Estimability Analysis and Optimal Design in Dynamic Multi-scale Models of Cardiac Electrophysiology

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BACKGROUND

The following set of equations represents a simplified version of the Hodgkin-Huxley model of sodium and potassium channel kinetics that give rise to cardiac action potentials. The model is expressed as a system of three partial differential equations in time (t) and one dimension of space (z), where the latter represents a long fiber of excitable cardiac tissue. The model has 13 free parameters and an input stimulus function I_{stim}. Setting $D = 0$ yields a single-cell version of the model.

$$\begin{aligned} \partial V/\partial t &= -I_{\text{ion}} - I_{\text{stim}} - D\partial^2 V/\partial z^2 \\ \partial m/\partial t &= (m_\infty - m)/\tau_m \\ \partial h/\partial t &= (h_\infty - h)/\tau_h \end{aligned} \qquad \begin{aligned} m_\infty &= [1 + e^{-(V-E_m)/k_m}]^{-1} \\ h_\infty &= [1 + e^{-(V-E_h)/k_h}]^{-1} \\ \tau_h &= 2\tau_{h0}\frac{e^{\delta_h(V-E_h)/k_h}}{1+e^{(V-E_h)/k_h}} \end{aligned}$$

The ion channel currents are expressed as follows, where m and h are gating variables that regulate the activation and deactivation of the fast sodium channel, respectively.

$$I_{\text{ion}} = g_{\text{Na}} m^3 h (V - E_{\text{Na}}) + g_{\text{K}}(V - E_{\text{K}}) e^{-(V-E_K)/k_r}$$

Figure 1 illustrates the single cell model solutions under a smoothed square wave stimulus lasting 2ms (top left panel). **Figure 2** illustrates the cross-section solution for a fiber of cardiac tissue under action potential propagation conditions (excitation is induced by neighboring tissue; $I_D = D\partial^2 V/\partial z^2$).

RESEARCH QUESTIONS

Can experimental observations of I_{ion} versus V, separately during depolarization and repolarization, and in single-cell and fiber cross-sections (i.e., four types of experimental data) be used to simultaneously estimate all of the model parameters? If not, what subset of the model parameters are estimable?

METHODS

Denote the vector of model parameters θ, then the nonlinear least-squares (NLS) estimate of θ satisfies the following estimating equations:

$$\boldsymbol{J}(\boldsymbol{x},\theta)^T(\boldsymbol{y} - \boldsymbol{\eta}(\boldsymbol{x},\theta)) = \boldsymbol{0}$$

Where $\boldsymbol{y}$ and $\boldsymbol{x}$ are the vectors of measured currents and voltages in each of the four experimental modes, $\boldsymbol{\eta}(\boldsymbol{x},\theta)$ is the model solution for current as a function of voltage and experiment type, and $\boldsymbol{J}(\boldsymbol{x},\theta)$ is a matrix of gradients of $\boldsymbol{\eta}(\boldsymbol{x},\theta)$ at each voltage $\boldsymbol{x}$, i.e., the **sensitivity matrix**.

$$\boldsymbol{J}(\boldsymbol{x},\theta) = \begin{bmatrix} \frac{\partial\eta(x_1,\theta)}{\partial\theta_1} & \cdots & \frac{\partial\eta(x_1,\theta)}{\partial\theta_p} \\ \vdots & \ddots & \vdots \\ \frac{\partial\eta(x_n,\theta)}{\partial\theta_1} & \cdots & \frac{\partial\eta(x_n,\theta)}{\partial\theta_p} \end{bmatrix}$$

Thus, θ is uniquely NLS estimable when the columns of the sensitivity matrix are linearly independent, or equivalently, when the information matrix $I(\boldsymbol{x},\theta) = \boldsymbol{J}(\boldsymbol{x},\theta)^T\boldsymbol{J}(\boldsymbol{x},\theta)$ is nonsingular. The reciprocal condition number (RCN) and other single-number summaries can be used to assess overall linear dependence. However, these methods do not distinguish the parameters that are inestimable.

