Anatomically Detailed Patient-specific Closed-loop Modeling of Heart-pacemaker Interaction

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Abstract

We present an anatomically detailed computational closed-loop model of whole-heart-pacemaker interaction based on patient-specific geometry. The whole-heart model includes tissue anisotropy and a fast conduction system simulating action potential propagation along the atrioventricular node and the His-Purkinje conduction system. We coupled the whole-heart model with a dual-chamber pacemaker model that processes the atrial and ventricular electrograms simulated by the heart model and coherently produces pacing stimuli.

Depolarization and repolarization sequences in our whole-heart model are coherent with clinical data in healthy and pathological scenarios. Moreover, our results showed that the closed-loop model can emulate the heart-pacemaker interaction in clinically relevant scenarios such as the insurgence of endless loop tachycardia. Thus, our closed-loop system provides a promising patient-specific environment for studying the interaction between the heart tissue and the stimulation device.

1. Introduction

In the last decade, pacemaker implantation has increased to treat drug-resistant cardiac arrhythmias [1]. However, recent studies have highlighted a non-negligible percentage of reports of malfunctioning stimulation devices [2]. Indeed, pacemakers are set with advanced algorithms to cope with the complexity and variability of cardiac arrhythmias, making the device behavior not easily predictable when coupled with the patient's specific cardiac activity [3,4]. For example, the combination of abnormal cardiac events, such as premature ventricular contractions (PVCs) or ventriculo-atrial (VA) conduction, and incorrect device programming can cause significant adverse effects, e.g., endless loop tachycardia (ELT). Additionally, open-loop testing procedures are non-exhaustive as they do not consider the heart response to external stimulation. In recent years, numerous studies have addressed the development of closed-loop systems for the validation and design of pacemakers under physiologically relevant conditions [5–8]. A closed-loop system consists of the interaction between a cardiac model, which simulates the generation and propagation of the action potential in the heart tissue, and the activity of a pacemaker (physical or virtual). Thus, closed-loop systems could be useful for model-based design when implementing pacemaker software and algorithms in simulation or hardware emulation.

The most critical component of closed-loop systems is the cardiac model. The cardiac model must be able to interact with the pacemaker (i.e., react to stimuli and generate meaningful electrograms) guaranteeing a physiologically realistic response capable of reproducing a wide range of cardiac conditions (e.g., normal sinus rhythm, tachycardia, bradycardia, atrioventricular blocks, etc.). At the same time, the model must be as simple as possible with a small number of parameters that are easily adaptable to different heart conditions. Furthermore, the cardiac model must be computationally efficient to allow closed-loop simulations in a reasonable time. Previous works developing closed-loop models represented the heart as an interconnected network of nodes representing specific cardiac regions and the specialized conduction system. For example, in the work of Ai et al. [7], the heart model is composed of a network of hybrid automata where the spatial organization of the cardiac regions was taken into account as a delay in the nodal connections allowing the reciprocal interaction between neighbor nodes. Even if finite automata are feasible for efficient simulations modeling the cardiac conduction system, their simplistic nature limits their application in a clinical scenario.

Thus, in this work, we described a novel patient-specific closed-loop model of heart-pacemaker interaction, where the cardiac tissue is modeled with the monodomain formulation in anatomically detailed whole heart geometries.

This paper extends our previous work introducing a simplified 2D closed-loop model of heart-pacemaker interaction [9]. As a case example, we employed our closed-loop system to analyze ELT in first-degree atrioventricular (AV) block condition. ELT is a common pacemaker-mediated tachycardia that arises when the pacing stimuli and the intrinsic heart activity interfere. Indeed, ELT consists of a sequence of ventricular stimuli (VP) followed by atrial sensed events (AS), generally maintained at the maximum ventricular rate. Basically, during ELT, VA conduction works as a retrograde reentrant circuit while the pacemaker works as a "virtual" AV conduction pathway.

2. Methods

We developed an anatomically detailed computational closed-loop model of whole-heart-pacemaker interaction based on patient-specific geometry. The cardiac geometry was obtained from a public repository [10]. Beyond atrial and ventricular chambers, we included in the model a fast-conduction system composed of the AV node and the His-Purkinje pathway. The His-Purkinje system was generated with a constrained optimization method based on the previous work by Ulysses et al. [11]. Fiber orientation in atrial and ventricular tissue was assigned with rule-based methods [12–14].

