemaker and the bioelectric system, when considered together, meet the defined requirements under all possible conditions (with a certain probability). The incorporation of probabilistic elements within the model precludes the possibility of a deterministic verification process in [UPPAAL](#).

9.4.1 Model Boundaries

The existing cardiac model is constrained in terms of the diseases that can be modeled and the interactions with the environment. These limitations are outlined below, along with an identification of the potential future improvements that could be realized through future integration of these factors.

Diseases The present model is unable, to represent [tachycardias](#) such as fibrillation, which thus renders it unsuitable for testing purposes involving defibrillators. Additionally, the model is incapable of illustrating the consequences of tissue damage and myocardial infarction, as it lacks the capacity to incorporate tissue structure into its modeling.

Threshold Values Moreover, in a real interaction between a pacemaker and a heart, hardware specific components, such as a necessary stimulus threshold and a voltage waveform, are included in the interpretation of electrical signals as heart signals. In the model presented here, the premise used for signals entering the pacemaker is that the transmitted signals have met these requirements. Similarly, for the stimulation of the [myocardium](#), this model assumes that it has exceeded the stimulation threshold necessary for stimulation of the [myocardium](#).

External Influences Currently, the modelling process does not incorporate external influences, such as vibrations, temperature fluctuations and electromagnetic fields. Although these factors are not included in the direct heart, they could be employed as a valuable testing parameter for the safety of the heart and pacemaker interaction, as their impact can be an important factor in the pacemaker's workflow. It may also be possible to incorporate some of the aforementioned environmental factors into the pacemaker model, in order to facilitate a superior adaptation process regarding the pacemaker generated heart rate.

9.4.2 Model Boundaries of the HIL Model

The hardware in the loop model is constrained to the specified tests and is therefore unable to assess state spaces. Consequently, the identification of stochastic or infrequent faults that may only manifest themselves under particular conditions is more challenging, as the pertinent parameters must be employed explicitly.

Furthermore, the software-hardware interface is currently configured to communicate only with single-chamber pacemakers due to the lack of input and output for a second chamber. Extending this area of inquiry would permit the capture of a broader array of failure scenarios.

9.4.3 Model Boundaries of the Formal Verification Model

The formal verification model permits the utilisation of more extensive ranges for the properties, thereby facilitating accelerated testing. However, this approach also gives rise to the state space explosion problem that arises when modelling very large systems. Due to the probabilistic parts of the heart model, it is not possible to verify the system deterministically without provoking a state space problem.

An advantage of formal verification is the unlimited possibility of input sources, in contrast to the [HIL](#) approach, where input elements are constrained by the hardware, provided that it cannot be modelled at a software level. However, the precise mapping of the environment, offers a limitation with respect to the abstraction of physical elements. In regard to signals entering the pacemaker, it is assumed that the transmitted signals have met the requisite criteria. Similarly, with respect to the stimulation of the [myocardium](#), this model assumes that the necessary stimulation threshold for the [myocardium](#) has been exceeded. Although the [HIL](#) model allows for the replication of this phenomenon through the use of circuits, tissue mimics, and voltage curves, the formal model inevitably exhibits a greater degree of abstraction than the [HIL](#) model.

Conclusion and Perspective

The system model presented in this thesis and in our paper [122] is capable of simulating the heart and testing its interaction with a pacemaker. This provides a suitable framework for the validation and verification of pacemakers in long-term experiments. The results presented in Figure 9.1 demonstrate that our calculations for adapting the APD to changing pacing intervals are comparable to the empirical measurements on the human heart reported in [123]. By dynamically adjusting the APD as a function of the pacing interval, it is possible to make more precise predictions about the timing of state changes in the ventricles, as illustrated in Figure 9.6. To the best of our knowledge, previous models lacked the capacity to monitor the different phases of the ventricles while interacting with a pacemaker. The presented model, however, enables monitoring of both the occurrence and duration of vulnerable phases and provides a method for evaluating the synchronization of ventricular activity in conjunction with a real pacemaker. Furthermore, the model is capable of performing more complex pulse patterns of a wider range of conditions over different time periods.

The model was successfully transferred into a HIL model and a formal verification model. Tests were performed on both of the models evaluating the safety criteria previously defined. The ECSH and ventricles were successfully simulated in order to test the model's functionality in response to different disease cases.

Hardware-in-the-Loop Setup To the best of our knowledge, previous models lacked the capacity to monitor the distinct phases of the ventricles in real time, which is a precondition for testing commercial pacemakers. The presented model facilitates the real-time monitoring of both the occurrence and duration of vulnerable phases and provides a methodology for the detection of synchronization of ventricular activity in conjunction with a real pacemaker. Moreover, the model is capable of conducting more intricate simulations of a broader spectrum of scenarios over varying time spans. Figures 9.9 and 9.10 illustrate that the time intervals generated by the heart model are comparable to those of an ElectroCardioGram (ECG) annotated by a physician.

The results of the tests with the HIL model demonstrate deficiencies in the commercial pacemaker employed with regard to the generated beat rate, the achieved coordination of the chambers and the vulnerable phase. This indicates that this type of pacemaker is not suitable for all diseases. Test runs with the heart model have demonstrated that in specific disease, states and stimulation intervals patients are susceptible to adverse outcomes including a potentially life-threatening reduction in the number of beats per minute. We also identified occurrences of stimulations into the vulnerable phase and non-essential pacing pulses.

The interaction of the heart model with a pacemaker in the HIL setup revealed a number of critical scenarios potentially occurring in the interaction between the two entities. These scenarios were previously identified during pacemaker implantation in patients and are documented in the medical literature. This very clearly demonstrates the value of pacemaker tests employing computer models.

Formal Verification The pacemaker model developed for formal verification exhibits comparable deficiencies with regard to the safety queries for our single-chamber pacemaker model to those observed in the tests with in a single-chamber pacemaker by the [HIL](#) model. However, it exhibits advantages over the commercial pacemaker in as it does not emit stimulations during the [vulnerable phase](#), with the exception of runs including the [AV Block 2 m](#). Furthermore, the dual-chamber pacemaker model demonstrates the ability to address pathologies that are beyond the scope of the single-chamber model.

10.1 Model Boundaries

The model is currently unable to represent fibrillation, which renders it unsuitable for testing with defibrillators. Furthermore, the model is similarly unable to visualize the effects of tissue damage and myocardial infarction due to the absence of tissue structure in the underlying modeling. With regard to implementation, the software-hardware interface is currently configured for single-chamber pacemakers only, due to the lack of input and output for a second chamber. Extension of this interface would facilitate the inclusion of a wider range of failure scenarios in testing. Moreover, the [HIL](#) approach is constrained by the necessity for repeated measurements of newly introduced [APD](#) parameters. Although the verification model has the capacity to incorporate bandwidth into the testing process, it lacks the capability to interact with a genuine pacemaker or to operate in real-time.

10.2 Outlook

Part of the future work is to optimize the model in terms of the requisite run-time and storage capacity. Furthermore, additional risk cases will be incorporated into the study of risk determination and risk prevention algorithms employed by pacemakers. For instance, we will examine the possibility of adjusting both the pacing rate and the ventricular conduction rate on an individual basis.

In order to accommodate various conditions of the patient, multiple approaches have been developed. These approaches are presented in Chapter 2. However, these models do not include the complete [ECSH](#) and all four heart chambers. Therefore, these models do not include all parameters required to evaluate the safety queries, to ensure a safe interaction between the heart and the pacemaker.

Extensions of the Framework

The environments for the [HIL](#) and the formal verification model can be enhanced in order to optimize the requisite run-time, the storage capacity, the executability and complexity of the developed heart and pacemaker models.

Hardware-in-the-Loop The environment for the [HIL](#) can be optimized by developing a portable system [HIL](#) environment that permits the pacemaker in the [HIL](#) to take into account supplementary influencing factors, such as vibrations and movements. This would facilitate the testing of a range of frequency adaptation limits, thus providing a more comprehensive evaluation of the system's performance.

Formal Verification The environment for formal verification can be further improved by the implementation of a user-friendly interface that facilitates the input of data for the models. Furthermore, the development of an effective method for reducing the state space would be beneficial in enabling the execution of queries for safety verification in more complex scenarios, such as the occurrence of stimuli during the [vulnerable phase](#) for [AV Block 2 m](#).

