



A simple analytical model of action potential duration profile in electrotonically-coupled cells



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ABSTRACT

Electrotonic interactions between cardiac cells modulate the dispersion of action potential duration (APD). This paper provides a complete mathematical analysis of a simple model of exponential-shaped repolarization in a network of electrotonically-coupled cells with different intrinsic APDs. The forward problem consists in computing the APD map in the coupled system from the intrinsic APD map. A closed-form algebraic formula is derived for the forward problem. The inverse problem, inferring the intrinsic APDs from an APD map, is proved to have a unique solution (if any). Perturbation analysis leads to an efficient and accurate Newton-based solver for this specific inverse problem. Finally, an analytical expression is obtained for the convolution filter that solves the forward problem in one dimension. This mathematical framework forms a solid theoretical basis for future development and validation of repolarization parameter estimation techniques in detailed models of cardiac tissue.

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1. Introduction

The action potential duration (APD) of a cardiac cell is a commonly-used parameter to quantitatively describe cardiac cell repolarization. The intrinsic APD of a cell is the APD measured when the cell is (or if it were) isolated. When cells are coupled through gap junctions, electrotonic currents tend to reduce the differences in action potential morphology between neighboring cells. As a result, the distribution of APD observed in a tissue may significantly differ from the distribution of intrinsic APD characterizing local cellular properties [1,2]. This is particularly true in the presence of intrinsic heterogeneities [3] and in small hearts [4,5]. Geometry, boundary effects [6], activation pattern [7], wavefront curvature [8], wavefront collision [9], and possible coupling with fibroblasts [10,11] also modulate APD dispersion.

Since altered dispersion of repolarization has been recognized to be arrhythmogenic [12], computer models have been developed to investigate these mechanisms. While *in vivo* experiments report APD measured in tissue or in isolated cells at a limited number of locations (e.g. biopsies), mathematical models need the spatial profile of intrinsic properties of cardiac cells as input parameters. The determination of the intrinsic APD of all the cells of a het-

erogeneous tissue based on the APD of the coupled cell network is a form of inverse problem. The corresponding forward problem consists in predicting the APD map of the coupled system from the intrinsic APD map. Defauw et al. [13] proposed a Gaussian Green's function model and a deconvolution approach to solve this problem.

In this paper, we explore the mathematical basis of these forward and inverse problems in a very simple model of repolarization in a coupled cell network. The model is amenable to analytical calculations for both the forward and the inverse problems, and enables the study of existence and uniqueness of the solution to the inverse problem.

2. Mathematical model

2.1. Minimalist cellular model

The simplest model of repolarization is given by an exponential decay. In that model, the membrane potential u is zero at rest, instantaneously rises to 1 when the cell is stimulated above threshold (at $t = 0$), and then $u(t)$ follows the (nondimensional) equation:

$$\frac{du}{dt} = -ku, \quad u(0) = 1, \quad (1)$$

where $k > 0$ is the only parameter of the cellular model. The shape of the resulting action potential $u(t) = \exp(-kt)$ is compared to that of a detailed atrial membrane model in Fig. 1. Although at

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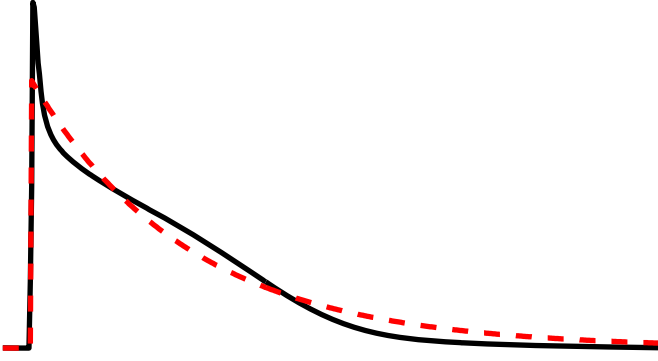


Fig. 1. Action potential morphology: Nygren et al. ionic model [15] (solid line) and exponential model (red dashed line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

least four state variables may be needed to replicate the morphology of a wide range of cardiac cell action potentials [14], the exponential model still reproduces the most basic feature of triangular-like atrial action potentials. Complex multi-variable models (except possibly a sum of exponentials) are unlikely to enable analytical calculations.

The action potential duration (APD), may be expressed as a function of the parameter

$$a = \frac{\int_0^{+\infty} t u(t) dt}{\int_0^{+\infty} u(t) dt} \quad (2)$$

where the integration starts at depolarization time ($t = 0$). This quantity represents the time interval between the onset of depolarization and the center of mass of the action potential waveform. In an isolated cell with parameter k , we have $a = 1/k$, which corresponds to the time constant of the exponential, or to the APD measured at 63% repolarization. The APD might be expressed as $\gamma \cdot a$, where $\gamma \approx 2$ for a spike-and-dome action potential with steep phase 3 repolarization and $\gamma \approx 3$ for a triangular-shaped action potential. In our case of exponentially-decaying action potentials, $1/a$ represents an estimate of the apparent parameter k of a cell with action potential $u(t)$. The choice $\gamma = 3$ would correspond to an estimate of the APD at 95% repolarization. In the sequel, for the sake of simplicity, the parameter a will be referred to as APD.

