In silico closed-loop system for the assessment of cardiac pacing algorithms

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Abstract. In this work, we report on the application of a closed-loop system, composed of a 2D reaction-diffusion heart model and a pacemaker model, for assessing pacemaker-heart interactions.
To demonstrate the potential of our approach, we replicated a clinical case report in which a ventricular pacing-minimizing strategy promoted the onset of Pacemaker-Mediated Tachycardia (PMT). To replicate the clinical case, we simulated an atrioventricular (AV) block condition and set the same pacemaker programming reported in the clinical case study. Our study aims to show the usability and potential of our framework by exploring different pacemaker settings coupled with specific electrophysiological heart conditions, thus allowing the assessment of the safety and efficacy of a particular pacing algorithm. The results from our heart model highlighted that the refractoriness of the AV node, in addition to the pacemaker setting (e.g., AV delay and Post Ventricular Atrial Refractory period), plays a crucial role in the onset of PMTs in patients with pacemakers programmed with an AV delay hysteresis algorithm.
We believe that our closed-loop system could represent a valuable auxiliary tool for a preliminary assessment and comparison of various pacing algorithms.

Keywords: In silico closed-loop framework, Heart modelling, AV delay hysteresis, Pacemaker-Mediated Tachycardia, Cardiac pacing

1 Introduction

Cardiac pacemakers are implantable medical devices widely used for the treatment of cardiac dysfunction. Pacemakers are set with advanced algorithms to cope with the complexity and variability of cardiac arrhythmias [1], making the device behavior not easily predictable when coupled with a specific heart condition.
Different algorithms have been proposed to reduce to minimum unnecessary ventricular pacing [2], in order to conserve the pacemaker battery and to avoid unfavourable effects of prolonged right ventricular pacing. Indeed, clinical trials have shown that long-term right ventricular pacing increases the risk of heart

failure and atrial fibrillation [3].
Algorithms designed to reduce the burden of right ventricular pacing are largely employed in modern pacemakers, and understanding the properties of these pacing methods, as well as their possible adverse events, is crucial. Nevertheless the good effectiveness, adverse phenomena may be induced by these ventricular pacing minimization strategies in specific heart conditions [4, 5]. The strategy of Atrio-Ventricular (AV) delay hysteresis to promote the restoration of intrinsic ventricular activation represents one of the concepts largely employed in cardiac pacemakers. AV delay hysteresis strategy consists of a periodical extension of the AV delay (i.e., time interval between an atrial event, sensed or paced, and the ventricular pacing) in order to help restore the ventricular intrinsic depolarization, thus minimizing the ventricular pacing. One of the algorithms adopting the AV delay hysteresis strategy is the Ventricular Intrinsic Preference (VIP, Abbott). When the VIP algorithm is activated, the device periodically extends the AV delay by a number of cardiac cycles to search for intrinsic AV conduction. If an intrinsic ventricular activation is sensed during the extended AV delay, the ventricular pulse is inhibited, and the AV delay remains extended until ventricular pacing occurs. Despite the undoubted effectiveness of this pacing strategy [6], in specific conditions it can promote adverse effects, such as the onset of Pacemaker Mediated Tachycardia (PMT) [5, 7, 8].
PMT is a reentrant tachycardia that occurs in patients with dual chamber pacemakers and intact Ventriculo-Atrial (VA) conduction. When ventricular pacing is delivered, if a retrograde VA conduction occurs, the retrograde atrial activation can be sensed by the pacemaker, which in turn triggers ventricular pacing, thus the pacemaker substitutes the anterograde pathway. Therefore, in patients with impaired AV conduction but preserved retrograde conduction, an extension of the AV delay may allow the complete repolarization of the cardiac tissue along the AV path, thus promoting VA conduction following the ventricular pacing.
Recently, many studies focused on the development of closed-loop systems, consisting of the interaction between the pacemaker activity and a cardiac model, for validation and verification of pacemakers [9, 10]. However, previous works modelled the heart as a network of timed automata or hybrid automata, which does not permit modelling of spatial inhomogeneities (e.g. transmural and myocardial heterogeneity), generation of accurate electrograms, and a spatial representation of electrodes.
In this work, we employed our previously published closed loop system [11] to simulate adverse interactions caused by the VIP algorithm when coupled with specific electrophysiological heart conditions. The closed loop system is composed of a 2D reaction-diffusion heart model and a simplified emulation of a DDD pacing mode. The heart model is based on our phenomenological myocyte model that showed to be capable of reproducing the most important electrophysiological properties of cardiac tissue, while still maintaining a low computational cost [12]. Additionally, the myocyte model can reproduce the electrophysiological properties of different types of myocytes allowing for tissue heterogeneity in the heart model [11]. The aim of this study is to assess the insurgence of PMTs

