

# Electrophysiological Closed Loop Model of the Heart as Supporting Tool for Cardiac Pacing

Niccolò Biasi<sup>1</sup>, Matteo Mercati<sup>1</sup>, Paolo Seghetti<sup>2,3</sup>, Alessandro Tognetti<sup>1,4</sup>

<sup>1</sup> Department of Information Engineering, University of Pisa, Pisa, Italy

<sup>2</sup> Scuola Superiore Sant'Anna, Pisa, Italy

<sup>3</sup> Institute of Clinical Physiology, National Research Council, Pisa, Italy

<sup>4</sup> Research Centre "E. Piaggio", University of Pisa, Pisa, Italy

## Abstract

*In this work, we developed a closed loop model of the interaction between the heart and a cardiac pacemaker. The main novelty of our framework is the employment of a reaction-diffusion heart model, which could enhance the assessment of cardiac pacing. Additionally, we provided a specific hardware setup for the deployment of our framework. Our results show that the heart model reproduces the healthy activation sequence and is feasible for closed loop simulations. Furthermore, we successfully simulated the interaction between heart and pacemaker models during the insurgence of endless loop tachycardia. Finally, we believe that our closed loop system could be an effective supporting tool to evaluate the safety and efficacy of the therapeutic effect of cardiac pacemakers.*

## 1. Introduction

Cardiac pacemakers are implantable medical devices largely employed for the treatment of drug-resistant cardiac arrhythmias. However, recent studies have highlighted that the rate of safety recall for cardiac implantable electronic devices (CIEDs) is still high [1]. Indeed, pacemakers are programmed with complex software, and, in general, it is not always easy to predict the device behaviour when coupled with a specific condition [2]. Thus, emulation and testing of cardiac pacemakers remains an important topic to be addressed. Open loop testing of pacemakers is non exhaustive because it does not consider how the heart reacts to the pacing stimuli, but it only evaluates the device behaviour upon receipt of pre-recorded cardiac signals. Recently, it has been shown that both the design and the assessment of pacemakers can be enhanced by employing closed loop systems that include models of the heart electrical activity [3–5].

A closed loop system for the design and validation of pacemakers consists of the pacemaker (system model, emu-

lated device, or physical device), the physiological model of the heart and the necessary interfaces [3]. The heart model should replicate the most important electrophysiological characteristics of cardiac tissue both in healthy and pathological conditions, while maintaining computational efficiency. Additionally, the heart model should react to pacing stimuli in the proper way and generate meaningful electrograms. Previous works developing closed-loop models represented the heart as a network of timed automata (TA) [3, 6], or hybrid automata (HA) [4, 5]. However, finite automata do not allow modelling of spatial inhomogeneities, such as transmural and myocardial heterogeneity, and do not represent the electrodes spatially. In this work, we preliminary developed a closed loop system composed of a DDD pacemaker model and a reaction-diffusion heart model, specifically designed for closed loop pacemaker design and validation. Additionally, we provided a dedicated hardware implementation of our closed loop system. To demonstrate the functionalities of our framework, we analyse a pathological case of endless loop tachycardia (ELT), which insurges when the pacing stimuli and the intrinsic heart activity interfere. Notably, current pacemakers are provided with anti-ELT algorithms to detect and terminate the ELT [6, 7].

## 2. Methods

### 2.1. Heart model

We built a two-dimensional cardiac model in which the cardiac tissue is divided into 6 distinct regions (Fig. 1, bottom right). For the interaction with a dual chamber (DDD) pacemaker we introduced two stimulation and sensing sites: an atrial electrode placed near the right atrial auricle and a ventricular electrode placed in the apical area of the right ventricle (light grey areas in the heart geometry of Fig. 1).

