Parameter identifiability and identifiable combinations in generalized Hodgkin-Huxley models

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Abstract

The use of Hodgkin-Huxley (HH) equations abounds in the literature, but the identifiability of the HH model parameters has not been broadly considered. Identifiability analysis addresses the question of whether it is possible to estimate the model parameters for a given choice of measurement data and experimental inputs. Here we explore the structural identifiability properties of a generalized form of HH from voltage clamp data. Through a scaling argument, we conclude that the steady-state gating variables are not identifiable from voltage clamp data, and then further show that their product together with the conductance term forms an identifiable combination. We additionally show that these parameters become identifiable when the initial conditions for each of the gating variables are known. The time constants for each gating variable are shown to be identifiable, and a novel method for estimating them is presented. Finally, the exponents of the gating variables are shown to be identifiable in the two-gate case, and we conjecture these to be identifiable in the general case. These results are broadly applicable to models using HH-like formalisms, and show in general which parameters and combinations of parameters are possible to estimate from voltage clamp data.

Keywords: identifiability, parameter estimation, Hodgkin-Huxley models, voltage clamp

1. Introduction

Since its introduction in 1952, the Hodgkin and Huxley (HH) model for membrane excitability in the squid giant axon has become one of the most commonly used formalisms in mathematical neuroscience, with citations now numbering in the tens of thousands \cite{1,2}. By partitioning membrane voltage change into currents caused by the flow of distinct ions, Hodgkin and Huxley created an illuminating characterization of the underlying cause of axon potentials. In the model, each ionic current is gated by channels, and the probability of the channels being open or closed is voltage-dependent. The original model assumes these gates operate independently, and, while subsequent work has shown this not to be the case, HH nonetheless provides a good description of ionic behavior at the appropriate scale and remains highly relevant in the literature today. Consequently, much work has been dedicated to parameter estimation for the HH equations \cite{3-10}.

Most treatments of HH parameter estimation have tackled the problem with a focus on practicality—estimating parameters given noisy and limited data. However, there has been relatively little examination \cite{5} of the more basic but essential question of structural identifiability: given perfect, noise-free data, can the parameters in the model be uniquely determined? While such perfect data is of course unrealistic, structural identifiability is a prerequisite for practical identifiability and successful parameter estimation. Furthermore, such structural identifiability information can be used to generate insights into ways to reduce the model to improve identifiability, or to guide collection of new data that will allow all parameters to be estimated. Thus, understanding the structural identifiability properties of the HH model provides an important foundation in efforts to connect HH-based models with data.

Here, we examine the identifiability of a broad class of generalized HH-type models. We elucidate the identifiable combination structure for this class of models, evaluate the role of initial conditions in identifiability, and consider what additional data is needed to ensure identifiability. Additionally, we show that the proof of identifiability of the time-constants for the gating variables allows us to develop a novel practical estimation approach for general HH-type models.

2. Methods

2.1. Generalized Hodgkin-Huxley Models

The HH equations for ionic current can be generalized for \( p_n \) ion channel gates of type \( n \) acting independently as

\[
I(t) = g(V - E) \prod_{i=1}^{p_n} m_i^p \prod_{i=1}^{m_i} n_i \tag{1}
\]

where \( g \) is the conductance associated with the ion channel, \( V \) is the voltage of the cell, \( E \) is the reversal potential of the ion, and the \( m_i \) terms represent the probability of a voltage-controlled gate being open. Each of the \( m_i \) is further taken to satisfy the differential equation

\[
\frac{dm_i}{dt} = \frac{m_{i,\text{in}}(V) - m_i}{\tau_i(V)} \tag{2}
\]
in which \(m_{\infty}(V)\) is the steady-state probability of the gate being open when the voltage is held at \(V\) and \(\tau_i(V)\) is the time-constant for the kinetics of the gate’s activation or inactivation at that same voltage. In cases similar to the classical HH model, where only two types of gate appear, the conventional notation \(m^p_i h^p_i\) may be used instead of \(m_i^\infty m_i^\tau_i\).

While the HH model represents a heavily approximated version of ionic channel dynamics (assuming all ion channels are independent, ignoring changes in reversal potential due to ion flow), its ability to reproduce action potentials and other properties of cell electrophysiology have led to it remaining highly relevant over the six decades since its publication.

Typically, the voltage-dependent parameters, \(m_{\infty}\) and \(\tau_i\), are estimated from voltage clamp experiments. In a voltage clamp, a feedback loop is used to hold voltage at a constant value, and the current required to maintain this constant voltage (theoretically, exactly cancelling the ionic currents) is recorded. Individual currents are isolated, either by blocking all other ionic currents, or by subtracting traces where the current in question is blocked from those where nothing is blocked. Once ionic currents, or by subtracting traces where the current in the ‘two independent gates’-type scenario, and evaluate how knowledge of the initial conditions of the gating variables alters the identifiability structure of the model.