as a function of the AVI extension used by the VIP algorithm and the AV node refractory period in presence of AV block. Our results showed that the refractoriness of the AV node plays a crucial role in determining the insurgence of PMTs. We believe that our study, while preliminary, could facilitate the understanding of the operating principles and promote pacemaker setting optimization.

2 Methods

2.1 Heart model

The heart model is based on the monodomain formulation of the cardiac tissue and is composed of six different cardiac regions: sinoatrial node, atrium, AV node, midmyocardium, epicardium and endocardium (Fig.1). The ionic current

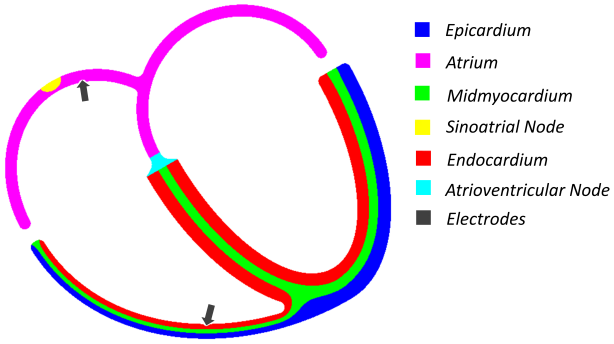

Fig. 1. Geometry of the bidimensional heart model. Black arrows indicate the position of the electrodes.

is defined according to our previously published phenomenological model [11, 12] simulating different electrophysiological properties in each region. Indeed, we fitted our phenomenological model to the electrophysiological properties of the different types of cardiac cells to reproduce the main characteristics of experimental action potential morphology, action potential duration and conduction velocity steady-state restitution curves. To mimic spontaneous activation, we added an additional stimulation current in the sinoatrial node. Furthermore, we added two stimulation and sensing sites, placed in the right atrial and near the apical area of the right ventricle. The diffusivity values (D) were set to replicate cardiac activation timings, such as the complete atrial and ventricular activation, and atrioventricular conduction. Moreover, we decreased γ_0 and γ_1 values of our ionic current model [12] to further slow the conduction in the AV node region. We varied the inverse of the time constant (model parameter e) of the recovery variable of the model to modulate the AV node refractory period. We

performed one-dimensional simulations on a homogeneous cable to determine the relation between the model parameter e and the effective refractory period (ERP) of the AV node. The cable was stimulated at one end with a 2 ms stimulus of strength twice the diastolic threshold. After 4 stimuli with a cycle length of 800ms, an extrastimulus was delivered at different time intervals. We defined the ERP as the longest time interval between the extrastimulus that generated a non-propagating action potential and the previous stimulus.
We used the centered finite difference (FD) method with a resolution of 0.005 cm for the spatial discretization of the monodomain equation. Time integration was performed by applying the forward Euler method with a time resolution of 0.0025 ms. Furthermore, we solved boundary conditions on the bidimensional geometry by using the smoothed boundary method [13, 14], thus allowing the use of the FD method on the non-trivial 2D geometry of the heart. We applied Neumann boundary conditions with imposed current flux different from 0 exclusively during pacing at electrodes interfaces.
We calculated the atrial and ventricular electrograms as the potential at the center of the electrode interfaces, assuming a homogeneous volume conductor. The heart model presents spontaneous SA node activation, receives pacing signals from the pacemaker, and transmits atrial and ventricular electrograms.