The heart model is based on the cardiac monodomain for-

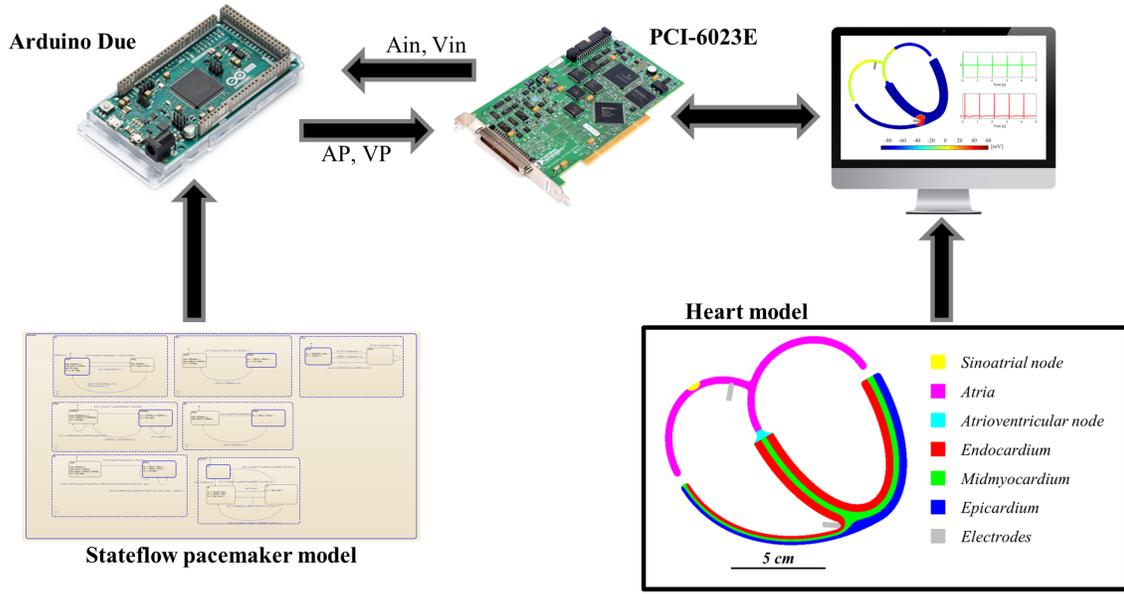


Figure 1. Overall scheme of the closed loop system (see text for details). On the bottom right the heart geometry is shown.

mulation, where the diffusivity values were selected to replicate time intervals corresponding to complete atrial activation [8], atrioventricular conduction [9], and complete ventricular activation [10]. For the definition of the ionic current ( $I_{ion}$ ), we adopted our previously published phenomenological model [11–13], which we fitted to the electrophysiological properties of the different types of cardiac cells. The fitting procedure is aimed at reproducing the main characteristics of experimental action potential morphology and action potential duration, and conduction velocity steady-state restitution curves. The model parameters for the ventricular tissues were already optimised in [13]. We applied the same procedure here to fit also atrial electrophysiological data [14–16]. In the sinoatrial node we introduced an additional stimulation current to allow for spontaneous activation.

We spatially discretized the monodomain equation by employing a centered finite difference scheme with a resolution of 0.02 cm, whereas we performed time integration by applying the forward Euler method with a time resolution of 0.02 ms. Moreover, we exploited the smoothed boundary method [17, 18] to implicitly solve boundary conditions on the non trivial 2D geometry, thus avoiding complex meshing of the domain. In particular, we enforced Neumann boundary conditions with imposed current flux different from 0 only at the electrodes interfaces. In addition, we evaluated the atrial and ventricular electrograms (i.e., the outputs of our cardiac model) by calculating the potential at the center of the electrode interfaces, in the hypothesis of homogeneous volume conductor.