Extensions of the Heart Model

Further research is required to extend the heart model to simulate additional physiological states and to verify different pacemaker models. Additional diseases which could extend the model for more purposes are:

AV Nodal Re-entrant Tachycardia AV nodal re-entrant [tachycardia](#) is a circulating pulse conduction in the region of the [AV node](#), resulting from the existence of two distinct paths through the [AV node](#). This phenomenon entails the repeated traversal of the electrical pulses through the [AV node](#) in a circulating manner, thereby stimulating the [atrium](#) and the [ventricle](#).

The AV nodal re-entry [tachycardia](#) can be modeled by two discrete conduction modules. One module exhibits fast conduction and a long refractory period, while the other module displays slow conduction and a short refractory period. Both the fast and slow modules are capable of conducting both [anterograde](#) and [retrograde](#) pulses, thereby enabling the modeling of both circulation directions.

Atrial and Ventricular Fibrillation In order to model [atrial fibrillation](#) respectively [ventricular fibrillation](#), an additional state can be integrated into the chambers. This state represents the randomly circulating activity of the corresponding chamber and the inability of the chamber to contract efficiently. Accordingly, it is not possible to reach a state of separate [systole](#) and [diastole](#) from the fibrillation state while the variable containing the criteria for fibrillation remains true.

However, the module can revert to normal chamber mode if the variable for fibrillation is set to false. This differentiation based on the duration of fibrillation is necessary, as a fibrillation episode lasting up to 30 seconds is benign, whereas a longer episode is life-threatening.

AV Node The physical examination of the correlation between the heart rate and the [PR interval](#) by [127] revealed a negative linear correlation between these two parameters for heart rates above 60 bpm. Nevertheless, [127] posits that individuals are so inherently disparate that it is challenging to formulate a unified assertion regarding the linear interdependence of the heart rate and the [PR interval](#).

The extension of the heart model to include the adaptation of the [AV node](#) for higher frequencies enables comprehensive testing of the chamber frequencies under load — when an increased heart rate is required. This allows for further development of rate adaptation procedures.

Extensions of the Pacemaker Model

Furthermore, the pacemaker model can be developed further to facilitate a further improved adaptation of the pacemakers to the diverse conditions that can arise in the human heart.

Algorithms and Modes The pacemaker models can be extended to incorporate a night mode, an energy-saving mode, and sufficient adaptation to diverse influences, including hormonal fluctuations, movement, and other physiological characteristics.

Interface - Sensing and Pacing An additional element that could be incorporated into the model is the introduction of supplementary interference pulses with varying pulse shapes. This would enable the testing of electromagnetic, magnetic and through-and-motion pulses from diverse sources up to their respective limits.

10.3 Final Conclusion

In conclusion, the combination of hardware-in-the-loop modeling and formal verification has been demonstrated to be an effective method for verifying the functional safety of pacemakers, thereby opening up new avenues for the development of more robust medical devices.

Moreover, the model is to be evaluated with a view on improving future adaptive pacemakers and on demonstrating its potential to support their development. The objective is to illustrate the advantages of utilizing standardized models for the purposes of validation and verification, and to facilitate the early detection of errors during the development of new software and hardware components. This approach facilitates the safer design of smart medical products and streamlines the development process.

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Glossar

β blocker β blockers are medications that inhibit the effect of adrenaline and noradrenaline in the body. Clinical applications include the treatment of hypertension, cardiovascular disease, anxiety disorders, and other conditions. However, these agents have been associated with adverse effects, including the potential for prolongation of the QT interval and an increased risk of arrhythmia. [17](#), [19](#)

510(k) A 510(k) submission is an approval process for a medical device that is comparable to an existing product on the market, by the FDA. [30](#)

anterograde Conduction direction of a stimulation pulse transmitted through the electrical conduction system - from top to bottom. [6](#), [8–10](#), [51](#), [55](#), [59](#), [86](#), [88](#), [102](#), [104–108](#), [151](#)

atrial fibrillation Atrial fibrillation is a cardiac arrhythmia characterized by irregular and excessive atrial contraction. The resulting irregular heart rhythm can manifest as palpitations, weakness and dizziness. Furthermore, the risk of stroke and a range of other adverse outcomes is elevated. [17](#), [18](#), [26](#), [79](#), [151](#)

atrial flutter Atrial flutter is a rapid and regular atrial rhythm that can result in a range of symptoms, including palpitations, weakness, dyspnea and thromboembolism. [18](#), [59](#), [88](#), [104](#), [105](#), [133](#), [170](#), [172](#)

atrioventricular valve The atrioventricular valves connect the atria with their respective [ventricles](#). They are opened and closed depending on the shape and thus the contraction status of the respective [ventricle](#). [v](#), [2](#), [14](#), [100](#), [102](#)

atrium The atria are the upper chambers on either side of the heart. They facilitate the connection between the incoming blood vessels from the body and the lungs with the [ventricles](#). Their contractions can increase the blood volume in the [ventricle](#). [8](#), [10](#), [13–15](#), [17](#), [18](#), [20–24](#), [26](#), [28](#), [29](#), [45–48](#), [50](#), [53](#), [59](#), [66–73](#), [75](#), [77–79](#), [83–85](#), [88](#), [97–101](#), [105](#), [109–113](#), [115](#), [120](#), [124–126](#), [128](#), [131–134](#), [138](#), [144](#), [151](#), [168](#), [169](#), [171](#), [172](#), [179–181](#)

bandpass filter A band-pass filter is a device that allows for the selective transmission of frequencies within a specified range, while rejecting those outside of that range, by narrowing the sensitivity across the frequency spectrum. [21](#), [25](#)

bradycardia Bradycardia is defined as a heart rate that is slower than is appropriate for the given situation. The term appropriate is thereby relative and depends on the context. For instance, the same heart rate may be appropriate for sleeping but too slow for exercise. [9–11](#), [17](#), [18](#), [58](#), [87](#), [103](#), [119](#), [169](#), [182](#)

bundle of his The bundle of His constitutes a component of the electrical conduction system, acting as a conduit between the [atrium](#) and the [ventricle](#). It is situated in a position inferior to the [AV node](#) and superior to the . [8](#), [15](#), [53](#), [89](#), [92](#), [105–108](#), [124](#), [170](#), [183](#)

cardiac arrest Cardiac arrest is defined as the absence of cardiac activity and blood flow, which ultimately results in organ failure and death. 18, 25, 26, 183

chronotropic incompetence A failure of the heart to increase its rate of contraction in response to heightened activity, such as that which results from sinus node impairment, frequently causes an inability to engage in physical exertion. 10, 18, 19, 28, 29, 58, 87, 103, 104

coordinated contractions In this thesis, the term "coordinated contractions" is defined as a series of timed contractions of the atrium and the ventricle. In this context, the atrium contracts while the AV valve is open, and this contraction is followed by a subsequent ventricular contraction occurring at a precisely timed interval. 10, 124–126, 138, 139, 142, 143

depolarization Depolarization represents the rising phase of the action potential, occurring when the voltage reaches the threshold value. It serves to transmit electrical impulses from nerve or muscle cells. For example, self-stimulation of the sinus node is based on spontaneous depolarization of the respective cells. 15, 27, 60, 101, 180, 182

diastole The diastole of the heart represents the relaxation and filling phase of the respective heart chamber. 14, 151, 180

ectopic node A type of tissue located in an atypical position within the organism. In the context of PAC and PVC, an ectopic node refers to an area of self-stimulating cells that, like the SA node, are capable of electrically stimulating the chamber in which they are situated. 17, 18, 59, 88, 105, 180

endocardium The endocardium represents the internal layer of cardiac tissue, situated within the chambers of the heart. 8

flutter Fluttering in the heart can occur in the atrium or in the ventricle. It refers to a rapid stimulation of the respective chamber by an additional self-stimulating node in the corresponding chamber. , 9, 10, 131, 141, 143

