Estimating parameters of the Hodgkin-Huxley cardiac cell model by integrating raw data from multiple types of voltage-clamp experiments

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BACKGROUND

The following set of equations are a simplified version of the Hodgkin-Huxley[1] model of sodium and potassium channel kinetics that give rise to cardiac action potentials. The model is expressed as a system of four ordinary differential equations (where V represents transmembrane potential and r represents gating variables m, h, and j) in time (t).

$$\begin{aligned} \partial V/\partial t &= -I_{\text{ion}} & r_\infty &= [1+e^{-(V-E_r)/k_r}]^{-1} \\ \partial r/\partial t &= (r_\infty - r)/\tau_r & \tau_r &= 2\tau_{r0}\frac{e^{\delta_r(V-E_r)/k_r}}{1+e^{(V-E_r)/k_r}} \end{aligned}$$

The ion channel currents are expressed as follows, where m, h, and j are gating variables that regulate the activation, an slow and fast inactivation of the sodium channel, respectively. The two addends represent the sodium and potassium channel currents, denoted I_{Na} and I_{K}, respectively. Excluding parameters associated with the I_{K}, the model has 14 free parameters.

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

Figure 1 illustrates the model solutions under I_{Na} 'activation' and 'recovery from inactivation' (RI) voltage clamp protocols. The former is used to study the activation and fast inactivation of the sodium channel, which is modeled by the variables m and h, respectively. The RI protocol is used to study the slow recovery from inactivation, which is modeled by the j gating variable. **Figures 1 and 2** illustrate the two protocols and the typical I_{Na} responses.

RESEARCH QUESTIONS

Can experimental observations of the raw I_{Na} versus time traces under the activation and recovery-of-excitability voltage clamp protocols, be used to simultaneously estimate all of the model parameters using nonlinear least squares (NLS)? If not, what subset of the model parameters are estimable?

METHODS

Denote the vector of model parameters θ, then the NLS estimate of θ satisfies the following estimating equations:

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

Where $\boldsymbol{y}$ and $\boldsymbol{t}$ are the vectors of measured currents and times in each sweep of the two voltage clamp protocols, $\boldsymbol{\eta}(\boldsymbol{t},\theta)$ is the model solution for current as a function of time, protocol, and sweep, and $\boldsymbol{J}(\boldsymbol{t},\theta)$ is a matrix of gradients of $\boldsymbol{\eta}(\boldsymbol{t},\theta)$ at each time, i.e., the **sensitivity matrix**.

$$\boldsymbol{J}(\boldsymbol{t},\theta) = \begin{matrix} \frac{\partial\eta(t_1,\theta)}{\partial\theta_1} & \cdots & \frac{\partial\eta(t_1,\theta)}{\partial\theta_p} \\ \vdots & \ddots & \vdots \\ \frac{\partial\eta(t_n,\theta)}{\partial\theta_1} & \cdots & \frac{\partial\eta(t_n,\theta)}{\partial\theta_p} \end{matrix}$$

Thus, θ is estimable when the columns of $\boldsymbol{J}(\boldsymbol{t},\theta)$ are linearly independent, or when the information matrix $I(t,\theta) = \boldsymbol{J}(\boldsymbol{t},\theta)^T\boldsymbol{J}(\boldsymbol{t},\theta)$ is nonsingular.

The Moore-Penrose generalized inverse was used to implement NLS, to ensure the uniqueness of an NLS solution. When the information matrix is nonsingular, this method returns the NLS solution with the smallest Euclidean norm.