2.2 Heart-Pacemaker: closing the loop

We developed a closed-loop system composed of our heart model and a DDD mode pacemaker model [11]. The heart model, detailed in section 2.1, was included in a Level-2 MATLAB S-function enabling its use in Simulink (R2022a, MathWorks, Natick, Massachusetts). In addition, we emulated the activity of a DDD mode pacemaker in Simulink by using the Stateflow toolbox of Matlab, as previously employed by Jiang et al.[15]. We refer the reader to [11] for a comprehensive description of the closed loop system implementation.

DDD pacemaker has pacing and sensing capabilities in both the atrium and the ventricle, and its basic timing cycle is composed of five components [15], which run in parallel. The lower rate interval (LRI) defines the longest interval between a ventricular pacing pulse and previous ventricular event, while the upper rate interval (URI) sets an upper bound for ventricular pacing rate. The atrioventricular interval (AVI) represents the time period from an atrial event to a ventricular pace, and it is designed to synchronize the ventricular pacing with the atrial activity. The Post Ventricular Atrial Refractory period (PVARP) defines the refractory period for atrial events following ventricular events. If the atrial activity occurs during the PVARP, it does not impact the pacing schedule. Likewise, the Ventricular Refractory Period (VRP) sets a blocking interval for ventricular events.

Moreover, we added a simplified replication of the VIP algorithm to the Stateflow pacemaker model. The VIP algorithm is defined by three parameters, which modulate its activity: the extension of the programmed AV delay applied during the search for the intrinsic ventricular activation (i.e., AVI extension), the number of consecutive cycles the device extends the AV delay (i.e, the search cycles)

and the time interval between each intrinsic conduction search (i.e, the search interval) [2]. We developed a graphical user interface in Simulink, whereby the non-expert users in cardiac modelling can both set pacemaker parameters (AVI, PVARP, LRI, URI, VRP, AVI, AVI extension, Search cycles, Search interval) and define the heart conditions (Heart rate, AV conduction properties).

Although extended AV delay limits ventricular pacing, it can inadvertently promote the onset of PMT, which will be entirely supported by pacemaker behaviour. In patients with intact ventricular-atrial (VA) pathway, long AV delay may facilitate retrograde conduction following the ventricular pacing. Additionally, the ERP of the AV node can be related to retrograde conduction, as described in [16]. Indeed, the mean ERP of the AV node seems to be significantly prolonged in patients without VA conduction [16].
In this work, we simulated an AV block and we analyzed the onset of the PMT caused by an AV delay hysteresis algorithm (VIP). In particular, we replicated the pacemaker setting reported in the clinical case report from Calton et Al. [5], and we assessed the induction of PMT by varying both the AVI extension and the AV node refractory period values. Thus, we highlighted how different pacemaker parameters coupled with particular electrophysiological heart conditions affect the efficacy of the pacing algorithms.

3 Results

Our heart model reproduces physiological electrograms, as previously reported in [11]. Atrial and ventricular electrograms are characterized by wide deflections due to the depolarization of neighbouring myocytes. The ventricular electrograms present a small T wave, generated by the transmural voltage gradient induced by the heterogeneity of the ventricular tissue during ventricular repolarization. In addition, our model reproduces healthy cardiac activation times in agreement with experimental data, such as: atrial depolarization ($\simeq$ 125 ms) [17], AV conduction time ($\simeq$ 130 ms) [18], complete ventricular depolarization ($\simeq$ 100 ms) [19].
To demonstrate the adaptability and flexibility of our framework, we analyzed and replicated the clinical case reported in [5]. We simulated a condition of AV block, in which the AVI extension imposed by the VIP algorithm promotes PMT in some cases. AV block condition was replicated by setting the diffusivity value to 0.12 $[cm^2/s]$, γ_0 to *1.5* and γ_1 to *8.25*, thus significantly reducing the conduction velocity in the AV node. We imposed the sinoatrial node activation rate to 75 bpm.
We set pacemaker timing with the following values: LRI=1000ms, URI=460ms, AVI=180ms, PVARP=275ms, VRP=200ms. We studied PMT occurrence caused by the VIP algorithm, varying the AVI extension parameter in a standard interval [50-200]ms and the refractory period of the AV node in the range [240-420]ms [18]. Fig.2 shows the results obtained. The grey region of Fig.2 represents the combination of AV node refractory period and AVI extension values which induced the onset of PMT. In particular, after two initial cycles with an AV delay

