

# Preface

The goal of this book is to present some of the most successful and advanced mathematical and numerical models used in the field of cardiac electrophysiology. The bioelectric activity of the heart is the subject of a vast and still growing interdisciplinary literature in medicine, physiology, bioengineering, mathematical biology, chemistry, physics and bioinformatics. The long history and diversity of this field of research is shown e.g. by the earlier monographs by Jack, Noble and Tsien [250], Peskin [383], Nelson and Gezelowitz [346], Pilkington and Plonsey [386], by the reference works by Pilkington et al. [387], Panfilov and Holden [369], Keener and Sneyd [273], Gulrajani [215], Plonsey and Barr [393], Efimov et al. [158], and by some of the periodic review books by Zipes and Jalife [588–590]. In the last decade, more specific monographs on computational electrocardiology were published by Sachse [446], Pullan et al. [406], Sundnes et al. [502]; see also Macfarlane et al. [312]. Since the emphasis of this book is on mathematical and numerical aspects of the models and algorithms presented, we hope that this monograph will present new elements and will complement the works above.

Electrocardiology deals with the description of both intracardiac bioelectric phenomena and the extracardiac electric field generated in the animal or human body. The practice of modern medicine relies on noninvasive imaging technologies, such as CT, MRI and PET, for diagnostic purposes and for driving therapeutic procedures. Even though cardiac arrhythmias are among the major causes of death and disability, a noninvasive imaging technique yielding an accurate and reliable diagnosis of the electrophysiological state of the heart is not yet available. Clinic Electrocardiography deals with the detection and interpretation of noninvasive potential measurements collected from the time course of the usual electrocardiograms (ECG) at a few points on the body surface or from the evolution of body surface maps, i.e. potential distribution maps on the body surface reconstructed from measures at numerous electrodes (100 or more, see the surveys by [504, 511]). Since the electrode location of the ECG is centimeters away from the heart surface and the current conduction from heart to thorax yields a strong signal

attenuation and smoothing, the information content of ECGs and body maps is limited and it is a difficult task to extract from these signals detailed information on pathological heart states associated with ischemia or sudden death. Indeed, the origin of arrhythmogenic activity or the existence of abnormal electrophysiological substrates in many cases may not be easily inferred from the sequence of cardiac excitation.

The scientific base of Electrocardiology is the so-called *Forward Problem of Electrocardiology*, i.e. modeling the bioelectric cardiac sources and the conducting media in order to derive the potential field. Of considerable applicative interest are also the so-called *Inverse Problems of Electrocardiography* in terms of potentials (see e.g. the review [216, 442] and [68, 69, 415]) or in terms of the cardiac sources (see e.g. [110, 439]).

In the past few decades, experimental electrophysiology has been increasingly supported by the mathematical and numerical models of computational electrocardiology. The formulation of models at both cellular and tissue levels provide essential tools in order to integrate the increasing knowledge of the bioelectrochemical phenomena occurring through cardiac cellular membranes. Detailed cellular phenomena are described in microscopic membrane models and the latter are then inserted in macroscopic tissue models in order to investigate their effects at tissue level. These coupled models are then validated by comparing simulated results with experimental in vitro and in vivo data, generating a feedback loop that may lead to improved and more detailed models and/or the redesign of new experiments. As a further step, these electrophysiological models are being increasingly coupled and integrated with mechanical models of tissue deformation, hemodynamical models of cardiac blood flow and more in general with models of the cardiovascular system. This complex integrative effort is the current focus of several research projects, for example such as the Physiome Project ([www.physiome.org.nz](http://www.physiome.org.nz)) and the EC-sponsored Virtual Physiological Human (VPH) Initiative ([www.vph-noe.eu](http://www.vph-noe.eu)). Ultimately, the integration of these models should provide new tools enabling the biomedical community to link genetic and proteomic databases to anatomy and to functions at the cellular, tissue and organ level.