IDLE In the context of automata, the term IDLE is used to describe a state in which the model is in a waiting state. 46–48, 51, 52, 55, 56, 63–71, 84, 86, 90, 102–104, 180

invariant An invariant in UPPAAL represents a condition that a model must satisfy in order to remain in a specified location. In the event that the condition is no met (anymore), the model is either required to vacate the location or is prevented from entering it. 38, 41, 99, 103, 104, 110, 111

long QT Long QT syndrome represents a pathological condition affecting the repolarization of the heart following a cardiac cycle. This results in an abnormally prolonged QT interval, which in turn increases the risk of developing an irregular heartbeat. Such an arrhythmia may manifest as syncope, drowning, seizures or sudden death. 9, 10, 60, 89, 105, 130

metabolic The term metabolic is used to describe processes that arise from or are dependent on the metabolism. 28

mode switch The xyz description delineates the alterations in operational mode that a pacemaker is capable of performing in accordance with the prevailing parameters. 10, 11, 29, 69, 75, 79, 81, 111, 115, 176

myocardium The myocardial tissue, which constitutes the largest portion of the cardiac wall, is composed of striated muscle fibres. It is responsible for the rapid and powerful contraction of the heart. 8, 146, 147, 182, 187

notified body A Notified Body of the European Union is an organization that has been designated and monitored by the state. It acts on behalf of manufacturers to monitor and control the conformity assessment of manufacturers of various types of industrial products. 30

oversensing The term oversensing is used to describe a situation in which a pacemaker incorrectly identifies signals as originating from the heart, when these signals are unrelated to the heart's activity. 10, 11, 25, 26, 181

P wave The P wave is a reflection of the propagation of excitation throughout the atria of the heart. The device is employed for the purpose of assessing and quantifying the interval between atrial stimuli. 15, 16, 21, 26, 123, 171

pacemaker syndrome Pacemaker syndrome is a condition that arises when the atrium repeatedly contracts against a closed AV valve, resulting in the pumping of blood back into the blood vessels rather than into the ventricle. The range of symptoms associated with this condition can vary from mild discomfort and lightheadedness to more severe manifestations such as unconsciousness. 2, 6, 9–11, 27, 29, 50, 120

potential of Hydrogen The pH value is defined as the logarithm of the reciprocal of the hydrogen-ion concentration in gram atoms per liter. It is used to quantify the acidity or alkalinity of a solution on a scale from 0 to 14, with 7 representing neutrality and values above 7 indicating a more basic solution, and values below 7 indicating a more acidic solution. vi, 188

PR interval The PR distance represents the interval between the onset of the oversensing and the subsequent R wave. 15, 19, 151

PR segment The PR distance represents the interval between the end of the oversensing and the subsequent R wave. 15

Premature-Atrial-Contraction Premature atrial contractions are initiated by additional self-stimulating nodes in the atrium. They are seldom perceived as brief episodes of heart palpitations, occasionally followed by a brief pause. In some instances, however, extra beats are so frequent that they precipitate symptoms such as dizziness, nausea, anxiety and restlessness. vi, 17

Premature-Ventricular-Contraction Premature ventricular contractions are initiated by additional self-stimulating nodes in the atrium. They are seldom perceived as brief episodes of heart palpitations, occasionally followed by a brief pause. In some instances, however, extra beats are so frequent that they precipitate symptoms such as dizziness, nausea, anxiety and restlessness. vi, 17

purkinje fibers The purkinje fibers constitute a component of the electrical conduction system, acting as a conduit between the AV node and the [ventricle](#). It is situated in a position inferior to the [tawara bundle](#) and superior to the [myocardium](#) of the [ventricle](#). [15](#), [183](#)

Q wave The Q wave represents the initial component of the [QRS complex](#), as observed in an electrocardiogram. It is oriented in a direction opposite to that of the [R wave](#). The [Q wave](#) represents the initiation of the ventricular contraction. [182](#), [187](#)

QRS complex The QRS complex corresponds to the [depolarization](#) of both [ventricles](#) and is characterized by a sharply jagged configuration. [15](#), [182](#)

QT interval The [QT interval](#) encompasses the [QRS complex](#), [ST segment](#), and [T wave](#). Its duration correlates with that of ventricular [systole](#). It indicates the total duration of ventricular excitation. It is dependent on the heart rate and may precipitate cardiac arrhythmia if prolonged. , [11](#), [15](#), [16](#), [19](#), [60](#), [87–89](#), [105](#), [129–132](#), [139](#), [172](#), [182](#), [187](#)

QTc interval The QTc interval is used to identify [QT interval](#) intervals that are either excessively prolonged in comparison to the stimulation interval. [16](#), [60](#), [89](#), [105](#)

R wave The R wave represents the positive deflection in the electrocardiogram (ECG), which is part of the [QRS complex](#). The device is employed for the purpose of assessing and quantifying the interval between ventricular stimuli. [21](#), [26](#), [181](#), [182](#)

repolarization The process of [repolarization](#) is the restoration of the resting potential of a cell, in particular a nerve cell, through the redistribution of ions at the cell membrane. It is a physiological process that follows [depolarization](#). [15](#), [26](#), [60](#), [182](#), [183](#), [187](#)

retrograde Conduction direction of a stimulation pulse transmitted through the electrical condition system - from bottom to top. [6](#), [8–10](#), [17](#), [45](#), [51](#), [52](#), [55](#), [59](#), [86](#), [88](#), [102](#), [104–108](#), [151](#)

sick-sinus-syndrome A range of conditions that originate in the sinus node and manifest as cardiac arrhythmias. The spectrum of this phenomenon includes sinus [bradycardia](#) (after exclusion of other causes), sinoatrial block (intermittent [sinus arrest](#) or a complete block between the sinus node and atrial [myocardium](#)), or tachycardia-bradycardia syndrome (an alternation between supraventricular [tachycardia](#), systolic pauses, and sinus [bradycardia](#)). [18](#), [20](#)

sinus arrest Sinoatrial arrest is a medical condition characterized by the cessation of electrical pulses generated by the sinoatrial node of the heart. [9](#), [10](#), [18](#), [58](#), [182](#)

slew rate The slew rate describes the rate of change in voltage over time in volts per second (V/s). [21](#), [25](#)

ST segment The ST segment is an isoelectric line that extends from the end of the [QRS complex](#) to the beginning of the T wave. [15](#), [182](#)

state explosion The issue of state explosion arises due to the exponential growth in the size of the state space with the number of processes. [8](#), [36](#), [40](#), [141](#)

- systole** The systolic phase is characterized by contraction and subsequent expulsion of a heart chamber. The contraction of the chamber results in a change in its shape. 14, 46–48, 77, 80, 95, 98, 99, 101, 151, 182
- T wave** The T wave is the result of the relaxation of the [ventricles](#) during the process of repolarisation. 15, 21, 26, 182, 183, 187
- tachyarrhythmia** Tachyarrhythmia is defined as a combination of arrhythmia and [tachycardia](#), encompassing a range of cardiac arrhythmias. 26, 27, 47, 48, 120
- tachycardia** Tachycardia is defined as a heart rate that is faster than is appropriate for the given situation. The term appropriate is thereby relative and depends on the context. For instance, the same heart rate may be appropriate for exercise but too fast for sleeping. 9–11, 17, 27, 76, 146, 151, 182, 183
- tawara bundle** The tawara bundle constitutes a component of the electrical conduction system, acting as a conduit between the AV node and the [ventricle](#). It is situated in a position inferior to the [bundle of his](#) and superior to the [purkinje fibers](#) fibers. 8, 89, 92, 107, 108, 170, 179, 182
- undersensing** The term undersensing is employed to describe a scenario in which a pacemaker erroneously blocks or misinterprets signals as interfering, yet originating from the heart. 10, 25, 26
- UPPAAL** UPPAAL is a well-established framework for formal verification. 4, 13, 36, 39–43, 97, 98, 100, 102–104, 106–108, 114, 117, 136–139, 142, 143, 145, 167, 170, 175, 177, 180, 191
- ventricle** Lower chamber at each side of the heart. Their contractions are responsible for blood pressure and blood circulation through the body. 6, 8, 11, 13–18, 20–24, 26–29, 45–48, 50, 53, 65–73, 75, 78, 79, 81, 83, 85, 86, 93, 97, 99–102, 109–113, 115, 120, 124–126, 128, 131–135, 138, 144, 149, 151, 167–169, 171–173, 179–183, 194–201
- ventricle-vessel valve** The [ventricle](#)-vessel valves connect the [ventricle](#) and the following subsequent vessel. vii, 14, 99, 101, 102
- ventricular fibrillation** Ventricular fibrillation represents a life-threatening cardiac arrhythmia, characterized by the occurrence of uncoordinated excitations within the [ventricles](#). The resulting disorderly contraction of the heart muscle precludes the generation of a pulse. If left untreated, this arrhythmia leads to death within minutes. 2, 18, 25, 26, 151, 183
- ventricular flutter** Ventricular flutter is a rapid and regular ventricular rhythm that can progress to [ventricular fibrillation](#) or [cardiac arrest](#).. 18, 134, 135, 172
- vulnerable phase** The vulnerable phase represents a portion of the [repolarization](#) phase of the cardiac cycle, during which incoming excitation impulses have the potential to precipitate [ventricular fibrillation](#). In the ECG, the ascending part of the [T wave](#) serves as an indicator of this phase. , 2, 6, 8–11, 16, 26, 29, 47, 48, 50, 60, 64, 67, 72, 75–77, 79–81, 83, 84, 86, 95, 97–102, 105, 109–113, 115, 120, 126, 127, 129, 130, 132, 133, 135, 136, 139, 141, 144, 145, 149–151, 171–173, 193–201

