MATHEMATICAL MODELING FROM ION CHANNEL TO ECG: AN INTRODUCTION

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Abstract

Mathematical modeling plays an important role in cardiac electrophysiology. The purpose of this paper is to outline what the present state of computer hardware and algorithm development permits us to model, and to show how mathematical models help us to understand the pathophysiology of the heart.

1. Introduction

Modeling and experimentation have complementary roles in science. The daily business of research is to test theories using observational data. It is crucial to determine which observations agree with the theory and which do not. This can be a difficult task if complex systems are involved. For example, one cannot state the diameter of the earth without first modeling it as a sphere. This model could be improved by observing that the planet is slightly shorter from pole to pole than across the equator. The resulting model has two parameters instead of one. This model too can be improved upon, by observing that the earth is in fact a little egg-shaped, the south pole being slightly flatter than the north. Obviously, this model ignores the mountains, and a model that includes a million extra parameters to describe the mountains still ignores the trees, et cetera. The true number of parameters is not even countable. The same is true for any system that is more complicated than a small molecule, and particularly for biological systems. The model one chooses to use depends on the investigation or application one envisages.

Models are often mathematical. In the case of the earth, an important scientific question could be answered by looking at it from a distance and observing that its shape is more like an orange than like a pancake. Successively more elaborate questions involve first numbers, then mathematics, and finally computers. If a model is so complex that a computer is necessary to evaluate it, we speak of a “numerical model” or “computer model.” Every model is a (mathematical) representation of the theory and the experiment, with simplifications that are believed to be acceptable. The model predicts what experimental observations should be made under given conditions if the theory is true and the simplifications are indeed acceptable. Importantly, a model is often necessary to give a meaning to descriptive terms, such as “the diameter of the earth.” In electrophysiology, the electrical resistivity of tissue is an example of a term that has no meaning unless a simplified model of the tissue is assumed, because the actual resistivity varies enormously on a sub-cellular scale.

In the biological sciences, complexity is an important challenge for models. The level of detail that is believed to be relevant can be high. Often, the simplifications used are more dictated by what is technically possible than by what is believed acceptable. The growing
performance of computers has therefore had a major impact on the reliability of mathematical models.

There are many topics in biology that are beyond the grasp of mathematical modeling, due to a lack of quantitative data. On the other hand, a mathematical approach is very well possible and indeed necessary in a field like cardiac electrophysiology. The electrical behaviour of individual cells is well known, and computational resources now permit us to build a model of an entire heart based on models of individual cells. The use of such models allows us to test whether hypothesized cellular-level changes may explain changes observed in clinically measurable signals such as the electrocardiogram (ECG) and endocardial catheter electrograms.

2. A brief history of cardiac models

The first mathematical model of the ECG was developed a century ago by Einthoven [8]. It considers the heart as a vector in a plane. The length and orientation of this vector can be determined from the potentials measured with three electrodes, on both arms and on the left leg of the subject. For any combination of measured potentials, there is a unique amplitude and orientation of the vector. Despite its simplicity, this model is still used today, for example to quantify the QRS angle in the frontal plane. Indeed, the notion “QRS angle” has no meaning if this model is not assumed.

Einthoven’s model only explains the three limb leads. To understand the precordial ECG leads, a lot more complexity must be added. We need more than one vector, and we must be more specific about what we mean by these vectors; they will have to become physical current dipoles. We must also specify mathematically how these current dipoles relate to the electrical potential on the torso, and we must find a way to decide how strong these dipoles are and in what direction they point. To do so, Miller and Geselowitz in 1978 [13] created a computer model with 4000 points. Activation could propagate from one point to another. When they activated a few early sites on the endocardium, the model would imitate the normal activation order of the heart, which by that time had been measured [5]. From the activation times, and a simple model of the action potential, they could calculate their dipole sources, and from these, through some complicated mathematics, they could compute the ECG. This simulated ECG resembled a normal ECG, demonstrating that the activation order measured in an explanted heart accounts for the measured shape of the QRS complex in the ECG.

An even more elegant demonstration of the power of mathematical models is the work of Hodgkin and Huxley in the 1950s [9]. They performed extensive measurements of ionic currents through the membrane of a squid’s giant axon. By studying the transient currents that resulted from imposed changes in membrane potential, they were able to devise mathematical models for the individual ionic currents. When they assembled these models into a model of the membrane as a whole, they were able to reproduce the neuron’s action potential. This, in the words of Noble and Rudy [15] “spectacularly succesful” model not only proved that these ionic currents are the most important determinants of the action potential, but also predicted the existence of distinct channels for sodium and potassium ions, which could be verified experimentally only decades later [8]. This work earned Hodgkin and Huxley a Nobel prize in 1963.

