Towards a physiologically accurate ECG from numerical simulations: comparative analyses in a simplified tissue model

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Numerical simulations of the human heart can guide medical doctors and researchers only if properly validated. This work presents a computational framework to validate mathematical models of cardiac electrophysiology at the tissue level. Specifically, we focus on the transmural wedge experiment as proposed by Antzelevitch in 1996. This experimental setup is easily reproduced and allows to probe key modeling assumptions and components before organ level simulations are performed. Our results highlight the need to further investigate the conductivity tensor, which, by modifying wave propagation, will affect the ECG morphology at the organ level.

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1 Introduction

Numerical simulations of cardiac electrophysiology (EP) can aid health care professionals in diagnosis and therapy planning only if properly verified and validated. Given its widespread clinical use and importance, the electrocardiogram (ECG) is a critical validation criterion for cardiac EP simulations. The ECG noninvasively measures the heart’s electrical activity based on changes in the surface potential field at specific locations on the patient torso. Based on the morphology, amplitude, and duration of different parts (waves) of the ECG, cardiac diseases can be diagnosed and medical conditions such as arrhythmias can be monitored. Despite its clinical importance, state of the art EP simulations with computed ECGs do not present the physiologically expected QRS complex and T wave, lacking the correct morphology, amplitude, and duration. One of the most commonly observed problems is the presence of QRS fractionations. Without being able to reproduce a physiologically accurate ECG for a healthy heartbeat, it is difficult to adopt these models in investigating cardiac arrhythmias, since any abnormal ECG features generated in the simulations can be due to numerical and modeling shortcomings and not to physiological causes. This fact limits the integration of numerical EP simulations into clinical practice.

2 A transmural wedge model for tissue level validation

Despite the large number of models to simulate cardiac tissue EP (Monodomain, Bidomain, Pseudo-Bidomain, Multidomain, Fractional Monodomain, Reaction-Eikonal, Eikonal, etc.), there is a comparably small amount of publications about their validation. Inspired by the seminal paper by Antzelevitch et al. [1] introducing the so-called transmural wedges to investigate drug-induced arrhythmias, we propose to adopt this idea as a first step to validate cardiac EP models at the tissue level.

This approach presents two main advantages. First, carrying out full heart simulations including the surrounding tissue from the beginning is computationally very expensive. Transmural wedges have the advantage of being significantly smaller and therefore computationally cheaper. Second, organ level simulations include additional modeling uncertainties such as the topology of the conduction system, heterogeneous conductivity of the torso, myofiber/sheetlet model, deformation state, ventricles/atria complex anatomy, and blood composition.

Since QRS complex fractionations are widespread in cardiac EP simulations, we want to rule out modeling and numerical limitations at the tissue level first through a transmural wedge setup. We adopt the Bidomain model to simulate tissue EP together with the PCG canine cell model [2] and the modified TNNP human cell model [3]. The Bidomain tissue model is directly coupled to a surrounding domain (modeled using the Laplace equation) by forcing the nodal values of the extracellular potential to be equal at the interface.

All simulations are initiated by a spherical electrical stimulus of radius 1 mm and amplitude 200 μA/mm². The stimulus is applied in the first 0.5 ms at the position of the current source in Fig 1, left. The ground electrode is modeled as a Dirichlet boundary condition, and all chamber outer boundaries are no-flux boundaries, modeling an insulating environment. The preferential aggregate cardiomyocyte (myofiber) direction is simplified to vary linearly from the endo- to the epicardial wall, with a variation of the helix angle from 60° (at endocardium) to −60° (at epicardium) and a constant 0° E2A. The employed numerical scheme is based on MFEM [4] for the spatial discretization (second order uniform hexahedral spectral elements with edge length ≈ 125 μm) and a standard first order Godunov-type operator splitting in time (Implicit Euler for the diffusion and Rush-Larsen-1 for the cell model) with Δt = 0.01 ms. Simulations were carried out with both cell models and several

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conductivity tensors \( \sigma \) proposed in the literature (See Table 1). Simulation results were compared using two bipolar ECGs, one in the endo- to epicardial direction and one in the circumferential direction as shown in Fig. 1,left.

![Fig. 1: Left: 7 mm \( \times \) 5 mm \( \times \) 3.5 mm chamber with a 4 mm \( \times \) 2 mm \( \times \) 2 mm centered transmural wedge. \( \Omega_B \) denotes the surrounding bath. The bath’s conductivity has been chosen as \( \sigma_B = 0.1 \text{ mS/mm} \). Mid & Right: Computed bipolar ECGs at the marked locations. Dashed lines correspond to simulations with the TNNP cell model, while solid lines correspond to the simulation with the PCG cell model. Colors correspond to the conductivity tensors as given in table 1. Measurement positions are marked with E1-E4.](image)

Table 1: Several cardiac tissue conductivity tensors \( \sigma \) presented in the literature. In the following all values are reported in \( \text{mS/mm} \).

|                | \( \sigma_{i,f} \) | \( \sigma_{i,s} \) | \( \sigma_{i,n} \) | \( \sigma_{e,f} \) | \( \sigma_{e,s} \) | \( \sigma_{e,n} \) | Model         |
|----------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|---------------|
| Clerc (1976)   | 0.17               | 0.019              | 0.019              | 0.63               | 0.24               | 0.24               | calf          |
| Roberts et al. (1979) | 0.28               | 0.026              | 0.026              | 0.22               | 0.13               | 0.13               | dog           |
| Roberts et al. (1982) | 0.34               | 0.06               | 0.06               | 0.12               | 0.08               | 0.08               | dog           |
| MacLachlan et al. (2005) | 0.3                | 0.1                | 0.032              | 0.2                | 0.17               | 0.14               | underspecified |
| Hooks (2007)   | 0.26               | 0.026              | 0.008              | 0.26               | 0.25               | 0.11               | pig           |
| Johnston (2015) | 0.24               | 0.035              | 0.008              | 0.24               | 0.2                | 0.11               | theoretical   |

### 3 Results and Discussion

As shown in Fig. 1, the bipolar ECG measurements in the E4-E3 and E1-E2 directions are strongly dependent on the chosen conductivity tensor. In contrast, the simulations carried out with the PCG canine cell model [2] and the modified TNNP human cell model [3] lead to very similar bipolar ECGs across all tested conductivity tensors. Given the significant effect of the conductivity tensor on the bipolar ECG, a sensitivity analysis in combination with experimental results is needed to estimate the physiological range for the conductivity tensor in health and disease.

The presented setup is computationally inexpensive, allows to validate key model components and numerical solvers at the tissue level, and it complements the N-version verification proposed by Niederer et al [11]. Furthermore, since the transmural wedge setup is well-known to experimental physiologists, this framework facilitates model calibration and validation based on experimental results.

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