FROM CELLULAR ELECTROPHYSIOLOGY TO ELECTROCARDIOGRAPHY

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INTRODUCTION

Since many cardiac pathologies manifest themselves at the cellular and molecular levels, extrapolation to clinical variables, such as the electrocardiogram (ECG), would prove invaluable to diagnosis and treatment. One ultimate goal of the cardiac modeler is to integrate cellular level detail with quantitative properties of the ECG (a property of the whole heart). This magnificent task is not unlike a forest ranger attempting to document each leaf in a massive forest. Both the modeler and ranger need to place fundamental elements in the context of a broader landscape. But now, with the recent genome explosion, the modeler needs to examine the “leaves” at even much greater molecular detail. Fortunately, the rapid explosion in computational power allows the modeler to span the details of each molecular “leaf” to the “forest” of the whole heart. Thus, cardiac modeling is beginning to span the spectrum from DNA to the ECG, from nucleotide to bedside.

Extending cellular detail to whole-heart electrocardiography requires spanning several levels of analysis (Figure 1.1). The one-cell model describes an action potential recording from a single cardiac myocyte. By connecting an array of these individual myocytes (via gap junctions), a linear network (cable), two-dimensional (2D) network or three-dimensional (3D) network (slab) model of action potential propagation can be constructed. The bulk electrophysiological signal recorded from these networks is called the local extracellular electrogram. Subsequently, networks representing tissue diversity and realistic heart geometries can be molded into a whole heart model, and finally, the whole heart model can be placed in a torso model replicating lung, cartilage, bone and dermis. At each level, one can reconstruct the salient electric signal (action potential, electrogram, ECG) from the cardiac sources by solving the forward problem of electrophysiology (Chapter 2).

Simply put, cardiac modeling is equivalent to solving a system of non-linear differential (or partial differential) equations, though vigorous reference must be made to numerous
FIGURE 1.1. Levels of Analysis. One-cell models include the study of compartments and ion channels and their interactions. The basic electrophysiological recording is the action potential. Network models investigate the connectivity of one-cell units organized in arrays. An electrical measure of bulk network activity is the extracellular electrogram. Finally, many patches molded into the shape of a whole heart (in addition to torso variables) gives rise to the ECG. See the attached CD for color figure.

laboratory experiments which aim to determine the nature and coefficients of each equation. These equations provide a quantitative measure of each channel, each cell, and networks of cells. As more experiments are done and data obtained, the model can be made more complex by adding appropriate differential equations to the system. Thus, as more information about the cellular networks, tissue structure, heart and torso anatomy are obtained, a better reconstruction of the ECG becomes possible. Until recently, however, modeling efforts have primarily focused on accurately reconstructing normal behavior. But with the accumulating experimental history of cardiac disease (such as myocardial ischemia, long-QT syndrome and heart failure), modelers have also begun to revise and extend the quantitative description of these models to include important abnormal behaviors.

This chapter will first focus on the theoretical one-cell equations, which are only solved in the time domain. Subsequently, the one-cell model will be expanded to represent multiple dimensions with the incorporation of partial differential equations in space. At each level of analysis, the appropriate electrical reconstruction is discussed in the context of relevant pathology to emphasize the usefulness of cardiac modeling.