From a macroscopic point of view, the Forward Problem of Electrocardiology is described by the so-called Bidomain model for the evolution of the intra, extracellular and extracardiac potential fields. The two main components of the Bidomain model are: (a) the dynamics of the ionic current flow through the cardiac cellular membrane, modeled by a system of ordinary differential equations and (b) a macroscopic representation of the cardiac tissue modeled as a bidomain superposition of the intra and extra cellular media characterized by anisotropic conductivity tensors associated with the fiber architecture of the myocardium. The Bidomain model is computationally expensive because of the involvement of different space and time scales. In fact, meaningful portions of cardiac tissue have sizes on the order of centimeters, while the steep potential gradient is localized in a thin layer about 1 mm thick, requiring discretizations on the order of a tenth of millimeter. Moreover, a normal heartbeat can last on the order of 1 s, while the time constants of the rapid kinetics involved range from 0.1 to 500 ms, requiring in

some phases time steps on the order of the hundredths of milliseconds (or less when currents or shocks are applied). Therefore, in realistic three-dimensional models it is possible to have discrete problems with more than  $O(10^7)$  unknowns at every time step and simulations have to be run for many thousands of time steps.

A simplified cardiac tissue model is the anisotropic Monodomain system, i.e. a parabolic reaction-diffusion equation describing the evolution of the transmembrane potential coupled with an ionic membrane model. This model has been widely used for three-dimensional simulations due to its reduced computational costs.

Current large-scale simulations of whole heartbeats using Bidomain and Monodomain models require adaptive and parallel tools in order to reduce their high computational cost. While both tools can in principle be applied to both space and time, most studies employ adaptive methods in time and parallel solvers in space, since the other alternatives are still the subject of current research even for simpler model problems in two dimensions. Therefore in this book, we present the main numerical techniques for efficiently simulating cardiac reaction-diffusion models. In particular, we focus on scalable parallel Bidomain solvers that are capable of efficiently scaling their performance for increasing processor counts in current and future multicore parallel computers.

Among the important aspects of cardiac modeling not covered in this book are cardiac mechanics, blood flow, electro-mechanical and fluid-mechanical coupling, and cardiac imaging. Research in these fields is also growing tremendously and a separate book would be necessary to properly present the main mathematical and numerical models available. For an overview of these related fields, we refer to e.g. the monographs [47, 140, 242, 369, 446], the works [138, 232, 246, 384, 385, 491] with the references therein, and the recent proceedings of the conferences FIMH (Functional Imaging and Modeling of the Heart) [21, 180, 266, 316, 327, 366, 447], CINC (Computing in Cardiology, <http://cinc.org/archives/2013/>, <http://cinc.org/archives/2012/>), STACOM (Statistical Atlases and Computational Models of the Heart) [74–76].

The book is structured in the following chapters.

In Chap. 1, we give a brief review of the basic physiology and anatomy of the heart, including the specialized cells of the cardiac conduction system, working cardiomyocytes, fibroblasts, extracellular matrix, collagen, gap junctions, connexin, cardiac stem cells and the fiber and laminar architecture of the ventricular myocardium. We then present the main phases of a cardiac action potential, its spatial and temporal heterogeneity, and continue by describing the main features of an electrocardiogram (ECG), with its leads, deflections, intervals and main alterations. The chapter concludes with a review of the main cardiac imaging techniques currently available.

Chapter 2, introduces the fundamental tools for modeling the bioelectric activity of excitable cells: the Nernst – Planck equation, the Goldman-Hodgkin-Katz (GHK) current-voltage relation, and the Nernst equilibrium potential, together with its thermodynamical derivation. Next, the Poisson-Nernst-Planck (PNP) electrodiffusion model is derived and two classical current – voltage relations are obtained in the short and long channel limits. With these tools, we can define the basic electrical

circuit model of the cellular membrane, where the transmembrane current, modeled as the sum of the capacitive and ionic currents through the membrane, must balance the given applied current. The ionic currents are then described by using the classical ion channel gating models, allowing us to build cardiac action potential models. We start with the celebrated Hodgkin-Huxley (H-H) model and briefly review some of the historical ventricular models based on the H-H formalism, such as the Beeler-Reuter, Luo-Rudy I and Luo-Rudy dynamic models, examining also how these ionic models satisfy the principle of charge conservation and how to derive the so-called restitution curve for the action potential duration of a given ionic model. Reduced models, such as the minimal FitzHugh-Nagumo model are also presented, together with their phase-plane analysis, bifurcation and frequency diagrams.