## 2.2. Closed loop model

We developed a closed-loop system composed of our heart model and a DDD pacemaker model (Fig. 1). The heart model, described in the previous section, was coded in a Level-2 MATLAB S-function enabling its use in Simulink (R2022a, MathWorks, Natick, Massachusetts). Additionally, we developed a pacemaker model in Simulink by using the Stateflow toolbox of Matlab. The DDD pacemaker model is the same previously employed by Jiang et al. [19] and it is based on five different timers (i.e., AVI, LRI, URI, PVARP, and VRP). We refer the reader to [19] for a comprehensive description of the pacemaker model. In each closed-loop simulation, we set the DDD pacemaker timing parameters with standard values: AVI=150ms, LRI=1000ms, URI=400ms, PVARP=185ms, VRP=200ms [20]. Notably, our pacemaker model replicates an algorithm aimed at terminating ELT, similar to the algorithms currently employed in cardiac pacemakers [6, 7].

ELT manifests itself as a sequence of ventricular pacing events (VP) followed by atrial sensed events (AS), generally maintained at the maximum ventricular rate (URI). Indeed, ELT involves ventriculo-atrial retrograde conduction, which combined with the pacemaker activity, sustains ELT. The algorithm detects ELT by recognizing 8 consecutive VP-AS cycles. In addition, ELT is confirmed only if the difference between each VP-AS interval and the first VP-AS interval detected is within  $\pm 32$  ms. Thus, the tachycardia is suppressed by increasing the PVARP to a fixed value of 500 ms for the next cardiac cycle, so that atrial

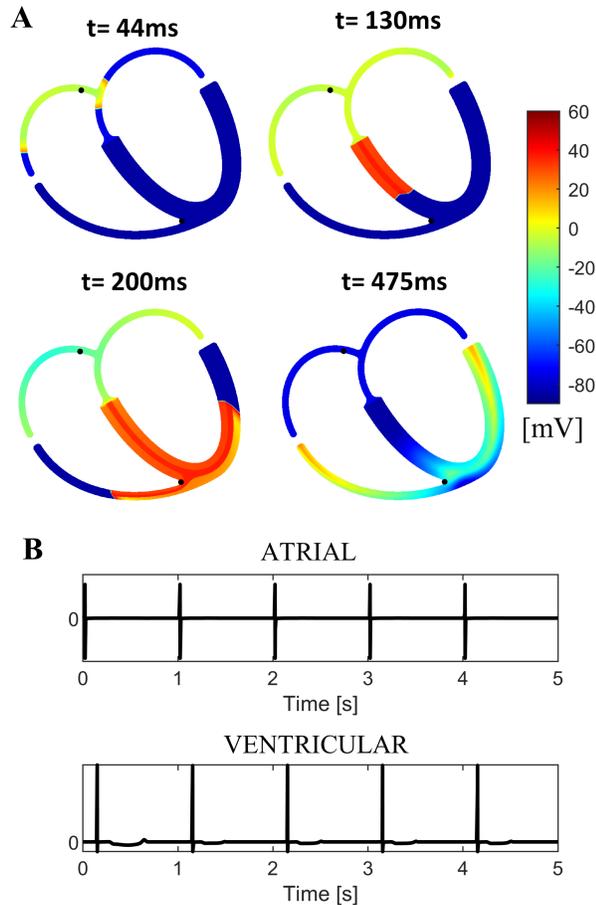


Figure 2. Open loop healthy simulation. A) Membrane potential maps in the main phases of the cardiac cycle. The black dots indicate the electrodes position. B) Simulated atrial (top) and ventricular (bottom) electrograms

activity induced by retrograde conduction is not sensed. We also provided a hardware setup for our closed-loop framework (Fig. 1). The pacemaker model was deployed on an Arduino Due board, whereas the heart model runs on a custom Workstation (CPU: AMD Ryzen Threadripper 3960X 24-Core 3.79 GHz; GPU: NVIDIA GeForce RTX 3090). The Workstation was also equipped with a data acquisition board (DAQ PCI-6023E, National Instruments), which allows the communication between the heart model and the pacemaker model. The heart model sends to the Arduino board the atrial and ventricular activation signals (Ain, Vin), which are obtained by processing atrial and ventricular electrograms. In turn, the pacemaker model eventually generates the pacing stimuli.