**2.2. Identifiability and differential algebra**

Identifiability addresses the question of whether the a given set of parameters can be uniquely estimated for a given model and data. Structural identifiability addresses this question in the case where we assume ‘perfect,’ noise-free data (i.e. complete knowledge of the measured variables for all time points). While this represents an unrealistic best-case scenario, it forms a necessary condition for estimation from real, noisy data, and indeed structural unidentifiability is quite common among mechanistic models [11,13,14]. The importance of identifiability and its place as a necessary precursor to fitting data are discussed further in [5,13,14].

Methods for determining structural identifiability have been developed in detail elsewhere [11,13,15,18], so we provide only brief overview here. Consider a model of the form:

\[
x'(t, p) = f(x(t, p), u(t), t; p),
\]

\[
y(t, p) = g(x(t, p); p),
\]

where \(p\) represents the (vector of) parameters, \(x\) is the unobserved state variable vector, \(u(t)\) are the known experimental input(s) into the system, if any, and \(y(t)\) represents the observed (measured) output (s). We also let \(x_0\) represent the vector of initial conditions for \(x(t)\). A model is said to be identifiable if \(p\) can be recovered uniquely from \(y\) and \(u\). Because there may be particular or degenerate parameter values and initial conditions for which an otherwise identifiable model is unidentifiable (e.g. initial conditions starting at a constant steady state), structural identifiability is often defined for almost all parameter values and initial conditions [11,12,19].

**Definition 2.1.** For a given ODE model \(\dot{x} = f(x, t, u, p)\) and output \(y\), an individual parameter \(p\) is uniquely (globally) structurally identifiable if for almost every value \(p^*\) and almost all initial conditions, the equation \(y(x, t, p^*) = y(x, t, p)\) implies \(p = p^*\). A parameter \(p\) is said to be non-uniquely (locally) structurally identifiable if for almost any \(p^*\) and almost all initial conditions, the equation \(y(x, t, p^*) = y(x, t, p)\) implies that \(p\) has a finite number of solutions.

**Definition 2.2.** Similarly, a model \(\dot{x} = f(x, t, u, p)\) is said to be uniquely (respectively non-uniquely) structurally identifiable for a given choice of output \(y\) if every parameter is uniquely (respectively non-uniquely) structurally identifiable, i.e. the equation \(y(x, t, p^*) = y(x, t, p)\) has only one solution, \(p = p^*\) (respectively finitely many solutions).

There are a number of approaches to determining identifiability; here, we use the differential algebra approach [11,13,20] which is briefly summarized as follows. For models with \(f\) and \(g\) rational, construct the input-output equations from the state variable equations and the output equations. Input-output equations are monic differential polynomials in the input and output variables and their derivatives with rational coefficients in the parameter vector \(p\) (i.e. with the state variables \(x\) and all of their derivatives eliminated from the equations). These can be generated in many ways, including using Ritt’s pseudo division or Groebner bases, among others [11,13,18,20,22]. The coefficients (rational in \(p\)) of the input-output equations are identifiable, and the structural identifiability of the model (i.e. injectivity of the map from parameters to output), can then be tested simply by checking injectivity of the map from the parameters to the coefficients.

As a simple example for illustrative purposes, we consider the HH model given in Eqs. (1) and (2) in the minimal case where \(n = p_1 = 1\). Then solving for \(m_1\) from Eq. (1) yields:

\[
m_1 = \frac{I(t)}{g(V-E)}.
\]

Plugging this into Eq. (2) yields

\[
\frac{I(t)}{g(V-E)} = \frac{m_{1,\infty} - \frac{m_1}{\tau_1}}{\tau_1}.
\]
To make this equation monic, we simply clear the coefficient for $I$, yielding our input-output equation:

$$0 = \dot{I}(t) - \frac{g}{\tau_1} m_{1,\infty}(V - E) + \frac{1}{\tau_1} I(t).$$

The coefficients of the input-output equation are identifiable, so that we see that $\tau_1$ is an identifiable parameter, while $g m_{1,\infty}$ forms an identifiable combination with neither parameter identifiable individually.