FIGURES

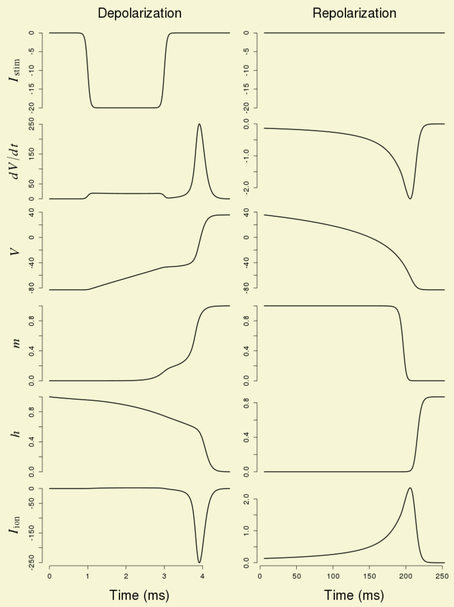

Figure 1. Single-cell solution

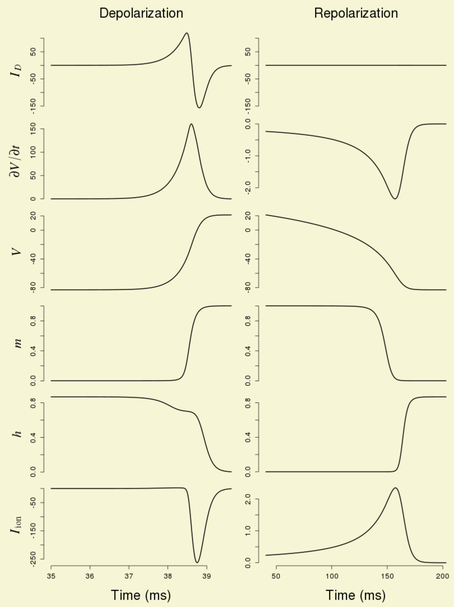

Figure 2. Fiber cross-section solution

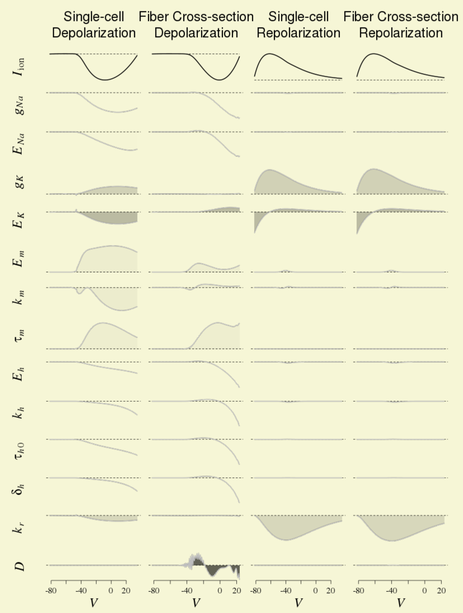

Figure 3. Augmented sensitivity plot

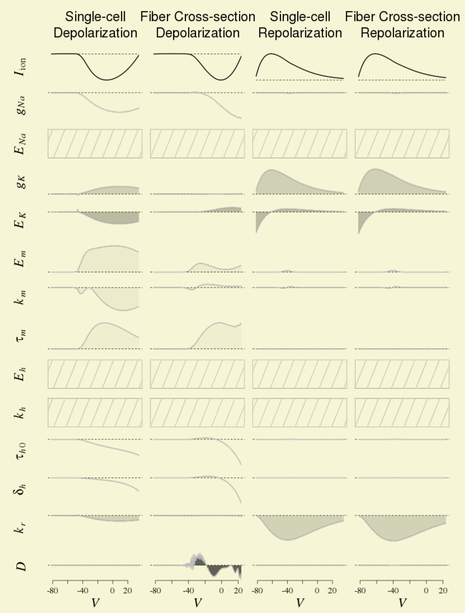

Figure 4. Fixing E_{Na}, E_{h}, and k_h

METHODS (cont.)

We present a graphical method to aid in the assessment of parameter estimability. The **augmented sensitivity plot** illustrates the values of the sensitivity matrix, organized by parameter and experiment. For each parameter, the shading intensity of the regions between zero and the plotted sensitivity values represents the degree of linear independence in the corresponding parameter sensitivities, and thus, the degree of estimability of the corresponding parameter. Specifically, for each parameter, the shading intensity is the proportion of variability in the corresponding sensitivity values that can be explained by a linear combination of the sensitivity values associated with each other parameter. This is computed using a linear least-squares method.

RESULTS

Figure 3 Illustrates the augmented sensitivity plot for the sensitivity matrix associated with the current-voltage curves (top row of panels) during depolarization and repolarization, for both single-cell and fiber cross-section experiments. The magnitude of currents during depolarization are much larger than during depolarization. The sensitivities for each experiment were scaled so that their contributions to the estimating equations were similar.

It is clear in Figure 3 that the repolarization data are most informative about the potassium channel kinetics (i.e., parameters g_{K}, E_{K}, and k_r), and the depolarization data are informative about sodium channel activation kinetics (i.e., E_m, k_m, and τ_m). Of course, the fiber cross-section data, but not the single-cell data, are informative about the charge diffusion parameter D. Some parameters (i.e., g_{Na}, E_{Na}, E_h, k_h, τ_{h0}, and δ_h) are weakly estimable given the information in the four current-voltage curves. The RCN for the scaled information matrix was 2.56×10^{-9}, indicating weak simultaneous estimability of the model parameters.

The shading of sensitivity values indicates that the pairs (g_{Na}, E_{Na}), (τ_{h0}, E_h), and (δ_h, k_h) are nearly co-linear. Thus, the figure suggests that one parameter of each pair may have improved estimability if the other parameter were fixed (or estimated by other means). **Figure 4** illustrates the augmented sensitivity plot corresponding to a reduced parameterization (i.e., fixing E_{Na}, E_{h}, and k_h). This improves the RCN by nearly ten fold (3.81×10^{-8}). The shading intensity associated with g_{Na} is marginally darker. However, the sodium channel deactivation parameters τ_{h0} and δ_h remain weakly estimable.

EXTENSIONS

The augmented sensitivity plot can be used to evaluate the estimability of model parameters under a variety of estimating frameworks, including weighted nonlinear least-squares and maximum likelihood estimation, including likelihood estimation associated with mixed-effects methods. This is important, since the estmability of model parameters can be heavily influenced by weighting and experimental uncertainty in the observed data. Indeed, weighting some experimental results more highly than others is a type of optimal experimental design, a process that may benefit from enhanced visualization techniques.