Action potential in cardiac tissue was governed by the monodomain model, whereas in the fast conduction system, an Eikonal model was adopted. Conduction velocity in the fast conduction system was set to 340 cm/s [15]. Diffusivity values in the ventricles were set to obtain conduction velocities of 70 cm/s longitudinally and 40cm/s transversely [16]. For the atrial tissue, diffusivity values were set so that conduction velocity in the fiber direction was 110 cm/s and 40 cm/s in the cross-fiber directions [17]. The cellular electrophysiology was represented with a phenomenological model previously developed by our group [9, 18] including tissue heterogeneities.

The AV node and Purkinje-muscular junctions are modeled with timed automata governing the connection between the muscular tissue and the fast-conduction system. At the level of Purkinje-muscular junctions anterograde delay (8 ms) and retrograde delay (3 ms) were introduced [19]. Additionally, a 300 ms effective refractory period was introduced at the level of Purkinje-muscular junctions. Regarding the AV node, we set equal anterograde (from atria to ventricles) and retrograde (from ventricles to atria) delay equal to 90 ms in the healthy case, coherently with AH and HA intervals recorded in clinics [20]. To reproduce first-degree AV block we increased the AV node delay to 190 ms [20].

The whole-heart model was coupled with a dual-chamber DDD pacemaker model previously developed by our group [9]. The pacemaker model processes the atrial and ventricular electrograms simulated by the heart model and coherently produces pacing stimuli. Pacemaker electrode were located in the septal wall of the right atrium and the right ventricles. In each closed-loop simulation, we set the DDD pacemaker timing parameters with standard values: AV interval(AVI)=150ms, lowest rate interval (LRI)=1000ms, upper rate interval (URI)=500ms, post-ventricular atrial refractory period (PVARP)=200ms, ventricular refractory period (VRP)=320ms [21].

The closed-loop system was implemented in Matlab and runs on GPU. The monodomain model was solved using the phase field method [22] with spatial and temporal resolution equal to 0.25 mm and 0.02 ms, respectively.

3. Results

Figure 1 shows the healthy activation sequence in the whole heart model. The depolarization starts at the sinoatrial node and spreads out through the right atrium. After 50 ms the AV node is activated. Complete atrial depolarization takes about 120 ms as reported in clinics [23], with the last activation in the proximity of the mitral valve. Through the AV node and the His-Purkinje system, depolarization achieves the Purkinje-muscular junctions and rapidly propagates toward the rest of the cardiac tissue. The time needed for complete depolarization of the ventricles is about 100 ms, as reported experimentally [24]. The base of the ventricles is the last to activate in agreement with ECG imaging studies [25]. The atrial repolarization occurs almost simultaneously with the ventricular depolarization. Lastly, the ventricles repolarize from the epicardium to the endocardium according to the transmural heterogeneity.

Then, we considered a first-degree AV block and we induced an ELT condition through an ectopic premature stimulation. The results are shown in Fig. 2. During sinus rhythm (67 bpm), the impaired AV conduction results in the activation of the cardiac pacemaker (ventricular stimulation) to maintain the AVI lower than 150 ms. After two cycles, we generated an ectopic activation in the left ventricle 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 up to the URI parameter value. The ELT can be terminated by increasing the PVARP parameter.

4. Conclusion

In this work, we described a closed-loop system composed of a DDD pacemaker model and an anatomically