3. Results and Discussion

3.1. Generalized Hodgkin-Huxley equation identifiability

As stated above, we consider the identifiability of a generalized form of Hodgkin-Huxley equations, given in Eqs. (1) and (2). Unless otherwise stated, we assume we are fitting a single voltage clamp trace and therefore that $V$ is fixed and known. Our output is thus given by $y = \dot{I}(t)$. Voltage steps in clamp experiments typically are preceded by a period of time in which the voltage is held fixed at a holding potential, $V_{\text{hold}}$, consistent across all trials; when this value is used, it will always be distinguished from the step value $V$. Typically, the reversal potential $E_{\text{ion}}$ is readily determined through experimental means [1, 2].

Proof. We start by considering the case where $\tau_i = 1$ for all $i$. Rescale the current trace by the steady state value $I_{\infty} = g(V - E) \prod_{i=1}^n m_{i,\infty}$. This value, while possibly very small, is non-zero. Next, let $m_{i}/m_{i,\infty} = z_i$ as previously and denote the rescaled current by $\tilde{I}(t) = I(t)/I_{\infty}$. Make the substitution $1 - \tau_i z_i = z_i$ to rewrite this current as

$$\tilde{I}(t) = \prod_{k=1}^n (1 - \tau_k z_k).$$

Expanding this product gives:

$$\tilde{I}(t) = 1 - \sum_{i} \tau_i z_i + \sum_{i < j} \tau_i \tau_j z_i z_j + \cdots$$

$$+ \sum_{i < j < \cdots < k} (-1)^{i+j+\cdots+k} \tau_i \tau_j \cdots \tau_k z_i z_j \cdots z_k + \cdots$$

Next, rescale $m_n$ so that $z_n = m_n \prod_{i=1}^{n-1} m_{i,\infty}$, so that

$$I = g(V - E)z_1 \cdots z_n,$$

and

$$\frac{dz_i}{dt} = \frac{1 - z_i}{\tau_i}$$

for $i = 1, \ldots, n - 1$ while

$$\frac{dz_n}{dt} = \frac{\prod_{i=1}^n m_{i,\infty}^p - z_n}{\tau_n}.$$

Again the identifiability structure is unchanged, but the steady-state parameters appear only once, grouped into a single term: $\prod_{i=1}^n m_{i,\infty}^p$. The individual steady-state parameters are thus not identifiable, nor is the product of any strict subset of the steady-state parameters and conductance term. Their full product with $g$ is identifiable because

$$\lim_{t \to \infty} \frac{I(t)}{V - E} = g \prod_{i=1}^n m_{i,\infty}^p$$

which, under the assumption of perfect data, is known. □

To illustrate this issue, Figure 1A shows two simulated sodium-type current traces, with gating variables of the form $m^3 h$, which are identical despite different $m_{i,\infty}$ and $h_{i,\infty}$ values; a similar example is included in [5].

3.1.2. $\tau$ identifiability

While the undentifiability of the steady-state parameters can be ascertained through scaling, to show the identifiability of the time constants using results from differential algebra requires a slightly more technical analysis.

Theorem 3.2. The time constants for the gating variable kinetics, $\tau_i$, are identifiable from voltage clamp data.

Proof. Start by considering the case where $p_i = 1$ for all $i$. Rescale the current trace by the steady state value $I_{\infty} = g(V - E) \prod_{i=1}^n m_{i,\infty}$. This value, while possibly very small, is non-zero. Next, let $m_{i}/m_{i,\infty} = z_i$ as previously and denote the rescaled current by $\tilde{I}(t) = I(t)/I_{\infty}$. Make the substitution $1 - \tau_i z_i = z_i$ to rewrite this current as

$$\tilde{I}(t) = \prod_{k=1}^n (1 - \tau_k z_k).$$

To illustrate this issue, Figure 1A shows two simulated sodium-type current traces, with gating variables of the form $m^3 h$, which are identical despite different $m_{i,\infty}$ and $h_{i,\infty}$ values; a similar example is included in [5].

Next, rescale $m_n$ so that $z_n = m_n \prod_{i=1}^{n-1} m_{i,\infty}$, so that

$$I = g(V - E)z_1 \cdots z_n,$$
Since \( \tau_i = -\tilde{\tau}_i / \tau_i \), we can write down successive derivatives of \( I(t) \) as:

\[
(-1)^{y+1} \tilde{p}^y(t) = - \sum_i \left( \frac{1}{\tau_i} \right)^y \tau_i \tilde{\tau}_i + \sum_{i<j} \left( \frac{1}{\tau_i} + \frac{1}{\tau_j} \right)^y \tau_i \tau_j \tilde{\tau}_i \tilde{\tau}_j + \cdots \\
+ \sum_{i<j} \sum_{k=j+1}^n (-1)^y \left( \frac{1}{\tau_i} + \cdots + \frac{1}{\tau_k} \right)^y \tau_i \cdots \tau_k \tilde{\tau}_i \cdots \tilde{\tau}_k \\
+ \cdots + (-1)^y \left( \frac{1}{\tau_i} + \cdots + \frac{1}{\tau_n} \right)^y \tau_i \cdots \tau_n \tilde{\tau}_i \cdots \tilde{\tau}_n
\]