FIGURES

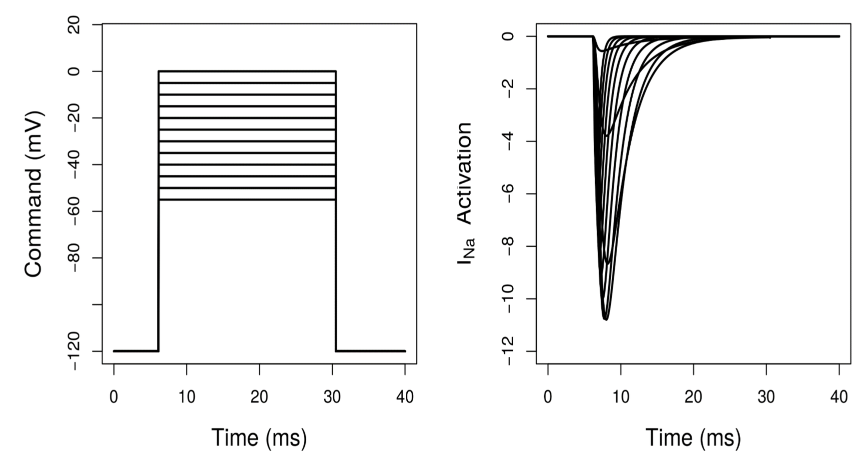

Figure 1. I_{Na} Activation Protocol

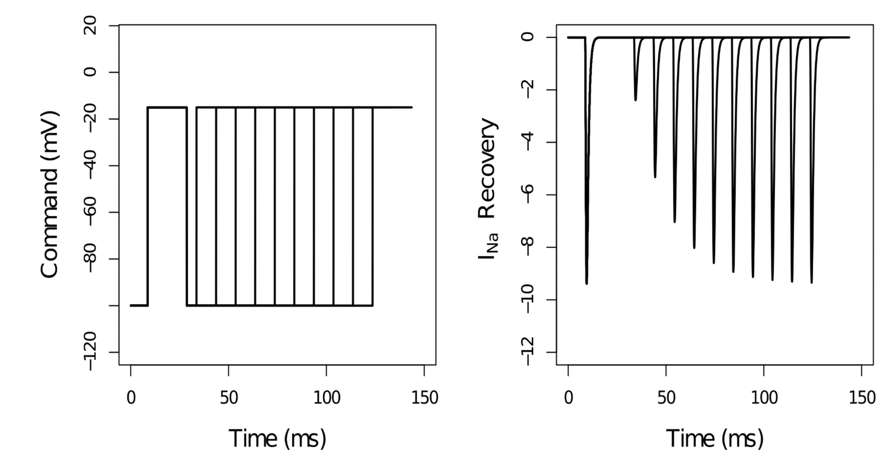

Figure 2. I_{Na} RI Protocol

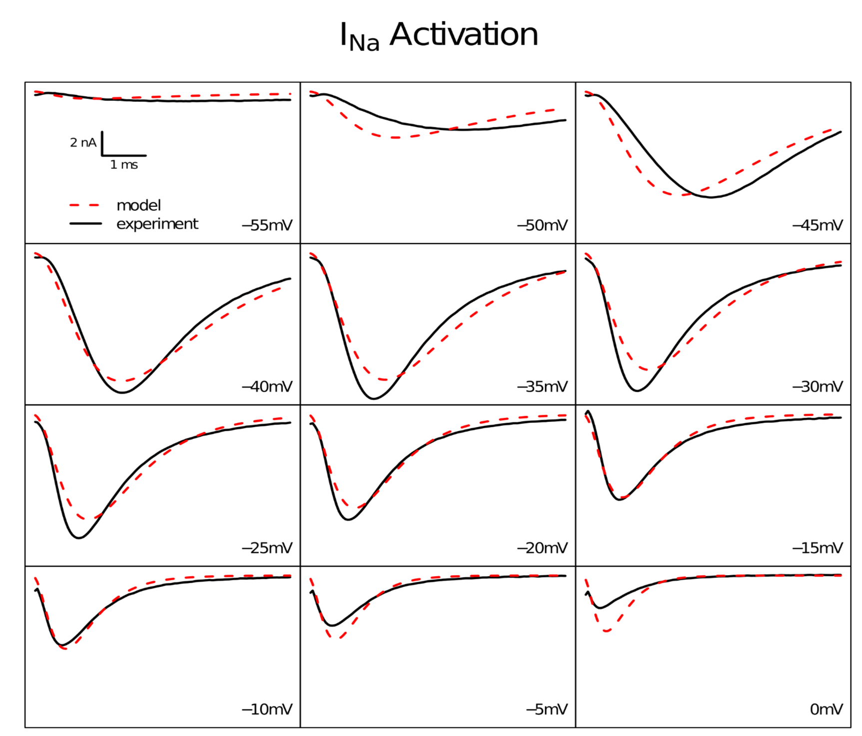

Figure 3. I_{Na} Activation Model Fit

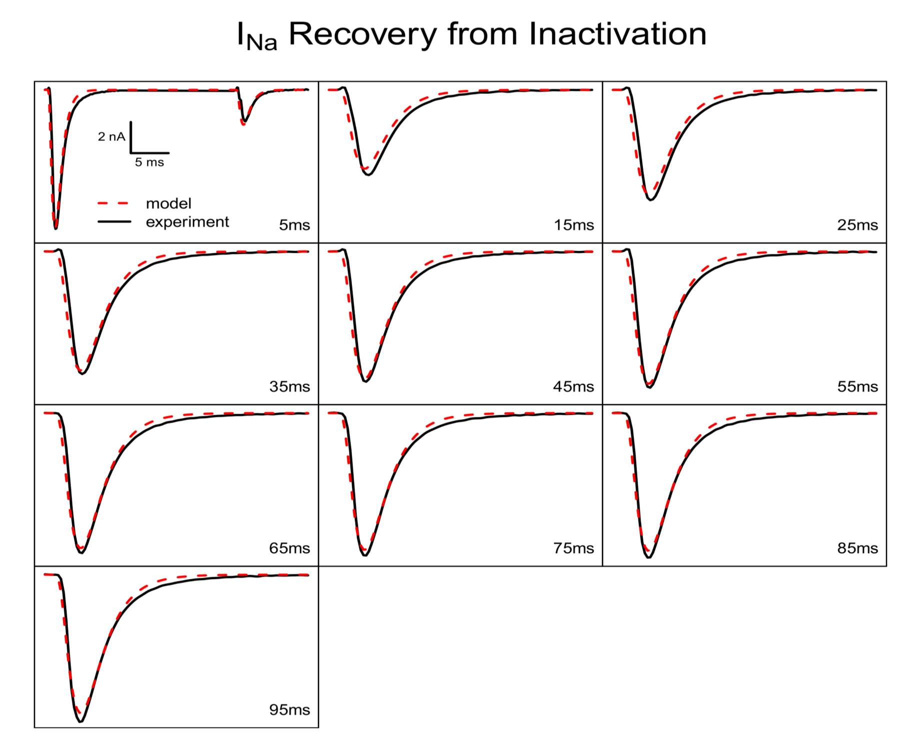

Figure 4. I_{Na} RI Model Fit

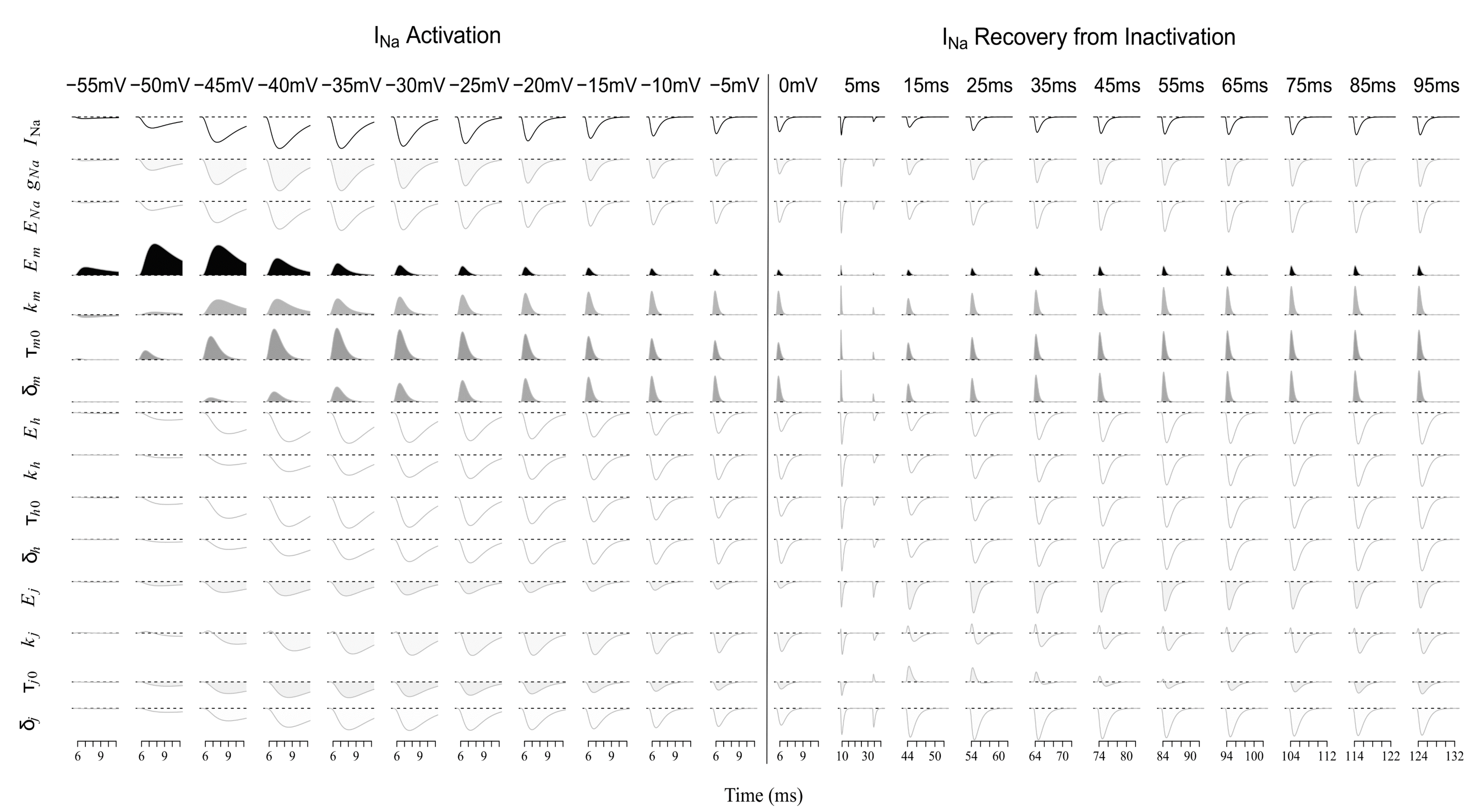

Figure 5. Augmented Sensitivity Plot for Estimated Parameters

METHODS (cont.)

We present a graphical method to aid in the assessment of parameter estimability. The **augmented sensitivity plot**[2] illustrates the values of the sensitivity matrix, organized by parameter and experiment. The shading intensity of the regions between zero and the plotted sensitivity values represents the degree of linear independence in the 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 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