Later, models for different cell types were developed, notably for cardiac myocytes. Models also became more complicated, some accounting for up to 20 different ionic currents. The models also generalized the Hodgkin-Huxley scheme, from a series of independent “gates,” which had a certain probability to open or close, to a model of a complex molecule that can assume different conformational states, with probabilities to flip from one state into another.
It is with such complicated models [23,25] that researchers nowadays attempt to predict the behaviour of anything from a single cell to an entire heart, and from there to simulate the ECG.

3. The present: reaction-diffusion models

Cell models can be coupled to model a piece of tissue. This coupling allows the simulation of propagating action potentials. Such a model is called a reaction-diffusion model. Reaction stands for the ionic current behaviour as a function of the membrane potential, and diffusion stands for the spread of current from one cell to another. The equation for the membrane potential accounts for this: current can not only come through the local membrane, but also through gap junctions from neighbouring cells, as a “diffusion current.” In practice, we usually do not assign a membrane model to each individual cell; we can let each membrane model represent a little block of tissue with a size in the order of a tenth to a quarter of a millimeter. The size of these blocks is dictated by the properties of the steep depolarisation wavefront, which must be captured accurately enough to obtain the correct propagation velocity.

This type of model differs from that by Miller and Geselowitz in that it does not use predefined action potential shapes and conduction velocities, but computes action potentials and their propagation simultaneously, based on what is assumed to be the underlying mechanism. With respect to the depolarisation sequence, such models allow accurate modeling of delayed activation for example due to sodium-channel malfunctions (Brugada syndrome), ischaemia, or tissue damage (Cardiomyopathy). Reaction-diffusion models also challenge our thoughts on ventricular repolarisation: It is generally accepted that the repolarisation order of the ventricles must be mostly opposite to the depolarisation order to obtain T-wave concordance (positive T waves in leads that have a predominantly positive QRS complex). The necessary dispersion of action potential duration can easily be constructed in models that use predefined action potentials. But a reaction-diffusion model in which action potential duration is based on experimental evidence on the membrane level does not reproduce this behaviour at all. As a temporary repair, these models are nowadays configured with a partly hypothetical dispersion of the repolarising current density, e.g. the slow component of the delayed rectifier current [26]. However, this failure plays an important role in pointing out that information is lacking on this point, and that in fact we do not understand why normal T waves on the ECG are concordant with the QRS complexes.

4. Bidomain models

The first reaction-diffusion models were based on the assumption that all the electrical resistance of the tissue comes from the connections between the cells. The extracellular medium was assumed to be a perfect conductor. This assumption was important to keep the mathematics tractable. More recently, it has become possible to account for the resistivity of the extracellular medium. This gives rise to so-called “bidomain” models [31]. In contrast to their “monodomain” predecessors, these models can account for the shape of the electric signals that can be measured with electrodes inserted in the myocardium (“electrograms”). However, because the numerical simulation of a bidomain model is more than an order of magnitude slower than the simulation of a monodomain model [24], the monodomain model continues to underlie many simulations of cardiac propagation and ECG. The validity of the monodomain model for these purposes was recently shown in a comparative study [17].
5. Applications

Thousands of papers and many books have been published on the development and application of cardiac models. An exhaustive review of model applications is therefore not the purpose of this section. Rather, a few examples will be cited, and one application will be treated in detail in the next section.

The model studies that are, from the physiologists or clinicians point of view, the most remote from the patient’s bedside are those in the field of nonlinear dynamics. These studies, published mostly in physics journals such as *Chaos* and *Physical Review E.*, deal with cardiac arrhythmia on the most basic level [4]. Such studies have contributed to the development of our understanding that ventricular fibrillation is not always completely chaotic, but can have organized components; to the hypothesis that dispersion of refractoriness is arrhythmogenic; and to the analysis of concealed pathways in ventricular tachycardia substrates [32].

Closer to the heart, spiral and scroll wave phenomena are studied extensively in models ranging from a simple sheet to the complete human ventricles [1,33]. Using realistic reaction-diffusion models, these studies now begin to address the sometimes non-intuitive effects of drugs on hypothesized arrhythmia mechanisms [1,30]. Model studies of this kind are found not only in the physics journals, but also in a wide range of biomedical-engineering, physiology, and cardiology journals such as *Annals of Biomedical Engineering*, and *Am. J Physiol. H*.