This unusual choice of APD definition and the very simplified action potential shape are (probably) necessary conditions to enable the derivation of exact analytical expressions in a network of coupled cells. Section 6 illustrates how the approach can be extended to more complex models and other definitions of APD when only numerical solutions are sought.

2.2. Network of coupled cells

If n cells with parameters k_1, \dots, k_n are coupled through gap junctions, the evolution of the membrane potentials $u_1(t), \dots, u_n(t)$ is governed by the system

$$\frac{du_i}{dt} = -k_i u_i - \sum_{j=1}^n g_{ij} (u_i - u_j), \quad u_i(0) = 1, \quad (3)$$

where $g_{ij} = g_{ji} \geq 0$ represents the coupling between cell i and cell j . The initial condition corresponds to the situation where all cells are stimulated simultaneously. This choice enables us to focus on repolarization. This equation is rewritten in matrix form

$$\frac{d\mathbf{u}}{dt} = -\mathbf{K}\mathbf{u} - \mathbf{G}\mathbf{u} \quad (4)$$

where the vector \mathbf{u} contains the components u_i , the diagonal matrix \mathbf{K} the components k_i and the symmetric semi-positive definite

\mathbf{G} the coupling conductances. The n -vector $(1, 1, \dots, 1)$ will be denoted by $\mathbf{1}$. Using that notation, $\mathbf{G}\mathbf{1} = \mathbf{0}$. The consequence is that $(\cdot)^t$ means transposed)

$$\mathbf{1}^t \frac{d\mathbf{u}}{dt} = -\mathbf{1}^t \mathbf{K}\mathbf{u} = -\mathbf{k}^t \mathbf{u}. \quad (5)$$

In the limit where all coupling conductances are scaled up until they uniformly tend to $+\infty$, all the u_i become identical to prevent an infinite current from flowing between the cells and the average of the membrane potentials follows the evolution of an isolated cell with $k = (k_1 + \dots + k_n)/n$.

The evolution of the coupled system can be easily calculated using the eigenvalues $\lambda_j > 0$ and eigenvectors \mathbf{v}_j of the symmetric positive definite matrix $\mathbf{M} = \mathbf{K} + \mathbf{G}$

$$\mathbf{u}(t) = \exp(-\mathbf{M}t) \mathbf{1} = \sum_{j=1}^n \exp(-\lambda_j t) \mathbf{v}_j \mathbf{v}_j^t \cdot \mathbf{1}. \quad (6)$$

3. Forward problem

The purpose of this section is to provide an analytical expression for the APD of all the coupled cells, $\mathbf{a} = (a_1, \dots, a_n)$, given their parameters $\mathbf{k} = (k_1, \dots, k_n)$, that is, to determine the mapping $\mathbf{a} = \mathcal{A}(\mathbf{k}, \mathbf{G})$.

3.1. Equation for the action potential duration

After substitution of the solution (6), the numerator of (2) is given by

$$\int_0^{+\infty} t \mathbf{u}(t) dt = \sum_{j=1}^n \frac{1}{\lambda_j^2} \mathbf{v}_j \mathbf{v}_j^t \cdot \mathbf{1} = \mathbf{M}^{-2} \cdot \mathbf{1} \quad (7)$$

since the matrix \mathbf{M}^{-2} has eigenvectors \mathbf{v}_j with eigenvalues λ_j^{-2} . Similarly,

$$\int_0^{+\infty} \mathbf{u}(t) dt = \sum_{j=1}^n \frac{1}{\lambda_j} \mathbf{v}_j \mathbf{v}_j^t \cdot \mathbf{1} = \mathbf{M}^{-1} \cdot \mathbf{1}. \quad (8)$$

If the matrix \mathbf{A} is defined as the diagonal matrix containing the elements of \mathbf{a} in its diagonal, then

$$\mathbf{A} \mathbf{M}^{-1} \mathbf{1} = \mathbf{M}^{-2} \mathbf{1}, \quad (9)$$

or, equivalently,

$$(\mathbf{K} + \mathbf{G})^2 \mathbf{A} (\mathbf{K} + \mathbf{G})^{-1} \mathbf{1} = \mathbf{1}. \quad (10)$$

This equation relates, for a given distribution of coupling, the APD (\mathbf{A}) to the intrinsic parameters (\mathbf{K}). The vector \mathbf{a} can therefore be computed by solving two linear systems instead of simulating the evolution.

In the absence of coupling ($\mathbf{G} = \mathbf{0}$), $\mathbf{A} = \mathbf{K}^{-1}$, that is, $a_i = 1/k_i$. These values are referred to as the *intrinsic* APD.

3.2. Scaling law

It appears that the evolution equation (3) is invariant when the conductances g_{ij} are scaled by g^{-1} , the parameters k_i by g^{-1} and the time by g . As a result,

$$\mathcal{A}(\mathbf{k}, \mathbf{G}) = g^{-1} \mathcal{A}(\mathbf{k}/g, \mathbf{G}/g). \quad (11)$$

This enables the elimination of one parameters for explicit calculations.

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