Chapter 3 presents mathematical models of periodic cardiac cells arrangements, beginning with one-dimensional fibers, deriving the cable equation, showing a one-dimensional homogenization technique and the main results on one-dimensional traveling waves, namely traveling fronts for the bistable equation and traveling pulses for the FitzHugh-Nagumo system with a diffusion term. We then move to models of cardiac tissue in more dimensions, illustrating a two-scale homogenization technique that allow us to derive an averaged Bidomain model, proving both well-posedness results for the cellular and the averaged models and convergence results based on  $\Gamma$ -convergence techniques. We then present an heuristic derivation of the anisotropic Bidomain model in both parabolic-parabolic and parabolic-elliptic forms. Well-posedness results are derived using different techniques, such as time semi-discretization, Faedo-Galerkin techniques, and fixed point arguments.

Chapter 4 presents the main reduced macroscopic cardiac models: the linear anisotropic Monodomain model, Eikonal models (both Eikonal-curvature and Eikonal-diffusion models), and the relaxed non-linear anisotropic Monodomain model. These model are then given in dimensional form and some well-posedness results are summarized. The chapter is concluded by a numerical comparison between activation time maps computed with these reduced models and the full Bidomain model.

Chapter 5 is devoted to the modeling of anisotropic cardiac sources, presenting both the differential and integral formulations of the potential field. Approximate representations of cardiac sources such as the heart surface and oblique dipole source models are given, as well as the cardiac sources splitting into axial and conormal components in both axially symmetric and orthotropic media. The chapter concludes with a numerical example illustrating this source splitting and its comparison with experimental results.

Chapter 6 briefly reviews the Inverse problem of Electrocardiology, in terms of cardiac sources, in terms of wavefront and in terms of potential alone, presenting the mathematical models of the cardiac electric sources and their numerical approximations.

Chapter 7 presents the main numerical techniques employed in the space and time discretizations of the Monodomain and Bidomain cardiac models. In particular, we apply the finite element method in space and finite difference methods in time. The latter can be fully implicit or semi-implicit, and can employ

decoupling techniques and operator splitting methods between the ordinary and partial differential equation components of the cardiac models. The chapter is concluded by a review of numerical methods for the eikonal–diffusion equation.

Chapter 8 is devoted to the construction and analysis of parallel solvers for the discrete Bidomain systems arising at each time step of an implicit or semi-implicit time discretization. Our parallel solvers are based on domain decomposition methods, more specifically on overlapping Schwarz methods, which provide scalable preconditioners accelerated with a Krylov space iterative method such as PCG or GMRES. After recalling the main results of the abstract Schwarz theory, we derive scalable convergence rate bounds for two-level and multilevel additive Schwarz preconditioners for the Bidomain system. We then present the results of several numerical tests with these Schwarz preconditioners in additive, multiplicative and hybrid form, showing their scalability on different parallel machines and investigating their performance with respect to the different discretization parameters. We also present how these Schwarz preconditioners can be combined with block-diagonal and block-factorized preconditioners suggested by the  $2 \times 2$  block structure of discrete Bidomain systems.

Chapter 9 illustrates how to apply the Bidomain and Monodomain solvers developed in the previous chapters to simulate and study some of the most important phenomena in cardiac electrophysiology. More precisely, we present detailed simulations of: (1) the genesis of cardiac excitation and virtual electrode phenomena, in particular anode/cathode make/break and strength-interval (S-I) curves; (2) the anisotropic propagation of excitation and recovery fronts in three dimensional domains; (3) the effects of cardiac heterogeneities (transmural and apico-basal) on fronts propagation and APD distribution; (4) the morphology of electrograms, in particular of the QRS complex and the T wave; (5) the computation of excitation and repolarization time markers; (6) the presence of ischemic regions and effects such as ST-segment depression and elevation; (7) the simulation of cardiac reentry phenomena.

An Appendix lists some of the main cardiac simulation research projects, software libraries, some related monographs and tables of physical units and constants used in the book.

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Pavia, Italy  
Milano, Italy  
Milano, Italy  
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Piero Colli Franzone  
Luca F. Pavarino  
Simone Scacchi

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Colli Franzone, P.; Pavarino, L.F.; Scacchi, S.

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