Glossar Pacemaker Modes

- A00** Pacing in the atrium without sensing nor adaption to cardiac activity. [22](#), [29](#)
- AAI** Pacing and sensing in the atrium with adaption to atrial activity. The pacing pulse is inhibited if an atrial [EIS](#) is recognized. [22](#)
- AAIR** Pacing and sensing in the atrium with adaption to atrial activity and rate-adaption. The pacing pulse is inhibited if an atrial [EIS](#) is recognized. [22](#)
- AAT** Pacing and sensing in the atrium with adaption to atrial activity. The atrium is paced if an atrial [EIS](#) is recognized. [22](#)
- D00** Pacing in the atrium and in the ventricle without sensing nor adaption to cardiac activity. [29](#)
- DDD** Pacing and sensing in the atrium and in the ventricle with adaption to atrial and ventricular activity. After sensing or pacing in the atrium the pacemaker paces the ventricle. The pacing pulse in both chambers are inhibited if [EIS](#) are recognized. [23](#), [29](#)
- DDI** Pacing and sensing in the atrium and in the ventricle with adaption to atrial and ventricular activity. The pacing pulse in both chambers are inhibited if [EIS](#) are recognized. [29](#)
- V00** Pacing in the ventricle without sensing nor adaption to cardiac activity. [29](#)
- VDI** Pacing in the ventricle with sensing and adaption to atrial and ventricular activity. The pacing pulse in both chambers are inhibited if [EIS](#) are recognized. [29](#)

Adaptive Pacing Sensors



This section provides a more detailed description and overview of the various sensors utilized for load detection in rate adaptive pacing in Section 3.3.1.

Vibration Sensors The two most prevalent categories of motion sensors are piezoelectric sensors and accelerometers. Piezoelectric crystals, respectively accelerometers, integrated into pacemakers convert mechanical vibrations into electrical signals. Both are capable of adapting to rapid changes in their operational environment. However, these devices are limited in their ability to isolate body vibrations from external motion, since external vibrations (e.g. from streetcar) may result in misinterpretation as physical load, while opposite limitations are observed when the upper body is at rest during load. Furthermore, pacemakers equipped with piezoelectric sensors elevate the frequency improperly in response to external pressure. A further crucial limitation of vibration sensors is their minimal responsiveness to vegetative alterations and psychological distress, including emotional states.

Respiratory Monitoring The approach is based on the assumption of a proportional relationship between the [Respiratory Minute Volume \(RMV\)](#) and the load intensity. Conclusions about changes in the [RMV](#) are drawn from the impedance between the proximal electrode and the pacemaker. In order to prevent an inadequate frequency increase resulting from discrete instances of deep breathing, a continuous average is derived from multiple breaths. This results in a relatively slow to medium-fast response time. A further problematic aspect pertains to the susceptibility of the method to interference from strong arm movements, such as those involved in swimming or gymnastic exercises.

Contractility Monitoring Techniques based on the contractility of the heart muscle include [Closed-Loop Stimulation \(CLS\)](#) and [Peak Endocardial Acceleration \(PEA\)](#). [CLS](#) is based on the concept that the contraction dynamics of the heart muscle are regulated by the cardiac vascular system, with the required cardiac output depending on the load. Alterations in contraction dynamics are assessed by continuous evaluation of the impedance between the electrode and the pacemaker. For [PEA](#) the contractility of the [myocardium](#) is monitored using a specialized electrode with an accelerometer at the distal end. The acceleration movement is then assigned to specific frequency profiles. This method is currently only employed in biventricular systems.

Other Approaches In [QT interval](#) based rate adaptation, the interval between ventricular stimulation ([Q wave](#) in the [ECG](#)) and [repolarization \(T wave\)](#) in the [ECG](#) is measured by the pacemaker. This interval is utilized for evaluating the stress state, with consideration of the impact of physical, physiological, and vegetative load. However, this approach is limited by a delayed reaction time and the necessity for a ventricular electrode. This technology is not employed in the most recent generation of pacemaker systems. Other approaches are based on the measurement of the temperature of the blood, the level of oxygen in the blood, or the

potential of Hydrogen (ph value) of the blood. These approaches all require at least a special electrode.

FDA Tests

In-Vitro Component Tests Each component is evaluated by individual tests in accordance with the individual specifications. Furthermore, logic and signal processing circuits must be evaluated under basic test scenarios, including the utilisation of a signal generator to generate synthetic EGM signals and an oscilloscope for the observation of component outputs.

In-Vitro Device Tests It is imperative that tests be conducted with devices that are representative of the marketable product. The tests must encompass a comprehensive range of scenarios to ascertain the operational parameters. These include conditions anticipated in the human body with regard to electrical properties, temperature ranges of 30°C to 40°C , and lead resistances between $300\ \Omega$ and $2000\ \Omega$. Additionally, the battery voltage behavior across the anticipated operational lifetime must be evaluated. All operating modes and the full spectrum of programmable parameters must be subjected to rigorous testing. Furthermore, the potential impact of any form of interference should be evaluated in relation to the device. This may encompass electromagnetic, mechanical, thermal, acoustic, or chemical interference. Moreover, the device should be evaluated for its response to environmental factors that may be encountered during shipping, handling, storage, or implantation, including vibrations, mechanical shocks, and temperature variations.

Animal Tests The objective of animal testing is to evaluate the performance of medical devices in a closed-loop setting, which differs from the methodology employed in previous tests, which were conducted in an open-loop manner. This approach enables the identification of potential errors in pacemaker functionality in interaction with a real biological system.

Biocompatibility Tests The objective of biocompatibility is to guarantee the safety of the patient. In order to achieve this, tests are conducted to ascertain that the implanted materials do not release any toxic substances into the body. All potentially harmful components are also hermetically sealed against any biological interface in order to prevent any adverse effects.

Clinical Investigation The process is constrained by a number of significant restrictions, including guidelines pertaining to the selection of both patients and investigators, as well as documentation, frequency, and duration of follow-ups, to ensure the health and well-being of patients while also ensuring the reliability of the results. The tests include physical exercise at a range of heart rates and an analysis of the efficacy of the rate adaptation. The four phases are delineated as follows: A total of 50 devices are implanted in Phase I, 250 in Phase II, 500 in Phase III, and 1,000 in Phase IV. Progression between each phase is contingent upon FDA approval.

Manufacturing It is imperative that the manufacturing process be meticulously documented to guarantee that the devices remain within the predetermined tolerances. Furthermore, the failure rate must be sufficiently low. Furthermore, quality control must be considered.

