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 \( t \)).

\[
\begin{align*}
\frac{dV}{dt} &= -I_{\text{ion}} \\
\frac{dr}{dt} &= (r_m - r)\tau_r \\
\frac{dm}{dt} &= (m_n - m)\tau_m \\
\frac{dh}{dt} &= (h_n - h)\tau_n
\end{align*}
\]

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.

\[
I_{\text{ion}} = g_{\text{Na}}(V - E_{\text{Na}}) + g_{\text{K}}(V - E_{\text{K}})e^{-(V - E_{\text{K}})/kT}
\]

**METHODS**

Denote the vector of model parameters \( \theta \), then the NLS estimate of \( \theta \) satisfies the following estimating equations:

\[
J(t, \theta)^	op (y - \eta(t, \theta)) = 0
\]

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

\[
J(t, \theta) = \begin{bmatrix}
\frac{\partial \eta(t_1, \theta)}{\partial \theta_1} & \cdots & \frac{\partial \eta(t_1, \theta)}{\partial \theta_p} \\
\vdots & \ddots & \vdots \\
\frac{\partial \eta(t_n, \theta)}{\partial \theta_1} & \cdots & \frac{\partial \eta(t_n, \theta)}{\partial \theta_p}
\end{bmatrix}
\]

Thus, \( \theta \) is estimable when the columns of \( J(t, \theta) \) are linearly independent, or when the information matrix \( J(t, \theta)^	op J(t, \theta) \) 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.

**RESULTS**

- 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 parameters.
- Use a flexible regression technique to explore alternative functional forms for the model equations, especially for \( \tau_r \).
- 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.

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**CITATIONS**