Figures 3 and 4 show the raw traces (solid black curves) and model fits (dashed red curves) under the activation and RI protocols, respectively. While the model fits the RI data well, there is some lack of fit in the activation data. This suggests inadequacy in the model functional forms.

Figure 5 shows the augmented sensitivity plot for the sensitivity matrix associated with the I_{Na} traces for each sweep of the activation and RI protocols (top row). It is clear that the two protocols are most informative about the m and j gating parameters, whereas the h gating parameters are poorly informed by these data. The RCN for the information matrix at the estimated parameters was 3.48×10^{-12}, indicating weak simultaneous estimability of the model parameters. Excluding h gating parameters, in addition to g_{Na}, and E_{Na}, the RCN associated with the remaining parameters was 1.37×10^{-8}, a significant improvement. Nevertheless, the estimates of δ_j and E_j are strongly correlated ($\rho = 0.987$).

FUTURE DIRECTIONS

- Integrate other types of voltage clamp protocols, and other data.
- Identify a minimal set of VC protocols that are sufficient to simultaneously estimate all of the model parameter.
- Use a flexible regression technique to explore alternative functional forms for the model equations, especially for τ_r.
- Compare the bias and efficiency of the current method (simultaneous estimation using raw data from a variety of sources) to the conventional method of piecewise estimation using summaries of the raw data from a single source.

ACKNOWLEDGEMENT

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CITATIONS

1. Hodgkin, A. L. and Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. Journal of Physiolgy 117, 500–544.
2. McLean, K. A. P. and McAuley, K. B. (2012). Mathematical modelling of chemical processes – obtaining the best model predictions and parameter estimates using identifiability and estimability procedures. The Canadian Journal of Chemical Engineering 90, 351–366.