Operators and Assignment Expressions

Table C.1: Operators and Assignment Expressions in according to [120]

Operator	Assignments	Description
()		Parenthesis alter the evaluation order
[]		Array lookup
.		Infix lookup operator for accessing process or structure type
!		Logical negation
<i>not</i>		Logical negation
++		Increment (prefix and postfix operator)
--		Decrement (prefix and postfix operator)
-	- =	Integer subtraction (and unary negation)
+	+ =	Integer addition (and unary plus)
*	* =	Integer multiplication
/	/	Integer division
%	% =	Modulo
<<	<<=	Left bitshift
>>	>>=	Right bitshift
<?		Minimum
>?		Maximum
<		Less than
<=		Less than or equal to
==		Equality operator
!=		Inequality operator
>=		Greater than or equal to
>		Greater than
&	& =	Bitwise and
^	^ =	Bitwise xor
	=	Bitwise or
&&		Logical and (conjunction)
and		Logical and (conjunction)
		Logical or (disjunction)
or		Logical or (disjunction)
?:		Inline if-then-else (ternary) operator
imply		Logical implication
forall		Forall quantifier
exists		Exists quantifier
sum		Sum expression

Pacemaker Onset After 4 Minutes

The following pages present the results of the interaction between the [HIL](#) model of the heart in interaction with a physical pacemaker, described in Section [9.2.4](#). The results are sorted according to the self-stimulation interval of the [SA node](#). For an enhanced overview,

- the stimulations in the [vulnerable phase](#),
- the generated beats per minute with the pacemaker connected to the atrium, and
- the generated beats per minute with the pacemaker connected to the ventricle

are displayed on the same page.

Pacemaker Onset After 4 Minutes for a Sinus Interval of 950

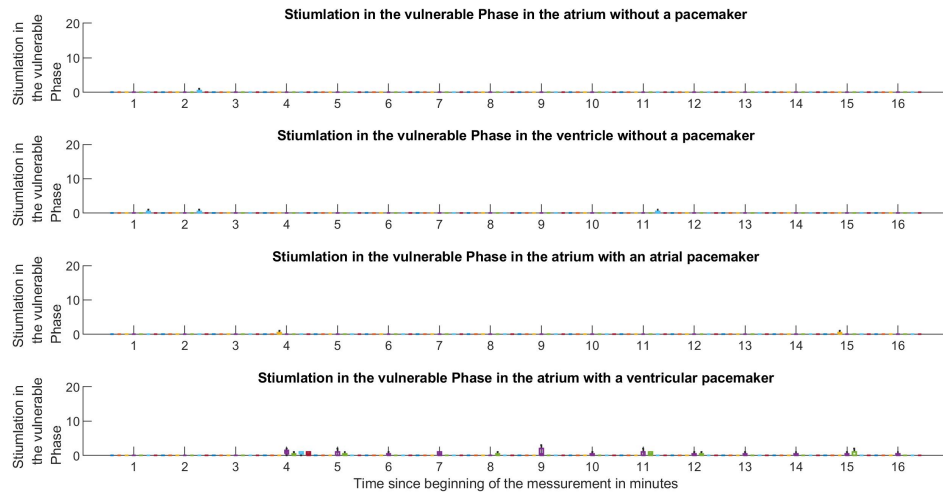


Figure D.1: Stimulation in the **vulnerable phase** of the **HIL** heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 950.

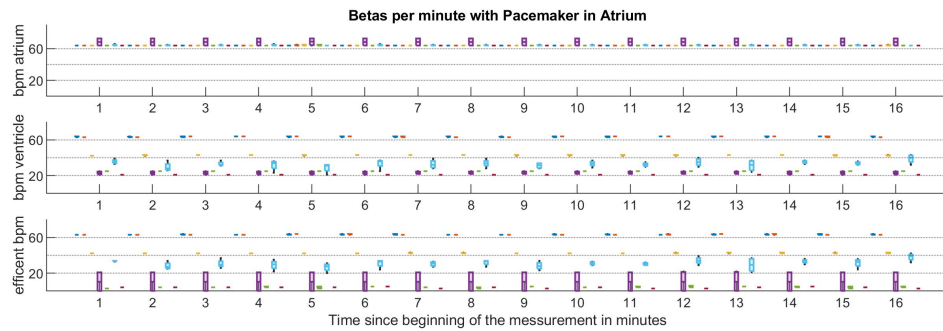


Figure D.2: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 950, recorded with a pacemaker connected to the atrium. The colour coding corresponds to the legend of Figure 9.11.

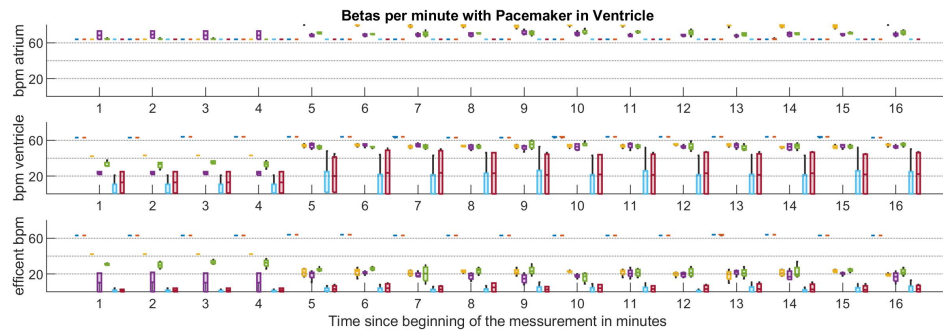


Figure D.3: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 950, recorded with a pacemaker connected to the **ventricle**. The colour coding corresponds to the legend of Figure 9.11.

Pacemaker Onset After 4 Minutes for a Sinus Interval of 1000

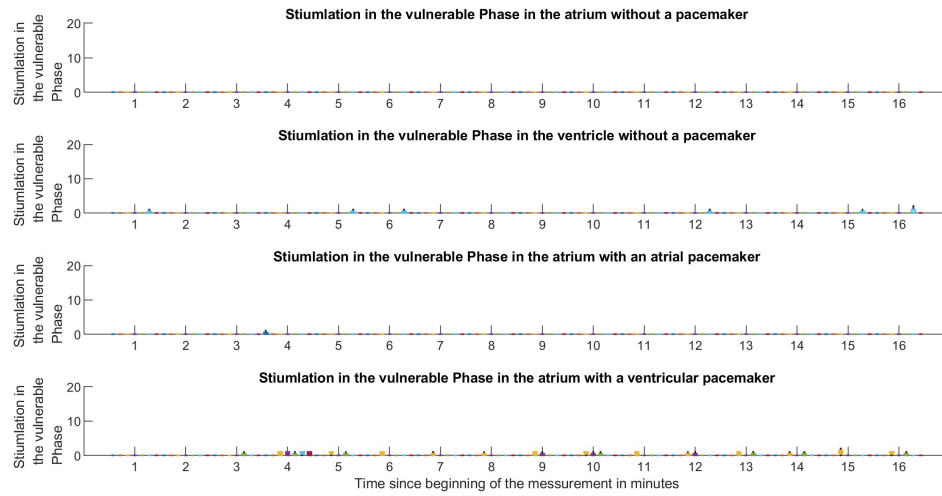


Figure D.4: Stimulation in the **vulnerable phase** of the **HIL** heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 1000.

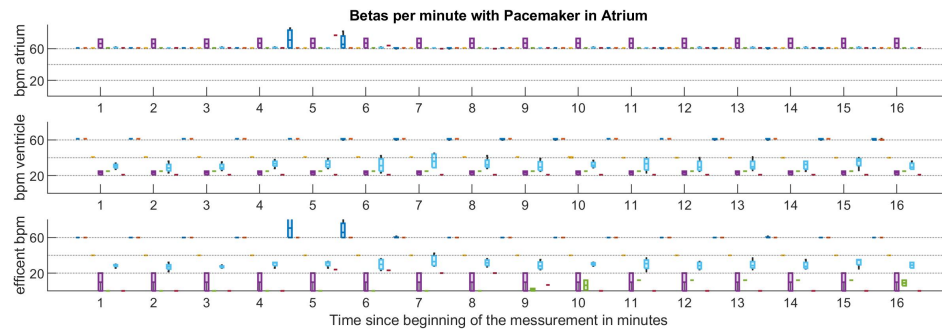


Figure D.5: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 1000, recorded with a pacemaker connected to the atrium. The colour coding corresponds to the legend of Figure 9.11.

