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Gradient flows and variational principles for cardiac electrophysiology: Toward efficient and robust numerical simulations of the electrical activity of the heart

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ABSTRACT

The computer simulation of the electrical activity of the heart has experienced tremendous advances in the last decade. However, the acceptance of computational methods in the medical community will largely depend on their reliability, efficiency and robustness. In this work, we present a gradient-flow reformulation of the cardiac electrophysiology equations, and propose a minimax variational principle for the time-discretized electrophysiology problem. Based on results from variational analysis, we derive bounds on the time-step size that guarantee the existence and uniqueness of the saddle point, and in turn of the weak solution of the electrophysiology incremental problem. We also show conditions under which the minimax problem is equivalent to an effective minimization principle, which is amenable to a Rayleigh–Ritz finite-element analysis. The derived time-step bounds guarantee the strict convexity of the objective function resulting from spatial discretization, thus ensuring the convergence of gradient-descent methods. The proposed theory is applied to the widely employed FitzHugh–Nagumo model, which is shown to conform to the variational framework proposed in this work. The applicability of the method and its implications on the robustness of time integration are demonstrated by way of numerical simulations of the electrical behavior in a single-cell and 3D wedge and biventricular geometries. We envision that the proposed framework will open the door to the development of robust and efficient electrophysiology models and simulations.

1. Introduction

Computational cardiology has experienced important advances in the last decade with the advent of supercomputing platforms. The computer simulation of the propagation of electrical impulses in the cardiac muscle has received a great deal of attention from the computational science community [33]. Currently, detailed anatomical computational models of the electrophysiology of heart are being used to study the physiology and pathology of the heart [45]. The majority of these models are multiscale in spirit, and therefore prove very useful in understanding the behavior of cellular- and tissue-level mechanisms from the study of organ-level behavior [23]. The translation of such computational models into the clinic is currently being advocated by many research groups around the world [20]. However, the acceptance of computational methods in the

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medical community will largely depend on their efficiency, robustness and reliability, which are currently open avenues of research.

Cardiac electrophysiology concerns the study of the propagation and interaction of electrical waves in biological tissue. The roots of the mathematical formulation of electrophysiological models date back to the efforts of Hodgkin and Huxley [22] on modeling the electrical propagation in squid giant axons. Following the seminal work of Hodgkin and Huxley, a large number of cardiac electrophysiology models of the Purkinjee fibers, myocardial tissue and pacemaker cells have been proposed in the literature, see [14] for a comprehensive survey. Today, we distinguish two main classes of electrophysiological models: biophysical and phenomenological models [38]. Biophysical models [34,3,30,44] aim at describing the complex exchanges occurring at the sarcolemma, or cell membrane, and organelles by quantifying the sub-cellular fluxes of Calcium, Potassium, Sodium and Chlorides ions through the several different mechanisms available, i.e., ion channels, pumps, exchangers and gap junctions. Phenomenological models [16,32,1,15] aim at modeling a larger spatial and temporal scale than biophysical models, and they consider a reduced set of state variables and parameters that do not necessarily have a direct physical meaning but make these models more tractable from a mathematical analysis and computational implementation viewpoint.

Regardless of their nature, virtually all deterministic cardiac electrophysiology models fall in the category of non-linear reaction–diffusion equations [27]. The numerical solution of cardiac electrophysiology equations has been predominantly carried out using finite-difference [42,8,36], finite-volume [21,26] and finite-element [40,48] approximations for the spatial discretization, whereas the time integration has been predominantly addressed by finite-difference schemes. The most traditional time-integration schemes used in cardiac electrophysiology are explicit Euler methods, which have proven particularly suitable for large-scale simulations where solving a large linear system of equations is generally avoided. However, it is well known that time-step bounds that arise from stability considerations for explicit methods become more stringent as the mesh size decreases, thus reducing the efficiency of those methods as a finer spatial discretization is considered. Moreover, the determination of stability conditions can become cumbersome or even intractable when dealing with highly non-linear systems. In the search of more stable algorithms, semi-implicit and fully-implicit [29] schemes have also been employed, allowing for larger time steps at the expense of solving a nonlinear set of equations at each time step. Depending on the electrophysiology model, the resulting set of equations can be highly nonlinear, and even contain discontinuous functions. As a consequence, the convergence of classical solution methods can hardly be guaranteed, thus hindering the robustness of implicit methods.

The mathematical analysis of electrophysiology models has been mainly developed during the last decade, following the popularization of the numerical simulation of cardiac electrical activity by the scientific computing community. The proof of existence and uniqueness of solutions to the phenomenological FitzHugh–Nagumo bidomain model was developed by Colli Franzone and Savaré [6] based on classical results from the general theory of evolution variational inequalities. Using the same abstract variational framework, Sanfelici [41] has shown the convergence of Galerkin finite-element approximations of the FitzHugh–Nagumo model. More recently, a multiscale analysis based on the Γ-convergence theory has shown the adequacy of the bidomain model to represent the microscopic behavior of cardiac tissue [37]. Recent advances showing the existence and uniqueness of solutions to more complex biophysical models have been addressed in [47].

Although it was observed in [6] that the FitzHugh–Nagumo equations have a variational structure, this fundamental property and its implications have not been exploited to date, neither by the biophysical nor the computational communities. In this work, we present a gradient-flow reformulation of the cardiac electrophysiology equations that allows one to understand these models in a new light, namely, in terms of variational principles such as minimization of free energy, maximization of entropy, and phase transitions, which are pervasive in the thermodynamics, mechanics, electromagnetism, and the biophysics literature. From a mathematical viewpoint, variational principles offer a wealth of analysis results regarding existence of solutions using the tools of the modern calculus of variations [9]. From a numerical point of view, variational principles are the underlying framework for some of the most celebrated numerical methods, like the finite element method [7]. Variational formulations for gradient-flow systems have been applied to a wide variety of physics and engineering problems, particularly by the computational mechanics community in the formulation and numerical solution of multiscale material models [35,24,25] and soft-tissue biomechanics [49,12].

The paper is organized as follows. Section 2 is concerned with the theoretical aspects of the variational principle for cardiac electrophysiology introduced in this work. We start by stating, in a general form, the initial boundary value problem that governs the electrical behavior of cardiac tissue. Generalized potentials are then introduced, and a gradient-flow reformulation of the electrophysiology problem based on such potentials is presented. Using a Backward-Euler time-discretization scheme, an incremental minimax variational formulation equivalent to the time-discretized governing equations is introduced, and conditions on the time-step size are stated in order to guarantee existence and uniqueness of saddle points. Exploiting the local nature of the evolution equations for the state variables, an effective minimization problem amenable to non-linear finite-element methods is derived. The phenomenological FitzHugh–Nagumo model is then analyzed in view of the proposed theory, and bounds on the time-step size that only depend on the parameters of the model are derived to ensure strict convexity of the effective minimization problem. The time-step bound, in turn, guarantees existence and uniqueness of the weak solution. In Section 3, we employ the proposed method to numerically solve three examples of increasing geometrical complexity. The convergence of the solution to the non-linear problem for each example is studied and analyzed based on the time-step bounds derived for the FitzHugh–Nagumo model. Section 4 ends with a discussion on the obtained results and future perspectives.