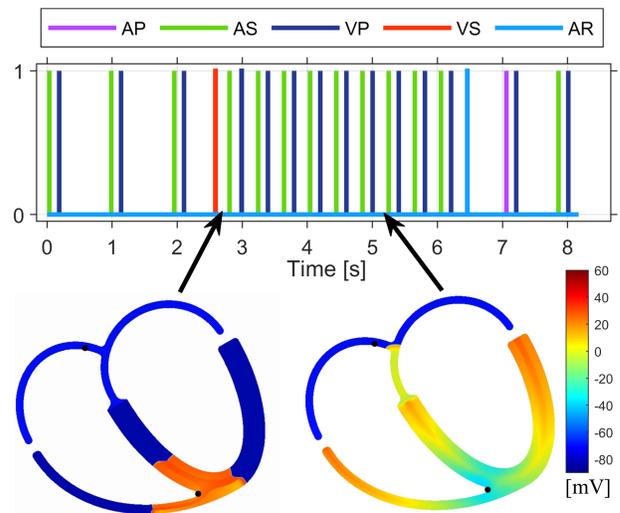


Figure 3. Simulation of ELT induced by an ectopic activation. Top: Pacing and sensing events of the pacemaker. Bottom: two snapshots of membrane potential during the simulation. The arrows indicate the time instants corresponding to the snapshots.

### 3. Results

In Figure 2 we report a healthy simulation of the 2D whole heart model in open loop. The results showed that our model reproduces healthy activation times through the heart (Fig. 2A). Complete atrial depolarization requires about 125 ms, in agreement with experimental data ( $116 \pm 18$  ms) [8]. Atrio-ventricular conduction time is about 130 ms, which is inside the range for healthy subjects (120-200 ms) [9]. Finally, complete ventricular depolarization requires about 100 ms, which is comparable to experimental data [10]. Atrial and ventricular electrograms (Fig. 2B) show wide deflections in correspondence of the depolarization of neighbouring tissue. Furthermore, thanks to the transmural heterogeneity of the ventricular tissue, the ventricular repolarization generates a small T-wave in the ventricular electrogram.

To demonstrate the potentialities of our framework, we simulated a condition of partial AV block and slowing of conduction, in which a premature ventricular contraction induces the onset of ELT. After three initial cycles in sinus rhythm, we generated an ectopic ventricular activation that propagates retrogradely towards the atria. The device detects the consequent atrial depolarization and marks the event as AS, which in turn triggers a ventricular stimulation. Thereby, the ventricular pacing generates a second retrograde conduction, establishing ELT. Therefore, the pacemaker paces the ventricle for every atrial activation, increasing the ventricular rate inappropriately. Afterwards, following the recognition of eight consecutive VP-AS pat-

terns, the device detects ELT and extends PVARP to 500 ms to terminate the undesired tachycardia.

## 4. Conclusion

In this work, we described a closed loop system composed by a DDD pacemaker model and a reaction-diffusion heart model, specifically designed for closed loop pacemaker design and validation. Additionally, we provided a specific hardware setup for the deployment of our closed loop model. Our results show that reaction-diffusion heart models are feasible for the development of closed loop systems aimed at assessing pacemakers functioning. We believe that the proposed closed loop framework may be an effective supporting tool to evaluate the safety and efficacy of the therapeutic effect of cardiac pacemakers.

## Acknowledgments

We acknowledge the support from the lab "Cloud Computing, Big Data and Cybersecurity" of the Information Engineering Department of the University of Pisa (Cross-Lab project, Dipartimenti di Eccellenza, Italian Ministry of University and Research).