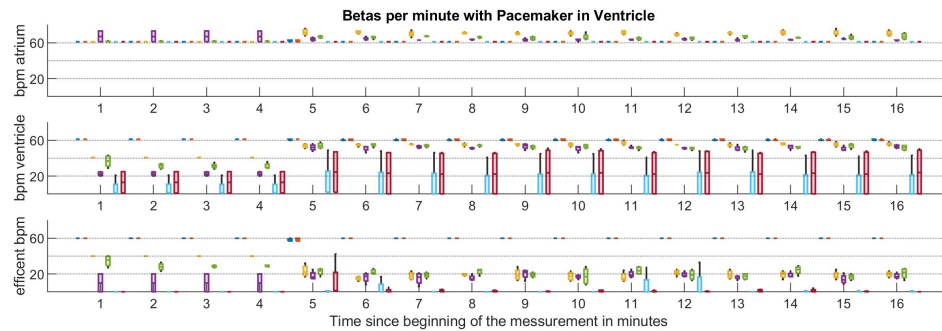


Figure D.6: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 1000, recorded with a pacemaker connected to the **ventricle**. The colour coding corresponds to the legend of Figure 9.11.

Pacemaker Onset After 4 Minutes for a Sinus Interval of 1050

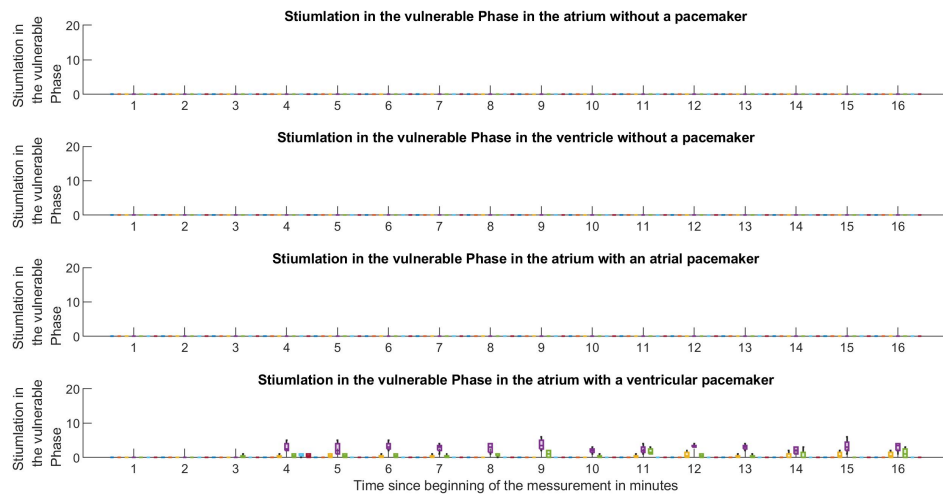


Figure D.7: Stimulation in the **vulnerable phase** of the **HIL** heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 1050.

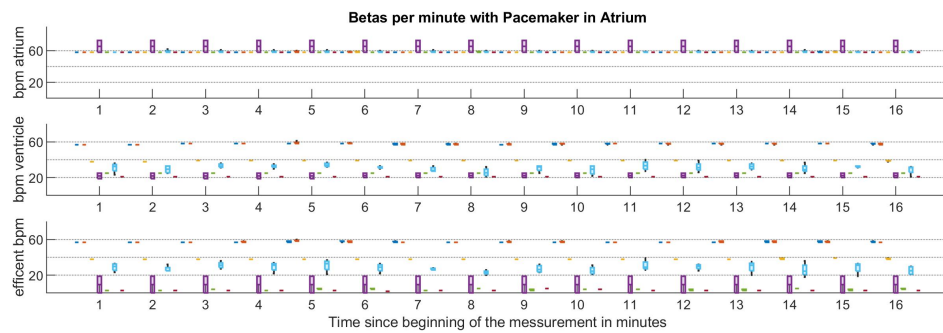


Figure D.8: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 1050, recorded with a pacemaker connected to the atrium. The colour coding corresponds to the legend of Figure 9.11.

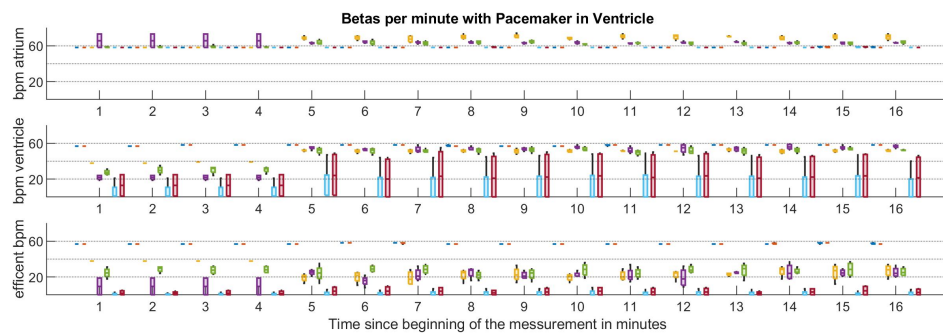


Figure D.9: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 1050, recorded with a pacemaker connected to the **ventricle**. The colour coding corresponds to the legend of Figure 9.11.

Pacemaker Onset After 4 Minutes for a Sinus Interval of 1500

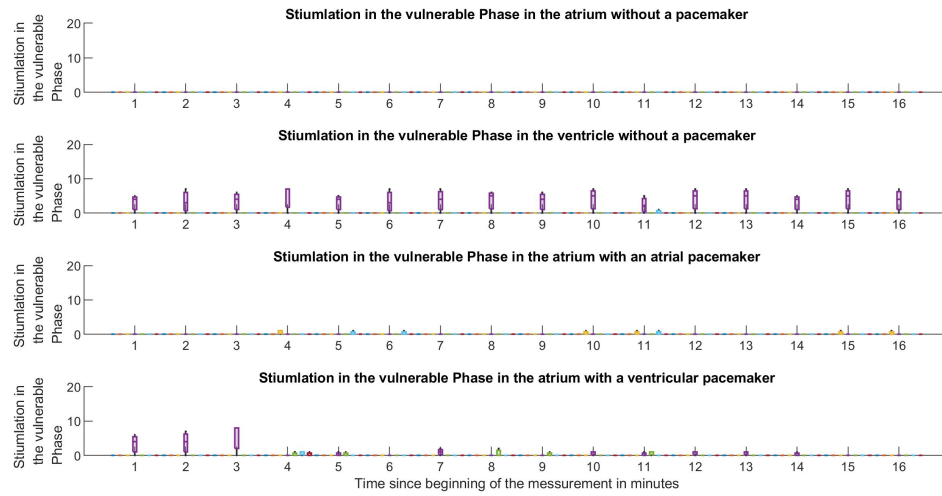


Figure D.10: Stimulation in the **vulnerable phase** of the **HIL** heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 1500.

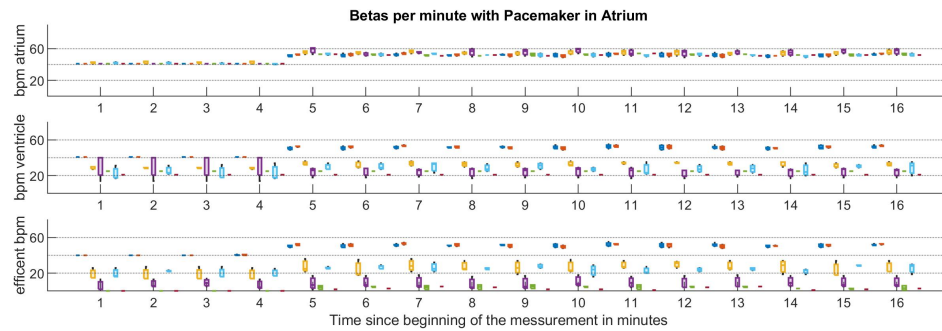


Figure D.11: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 1500, recorded with a pacemaker connected to the atrium. The colour coding corresponds to the legend of Figure 9.11.

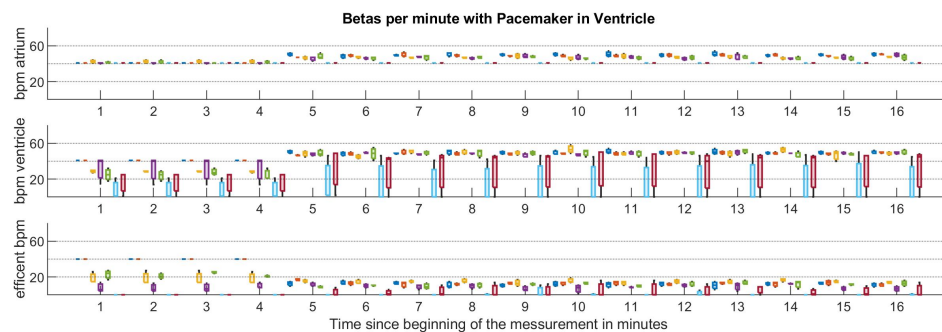


Figure D.12: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 1500, recorded with a pacemaker connected to the **ventricle**. The colour coding corresponds to the legend of Figure 9.11.