of 180 ms, as imposed by the AVI component, we provided the VIP activation, thus the AVI was extended for one search cycle. Fig.3 shows pacemaker signals recorded during the simulation with AVI extension fixed to 150 ms and the AV node refractory period set to 280 ms. This configuration promoted the PMT generation. Fig.4 illustrates some membrane potential maps captured during the PMT onset of the simulation described in Fig.3.

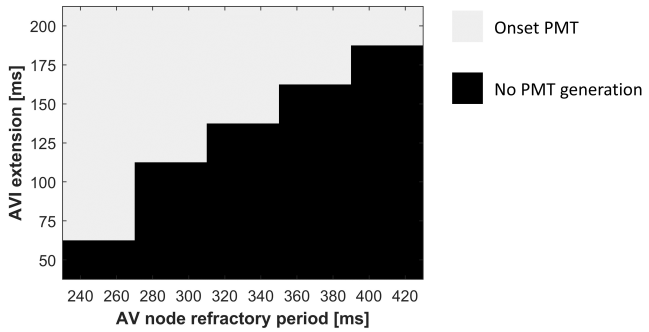

Fig. 2. Results obtained in our heart model, by ranging the AV node refractory period within the interval [240 - 420] ms and the AVI extension parameter of the VIP algorithm within the range [50 - 200] ms. The grey area illustrates the AV node ERP values combined with the AVI extension values which promoted PMT.

4 Discussion

The results obtained with our heart model (Fig.2) show a clear impact of the AV node refractory period for the PMT occurrence during the VIP action. Higher values of the AV node refractory period allow the use of higher AVI extension values with a reduced risk of PMT onset. On the other hand, our results suggest using a lower AVI extension or even disabling the VIP algorithm for lower AV node refractoriness. Thus, our approach could be used to identify the safer case for the specific use of AV delay hysteresis pacing algorithms, such as VIP. In addition, our closed loop system could allow the optimal setting of a proper PVARP in order to avoid the induction of PMT in critical cases. We believe that our bidimensional monodomain heart model could be satisfactorily fitted to specific heart conditions by adjusting the heart geometry, conduction velocity and refractory period of different cardiac tissues, so that it could provide patient-specific prediction of PMT insurgence.
Despite the potentiality of our closed loop framework, our work is still preliminary and showed some limitations. We modelled the AV node as a cardiac tissue

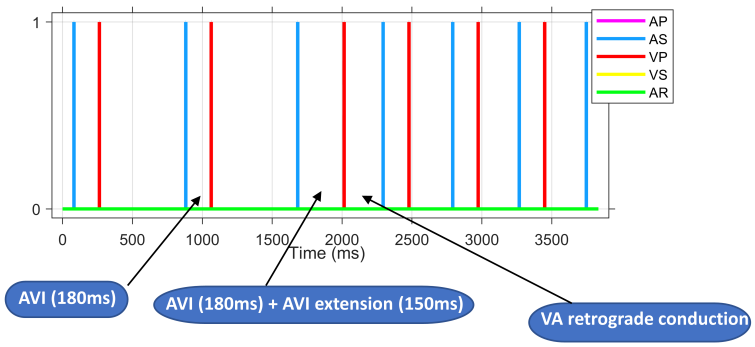

Fig. 3. Pacemaker signals recorded during the simulation with AV node refractory period and AVI extension set to 280 ms and 150 ms, respectively. After two initial cycles, the AVI extension was added to the AVI value for one search cycle, as imposed by the VIP algorithm. Thus, ventricular pacing was sent with an extended AV delay, which induced retrograde VA conduction and consequently PMT.
AP: atrial pacing; AS:atrial sensing; VP ventricular pacing; VS: ventricular sensing, AR: atrial rejected.

