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Computational modeling of non-linear diffusion in cardiac electrophysiology: A novel porous-medium approach

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Abstract

The electrophysiological behavior of excitable biological media has been traditionally modeled using a nonlinear reaction–diffusion equation commonly known as the cable equation. To account for the propagating nature of electrical waves, virtually all cardiac electrophysiology formulations proposed to date consider a linear diffusion flux, a constitutive relation known in biology as Fick's law. In this work, motivated by the porous nature of intercalated discs in cardiac muscle cells that mediate intercellular communication and ultimately tissue conductivity, we propose a novel formulation of cardiac electrophysiology that incorporates a nonlinear diffusion term of the porous-media kind. To solve the resulting system of non-linear partial differential equations we develop a non-linear implicit finite-element scheme that is suitable to simulations of large-scale cardiac problems. We show that the proposed porous-medium electrophysiology model results in propagating action potentials that have well-defined wavefronts and travel with finite speed. We also show that the proposed model captures the restitution properties of cardiac tissue similar to the cable model. We demonstrate the capabilities of our method by simulating the activation sequence of a three-dimensional human biventricular heart model, where important microstructural features like cardiomyocyte fiber orientation and the His–Purkinje activation network are successfully incorporated into the simulation.

Keywords: Nonlinear diffusion; Nonlinear finite element method; Cardiac electrophysiology; Computational cardiology; Porous medium equation

1. Introduction

Computational modeling of the heart is an active research field, with important contributions being provided by the computational science community. The development of advanced mathematical models of the electrical activity of the heart, along with the computational power currently available, have been key to understand the onset and development of heart disease at the organ level, as arrhythmias [1]. Remarkable advances have been also conducted at the tissue level

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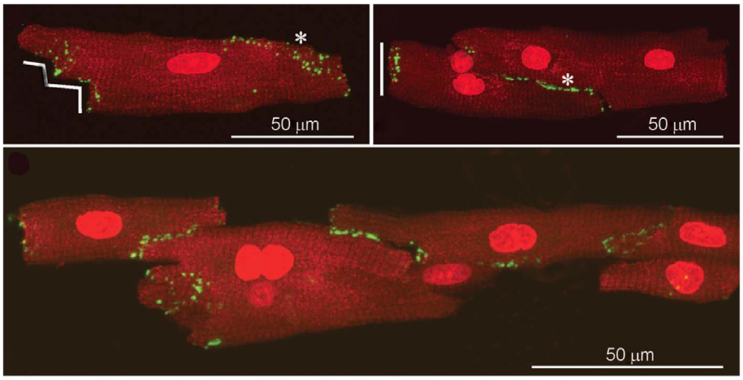

Fig. 1. Confocal micrograph showing the distribution of gap junctions (Connexin 43, in green) in rat atrial myocytes, predominantly in step-like and straight-end intercalated discs configurations. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Source: Reproduced with permission from [16].

by means of phenomenological models able to reproduce several spatio-temporal experimental observations [2,3]. These advances notwithstanding, the complexity of biological tissue with newly discovered cellular mechanisms call for more complex computational models that result in computationally intensive simulations [4–6]. Thus, excitable tissue modeling continues to pose great challenges at both the theoretical and computational levels [7].

Virtually all mathematical models of excitable media derive from the seminal work of Hodgkin & Huxley on the squid giant axon [8] and are typically formulated in terms of the cable equations, either in their monodomain [9] or bidomain [10] version. The resulting set of equations constitute a nonlinear reaction–diffusion system [11] in which spatial propagation of electrical potentials are coupled to evolution equations describing the ion-channel, exchanger and pump gate dynamics. The classical cable theory describes the propagation of electric current across the cell membrane and tissue by assuming the excitable cells as Ohmic cylindrical conductors. From an electrical point of view, cells are characterized by segments with transmembrane nonlinear resistances and capacitances, and axially connected via linear resistances, i.e., the gap junctions [12].

It is currently well established from histological studies that both the intracellular and extracellular spaces in myocardium constitute a highly heterogeneous and anisotropic medium, mainly composed of blood vessels, collagen, fibroblasts, and fat, among others. On such a basis, the homogenization assumptions [13] usually made on the monodomain and bidomain formulations have limitations in reproducing the highly nonlinear dynamics emerging from the ensemble of connected cells. Further, ionic current in the longitudinal direction of cardiomyocytes, for example, has long been recognized as a continuous–discontinuous process [14,15], with the cytoplasmic domain having a low resistivity, and the intercalated discs presenting a high resistivity mainly controlled by gap junctions. Modern microscopy techniques [16] have revealed that intercalated discs can be considered as a porous membrane at the submicron scale, where ions can only pass through gap junctions, which are embedded in the non-conductive sarcolemma, see Fig. 1. Further, the electrical conduction of ions through gap junctions has a markedly non-linear relationship dependent on the electrical potential: gap junctions in regions where voltage is close to the resting potential will conduct at much slower speed than those in regions of voltage closer to activation levels, with conductivity values typically displaying four-fold changes [17].

The non-ohmic nature of ion conduction at the sub-cellular level is in contrast with the standard linear-diffusion flux employed in the cable theory which is valid only for ohmic materials, and for which a natural solution are propagating waves of the electrical potential with smooth Gaussian profiles that asymptotically decrease towards, but theoretically never reach the resting potential. This is equivalent to saying that the resulting traveling wave has a finite speed with infinite support [18]. Such a lack of proper mathematical representation for the non-linear conductivity of the spatial propagation of ionic flux calls for novel approaches in the modeling of the intra- and extra-cellular ionic flow in order to take into account the intrinsic tissue multiscale architecture, always focused on local heterogeneities and applied to realistic scenarios [19].

The porous medium equation, first proposed by [20], is a simple and mathematically sound generalization of the heat equation, where the linear diffusion term that results from Fourier's law of heat conduction is replaced