Pacemaker Onset After 4 Minutes for a Sinus Interval of 2000

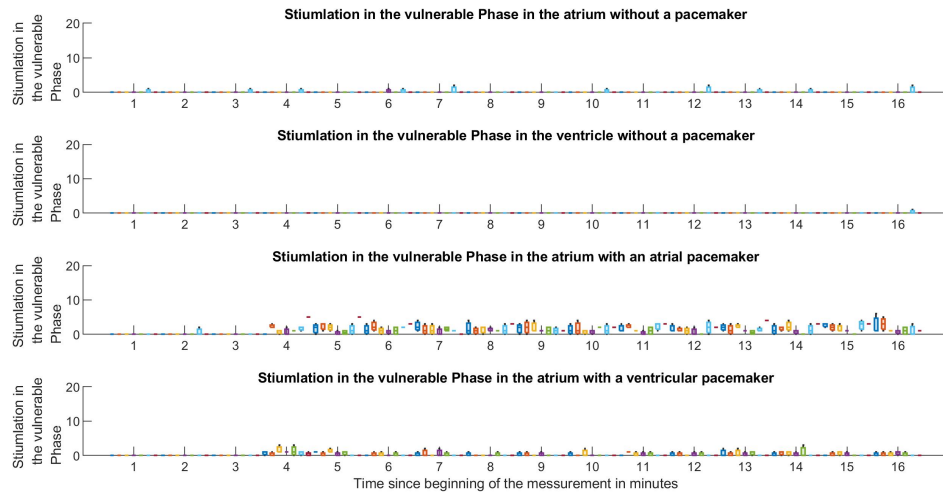


Figure D.13: Stimulation in the **vulnerable phase** of the **HIL** heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 2000.

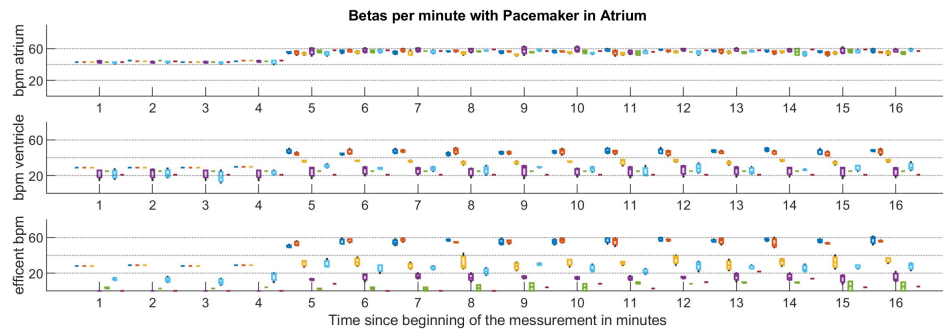


Figure D.14: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 2000, recorded with a pacemaker connected to the atrium. The colour coding corresponds to the legend of Figure 9.11.

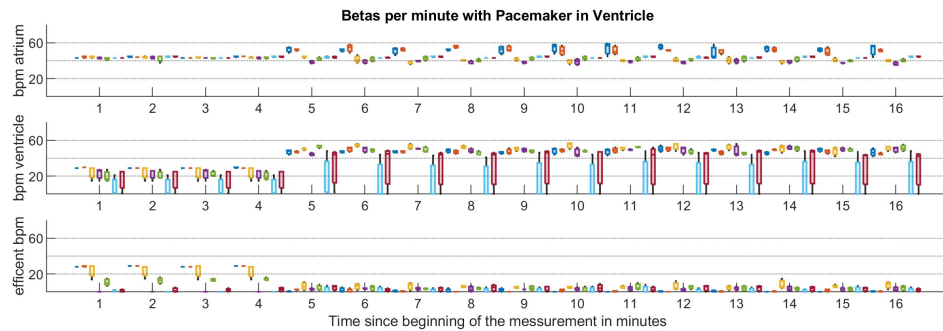


Figure D.15: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 2000, recorded with a pacemaker connected to the **ventricle**. The colour coding corresponds to the legend of Figure 9.11.

Pacemaker Onset After 4 Minutes for a Sinus Interval of 2500

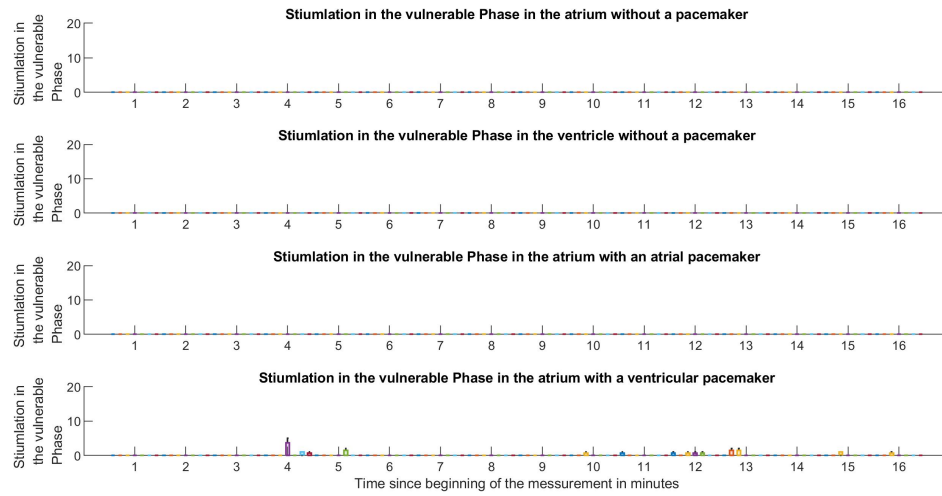


Figure D.16: Stimulation in the **vulnerable phase** of the **HIL** heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 2500.

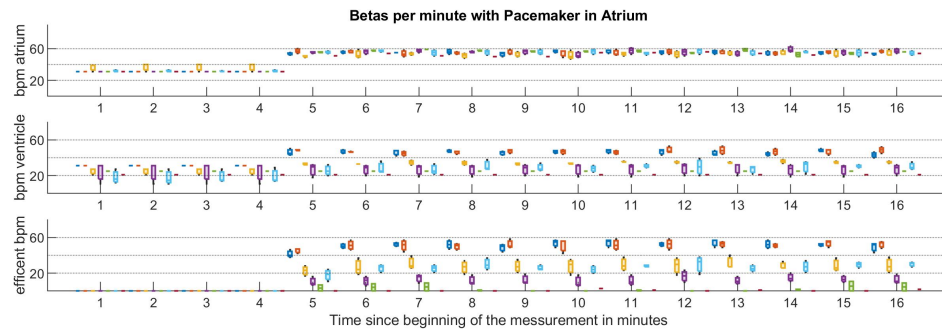


Figure D.17: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 2500, recorded with a pacemaker connected to the atrium. The colour coding corresponds to the legend of Figure 9.11.

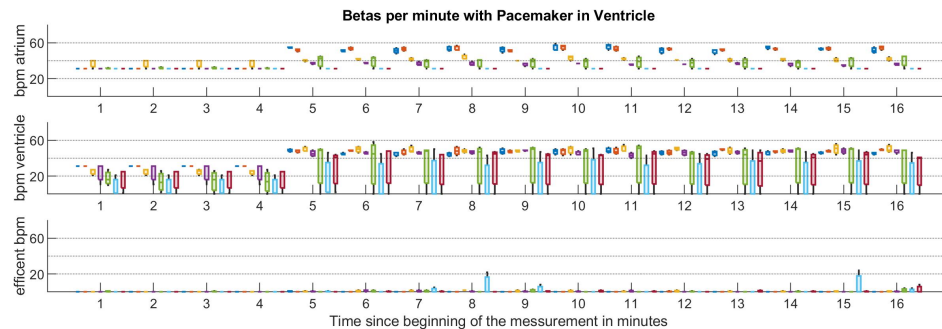


Figure D.18: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 2500, recorded with a pacemaker connected to the **ventricle**. The colour coding corresponds to the legend of Figure 9.11.