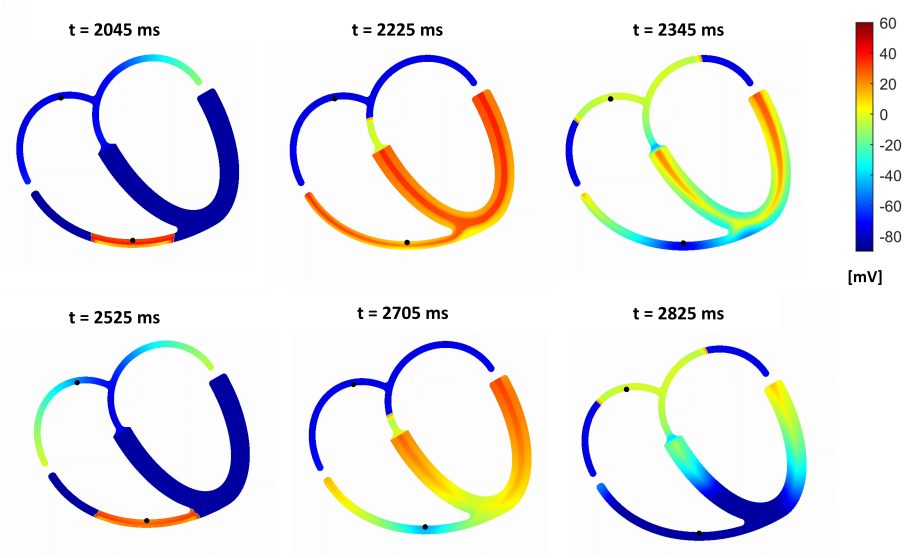

Fig. 4. Membrane potential maps captured during the simulation reported in Fig.3. These snapshots show the generation of retrograde conduction which induced PMT.

that delays the action potential conduction, without delving into a more electrophysiologically accurate AV node modelling [20, 21].
Furthermore, the reported results are consistent within our heart model, but we do not provide clinical validation.
Lastly, patient-specific heart modelling is a highly complex task due to the high inter-subject variability of electrophysiological properties and lack of a complete set of measurements (e.g., refractory period, conduction velocity) for each cardiac region.

5 Conclusion

In this work, we proved the suitability of our heart model to reproduce the specificity of a clinical case report about reduced ventricular pacing. We illustrated how parameters of our heart model (e.g. D, γ_0, γ_1, e) can be related to electrophysiological properties such as conduction velocity and refractoriness. Furthermore, we reported an example of application of our framework closed loop, showing the contribution that it would provide for the assessment of the efficacy and safety of AV delay hysteresis algorithms. The same approach may be extended to other pacing algorithms or to new pacing strategies, whose safety and efficacy would be readily tested in closed loop. For future works, we envision the introduction of more realistic AV node modelling to enhance the accuracy of our heart model.
Despite the current limits, we believe that our closed loop system may represent a useful supporting tool for a preliminary evaluation and comparison of pacing algorithms and pacemaker configuration.

Acknowledgments

We acknowledge the support from the lab "Cloud Computing, Big Data and Cybersecurity" of the Information Engineering Department of the University of Pisa (CrossLab project, Departments of Excellence, Italian Ministry of University and Research). The work is partially supported by the Italian Ministry of Education and Research (MIUR) in the framework of the FoReLab project (Departments of Excellence).

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