## References

- [1] Dhruva SS, Whooley MA, Turakhia MP, Raitt MH, Tarasovsky G, Rosman L, Matheny ME. Using the va national cardiac device surveillance program to monitor the safety of cardiovascular implantable electronic devices. *Circulation Cardiovascular Quality and Outcomes* 2019; 12(Suppl\_1):A119–A119.
- [2] Perez MV, Al-Ahmad AA, Wang PJ, Turakhia MP. Inappropriate pacing in a patient with managed ventricular pacing: What is the cause? *Heart Rhythm* 2010;7(9):1336–1337.
- [3] Jiang Z, Pajic M, Mangharam R. Cyber-physical modeling of implantable cardiac medical devices. *Proceedings of the IEEE* 2011;100(1):122–137.
- [4] Ai W, Patel ND, Roop PS, Malik A, Trew ML. Cardiac electrical modeling for closed-loop validation of implantable devices. *IEEE Transactions on Biomedical Engineering* 2019;67(2):536–544.
- [5] Ai W, Patel ND, Roop PS, Malik A, Trew ML. Closing the loop: Validation of implantable cardiac devices with computational heart models. *IEEE Journal of Biomedical and Health Informatics* 2019;24(6):1579–1588.
- [6] Jiang Z, Pajic M, Alur R, Mangharam R. Closed-loop verification of medical devices with model abstraction and refinement. *International Journal on Software Tools for Technology Transfer* 2014;16(2):191–213.
- [7] Boston Scientific. ALTRUA and INSIGNIA I Reference Guide, 2019.
- [8] Lemery R, Birnie D, Tang AS, Green M, Gollob M, Hendry M, Lau E. Normal atrial activation and voltage during sinus rhythm in the human heart: an endocardial and epicardial mapping study in patients with a history of atrial fibrillation. *Journal of Cardiovascular Electrophysiology* 2007; 18(4):402–408.
- [9] Josephson ME. *Clinical cardiac electrophysiology: techniques and interpretations*. Lippincott Williams & Wilkins, 2008.
- [10] Durrer D, Van Dam RT, Freud G, Janse M, Meijler F, Arzbaecher R. Total excitation of the isolated human heart. *Circulation* 1970;41(6):899–912.
- [11] Biasi N, Tognetti A. A computationally efficient dynamic model of human epicardial tissue. *Plos One* 2021; 16(10):e0259066.
- [12] Biasi N, Seghetti P, Tognetti A. Diffuse fibrosis and repolarization disorders explain ventricular arrhythmias in brugada syndrome: a computational study. *Scientific Reports* 2022; 12(1):1–15.
- [13] Biasi N, Seghetti P, Tognetti A. A transmurally heterogeneous model of the ventricular tissue and its application for simulation of brugada syndrome. In *2022 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)*. IEEE, 2022; 3951–3954.
- [14] Christ T, Wettwer E, Voigt N, Hala O, Radicke S, Matschke K, Varro A, Dobrev D, Ravens U. Pathology-specific effects of the *ikur/ito/ik*, *ach* blocker *ave0118* on ion channels in human chronic atrial fibrillation. *British Journal of Pharmacology* 2008;154(8):1619–1630.
- [15] Wang Z, Fermi B, Nattel S. Delayed rectifier outward current and repolarization in human atrial myocytes. *Circulation Research* 1993;73(2):276–285.
- [16] Osaka T, KODAMA I. Action potential remodeling in the human right atrium with chronic lone atrial fibrillation. *Pacing and Clinical Electrophysiology* 2000;23(6):960–965.
- [17] Fenton FH, Cherry EM, Karma A, Rappel WJ. Modeling wave propagation in realistic heart geometries using the phase-field method. *Chaos An Interdisciplinary Journal of Nonlinear Science* 2005;15(1):013502.
- [18] Yu HC, Chen HY, Thornton K. Extended smoothed boundary method for solving partial differential equations with general boundary conditions on complex boundaries. *Modelling and Simulation in Materials Science and Engineering* 2012;20(7):075008.
- [19] Jiang Z, Pajic M, Connolly A, Dixit S, Mangharam R. Real-time heart model for implantable cardiac device validation and verification. In *2010 22nd Euromicro Conference on Real-Time Systems*. IEEE, 2010; 239–248.
- [20] Boston Scientific. *PACEMAKER System Specification*, 2007.

Address for correspondence:

Niccolò Biasi  
L.go Lucio Lazzarino, 2, 56122 Pisa  
niccolo.biasi@phd.unipi.it