Strong links with experimental research are present in studies where the relation between ion-channel heterogeneity, mutations, cellular behaviour, and tissue behaviour are investigated. For example, modeling studies demonstrated that known ion-channel heterogeneities can explain many features of the ECG [7], and that paradoxical effects of mutations can be mechanistically understood [2,22]. Other studies involved reaction-diffusion models to investigate arrhythmia development in ischaemic myocardium [21].

Bidomain reaction-diffusion models are applied by many researchers to investigate the determinants of success or failure of defibrillation shocks [27]. Modeling studies of applied currents for stimulation and defibrillation have predicted the phenomenon of “virtual electrodes” [6]. Another highly relevant application of bidomain models is the elucidation of the mechanisms underlying such important experimental and clinical tools as monophasic action potentials and activation-recovery intervals [3,20,29].

Presently, while reaction-diffusion models have taken their place in simulations of relatively small tissue preparations, most simulations of the ECG are still based on relatively simple models, similar to the Miller-Geselowitz model discussed above, only more detailed, or easier to operate. An excellent example here is the freely available ECGSIM program [16]. The continued use of relatively simple models here is well justified, because the ECG changes due to many phenomena (e.g. ischemia, repolarisation disorders, ectopic beats) can be very well understood in terms of such simple models. However, these models do have their limitations, and several groups have now made their first steps towards models that will be able to simulate all the way from the most obscure ion-channel abnormality to the most ubiquitous diagnostic tool in cardiology [12,28].

6. An example

This section is devoted to a single example, in which a large-scale model of the human heart was applied to the study of “primary ST-segment depression” in the ECG. The ST segment is the part of the ECG between the QRS complex, which represents the depolarisation of the ventricles, and the T wave, which represents their repolarisation. In a normal ECG, the ST segment is more or less isoelectric, because at that time all cells have approximately the same
membrane potential. In case of myocardial ischaemia, a part of the myocardium has an elevated resting membrane potential. This leads to changes in the part of the ECG between the T wave and the following QRS complex. However, for technical reasons this part of the ECG is defined to have zero potential. Therefore, it is the ST segment that appears to be modified, and the diagnosis of ischaemic symptoms is said to be based, among other ECG features, on the ST segment.

It is relatively easy to understand how the ST segment changes in case of ischaemia affecting the entire thickness of the ventricular wall in a limited part of the heart muscle. For example the work of Holland and Brooks [10] predicted this correctly, based on a very simple non-numerical model of the heart. Such “transmural” ischaemia leads to ST elevation measured on ECG electrodes that overly the affected region of the heart. However, the same authors also made predictions with respect to ischaemia affecting only the inner layers of the wall, which is believed to occur as a result of partial occlusion of a coronary artery. In this case, they predicted ST depression on the same electrodes. This prediction is cited in many textbooks of cardiology and has strongly influenced the way clinicians think about ST-depression phenomena. However, later work with numerical models has shown that it does not agree with current knowledge of the heart. Oversimplification was the culprit in this case. Holland and Brooks, and other authors in the same epoch [10,14] assumed that the conductivity of the heart was the same in all directions. Under this assumption, numerical models also predict ST depression [11,18]. However, the cardiac muscle is profoundly anisotropic, with a much larger conductivity along than across the fibers. This anisotropy is believed to be 4 times stronger inside the networks of cells and gap junctions than in the interstitium. This unequal anisotropy causes a reversal in the sign of the ST-segment changes caused by non-transmural ischaemia. Present-day models predict a small ST elevation in this case [11,18].

Thus, recent modeling work has thus refuted the hypothesis that regional nontransmural ischaemia underlies ST depression in the ECG. Still, ST depression is known to occur, and to be related to partially obstructed coronary arteries. To resolve this paradox, we investigated the influence of the extent of a nontransmural ischaemic region on the sign of ST-segment changes. We found that if the region covers more than two thirds of the heart, ST depression can occur [18]. Moreover, if the region covered the whole heart, the simulated ECG resembled the ECG shape that is typically obtained during stress testing in patients with non-ST-elevation ischaemic syndromes [19]. This leads to the new hypothesis that a global nontransmural ischaemia underlies this particular ECG morphology.

A regional non-transmural ischaemia is thought to occur when a single coronary artery is malfunctioning. In contrast, for global nontransmural ischaemia to occur, either a multivessel disease or a global malfunctioning of the coronary vasculature must be assumed. This suggests that ST depression does not signal a single blocked artery. Rather, it indicates that two or three arteries are affected, or that the heart has become too weak to support its own blood supply.

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