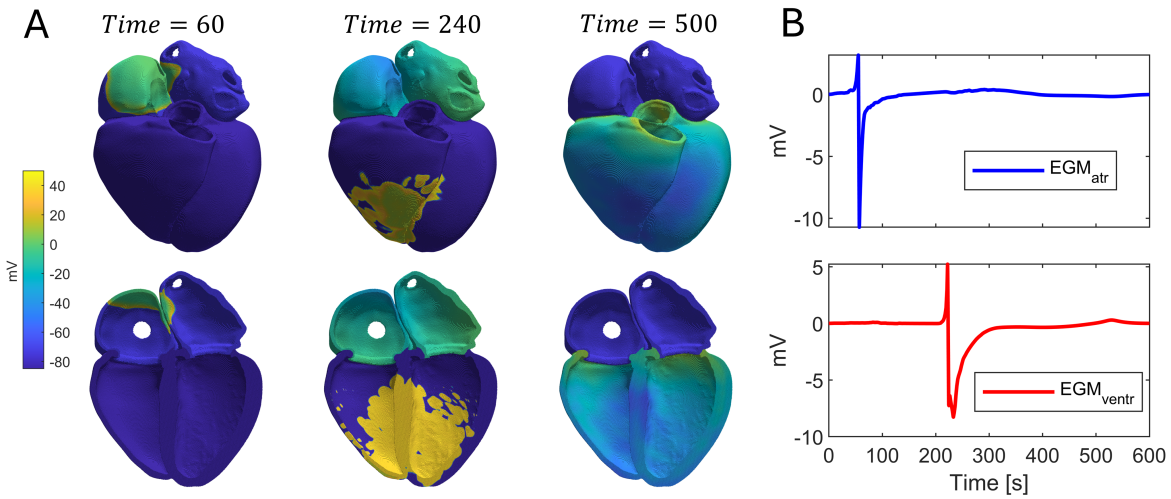

Figure 1. Healthy simulation whole-heart electrophysiology simulation. A) Membrane potential maps showing atrial depolarization, ventricular depolarization, and ventricular repolarization. The entire heart is shown in the first row, whereas the posterior endocardial side is visible in the second row. B) Atrial (blue) and ventricular (red) electrograms.

detailed patient-specific whole-heart model. While preliminary, our results showed that 3D anatomically detailed reaction-diffusion cardiac models are feasible for the development of closed-loop systems aimed at assessing pacing performance. Indeed, despite the model complexity, the computational time was only about 25 minutes for each second of simulated activity. Thus, 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 in a clinical and patient-specific context.

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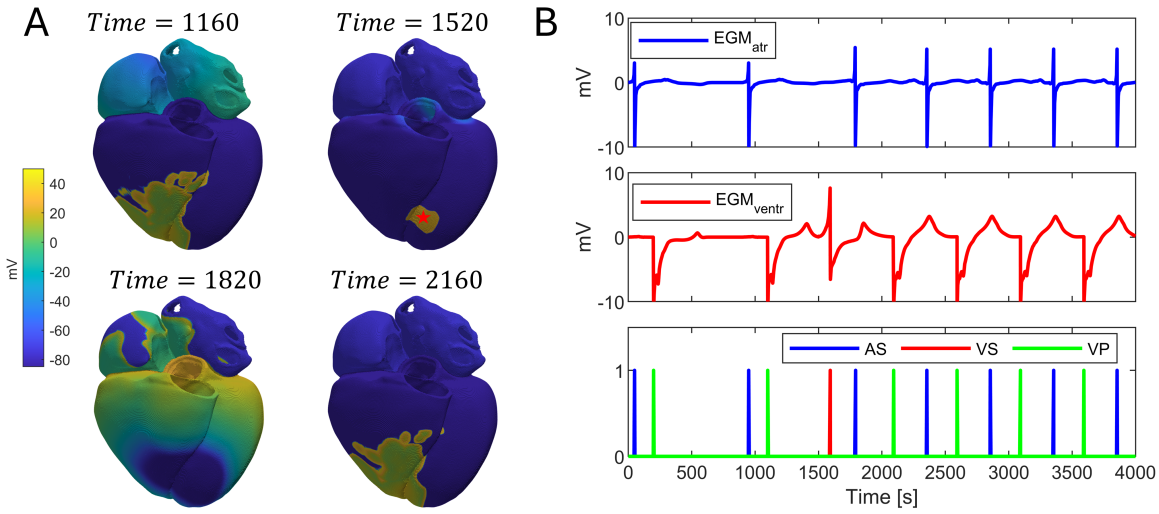

Figure 2. Closed-loop simulation of ELT insurgence in bradycardia conditions. A) Membrane potential maps showing ELT initiation. The red star denotes a PVC. B) Atrial (blue) and ventricular (red) electrograms, and pacemaker signals.

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