Pacemaker Onset After 4 Minutes for a Sinus Interval of 3000

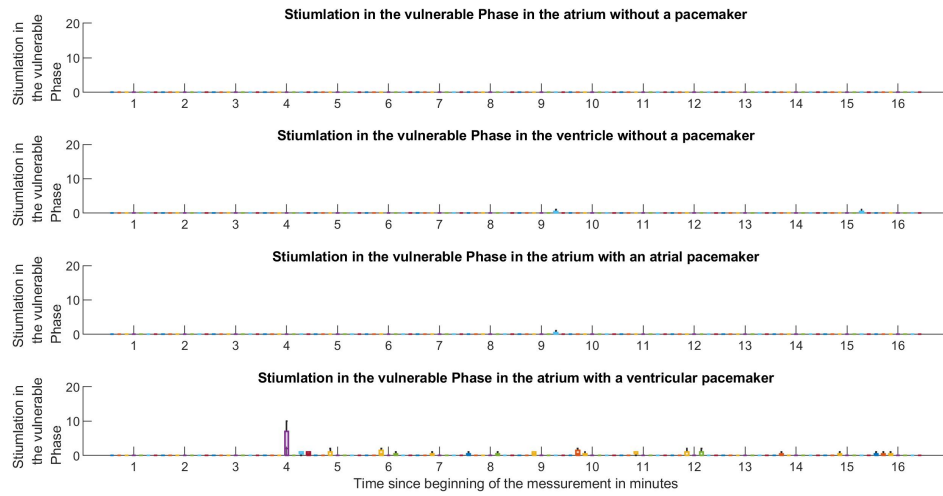


Figure D.19: Stimulation in the **vulnerable phase** of the **HIL** heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 3000.

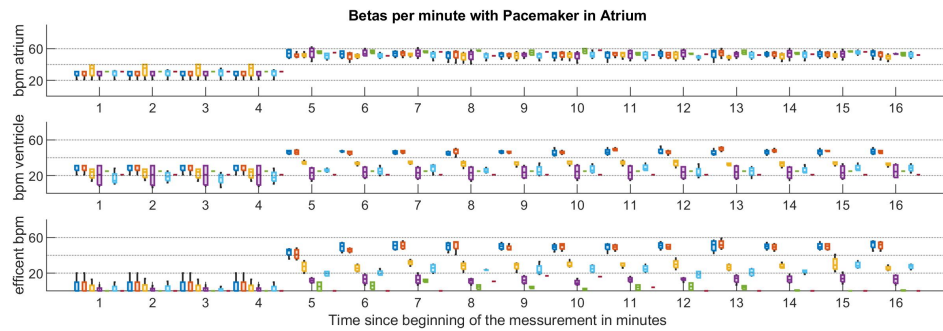


Figure D.20: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 3000, recorded with a pacemaker connected to the atrium. The colour coding corresponds to the legend of Figure 9.11.

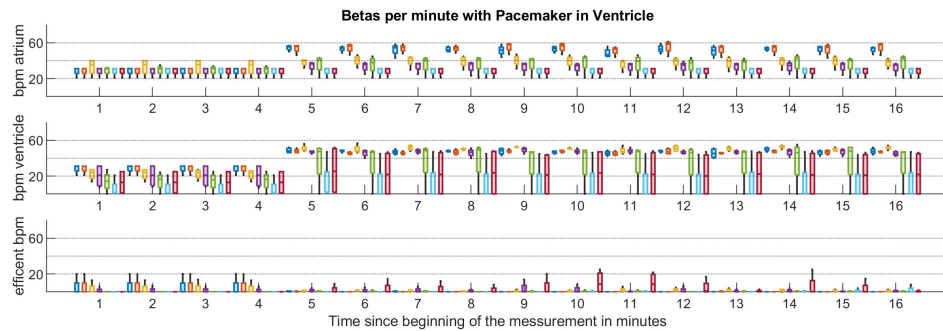


Figure D.21: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 3000, recorded with a pacemaker connected to the **ventricle**. The colour coding corresponds to the legend of Figure 9.11.

Pacemaker Onset After 4 Minutes for a Sinus Interval of 3500

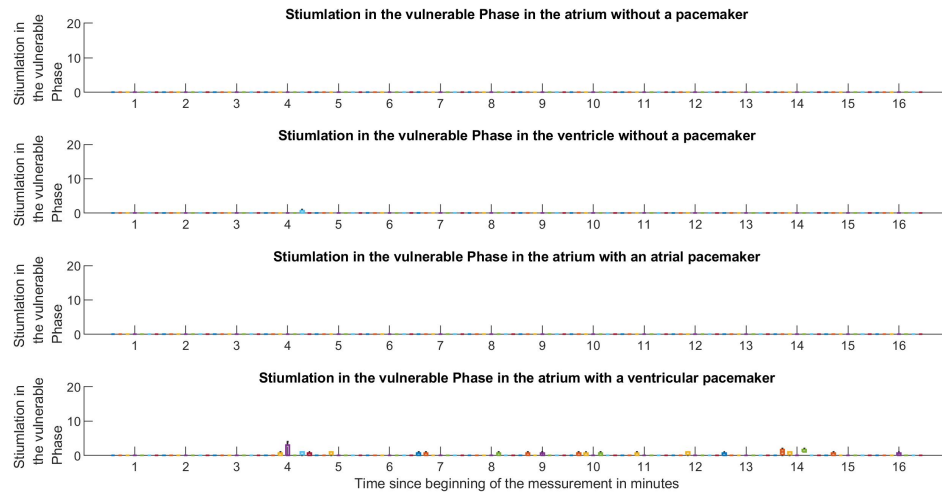


Figure D.22: Stimulation in the **vulnerable phase** of the **HIL** heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 3500.

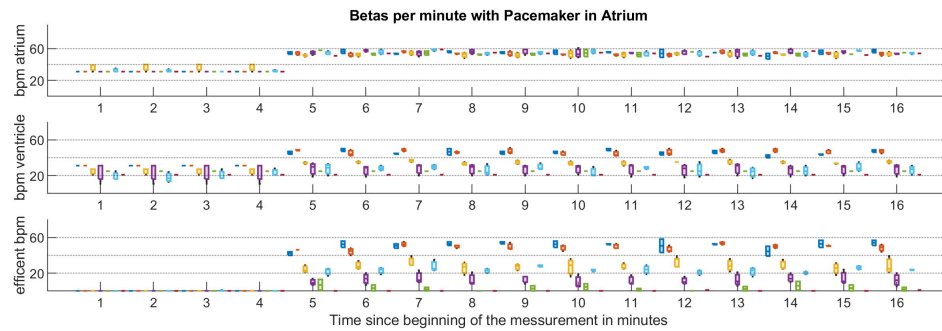


Figure D.23: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 3500, recorded with a pacemaker connected to the atrium. The colour coding corresponds to the legend of Figure 9.11.

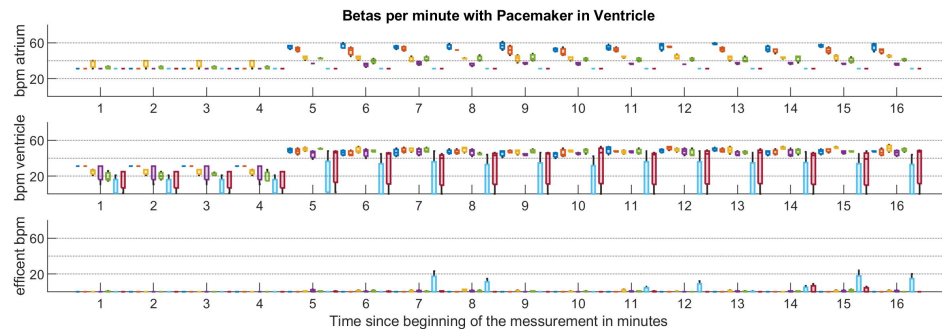


Figure D.24: Generated bpm of the heart model for the pacemaker Onset After 4 Minutes for a **SA node** self-stimulation interval of 3500, recorded with a pacemaker connected to the **ventricle**. The colour coding corresponds to the legend of Figure 9.11.