From the first \( 2^n - 1 \) derivatives of \( I(t) \), we can write down the system:

\[
\begin{pmatrix}
1 & 1 & \cdots & 1 \\
\lambda_1 & \lambda_2 & \cdots & \lambda_{2^2-1} \\
\vdots & \vdots & \ddots & \vdots \\
\lambda_1^{2^n-2} & \lambda_2^{2^n-2} & \cdots & \lambda_{2^n-1}^{2^n-2}
\end{pmatrix}
\begin{pmatrix}
-\tau_1 \tilde{\tau}_1 \\
\vdots \\
\vdots \\
-\tau_n \tilde{\tau}_n
\end{pmatrix} = 
\begin{pmatrix}
\tilde{I} \\
\vdots \\
\vdots \\
\tilde{p}^{n-1}(t)
\end{pmatrix}
\]

where \( I = \tilde{I}(t) - 1 \) and the \( \lambda_i \)'s represent a sequential indexing of the possible \( \sum -\frac{1}{\tau_i} \) quantities with \( \lambda_i = -\frac{1}{\tau_i} \) for \( i = 1 \cdots n \) and

\[
\lambda_{2^n-1} = - \sum_i \frac{1}{\tau_i}
\]

Denote this Vandermonde matrix by \( V \) and this system as \( VX = Y \), with

\[
x = \begin{pmatrix}
-\tau_1 \tilde{\tau}_1 \\
\vdots \\
(-1)^y \tau_1 \cdots \tau_k \tilde{\tau}_j \cdots \tilde{\tau}_k \\
\vdots \\
(-1)^y \tau_1 \cdots \tau_n \tilde{\tau}_1 \cdots \tilde{\tau}_n
\end{pmatrix}
\]

The \( 'L' \)-Vandermonde matrix is invertible as long as \( \lambda_i \neq \lambda_j \), which occurs with probability 1, so \( x = V^{-1} y \) (with \( i \)th entry denoted \( x_i \)). We can next observe that

\[
\prod_{i=1}^n x_i = (-1)^y \tau_1 \cdots \tau_n \tilde{\tau}_1 \cdots \tilde{\tau}_n = x_2^{n-1}.
\]

Since all \( x_i \) can be written as a linear combination of the derivatives of \( \tilde{I}(t) \), the equation \( \prod_{i=1}^n x_i = x_2^{n-1} \) gives a polynomial in \( \tilde{I}(t) \) and its derivatives with coefficients in the parameters: an input-output equation.

Furthermore, the coefficients of the monomials of the form \( \tilde{I}^{(k)}(t) \) (or \( \tilde{I} \), \( \tilde{I} \)-"singletons") are the entries of the last row of the inverse Vandermonde matrix. Note that the entries of the last row are also the coefficients \( a_k \) of the polynomial \( \sum_{k=0}^{2^n-1} a_k x^k \), the \( 2^n-2 \) roots of which are \( \lambda_1 \cdots \lambda_{2^n-2} \) (\( \lambda_{2^n-1} \) can be recovered by summing over all the roots and dividing by \( 2^n - 1 \)). These roots are invariant under scalings of the coefficients; hence, by finding the roots of the polynomial with coefficients taken from these monomials, we can recover the set of \( \tau_i \) from them. This implies that the \( \tau_i \)'s are identifiable parameters.

It remains to consider the case where \( p_j \) is not necessarily 1. Let \( N = \sum p_i \), and note that we can use a \( (2^N - 1) \)-by-\( (2^N - 1) \) Vandermonde matrix in writing a linear system \( VX = Y \) similar to the one above, with the key difference being that now certain \( \lambda \) are equal. \( V \) in this case will not be invertible; however, by eliminating the repeated columns and collapsing all duplicate entries of \( x \) into single entries (e.g. Replacing \( x_1 = x_2 = x_3 = \tau_1 \tilde{\tau}_1 \) with \( x_1 = 3 \tau_1 \tilde{\tau}_1 \)), we can rewrite the system so that \( V \) is \( (2^N - 1) \)-by-\( p \), \( x \) is \( p \)-by-1, and \( y \) is \( (2^N - 1) \)-by-1, where \( p \) is a quantity that emerges from the partitioning of \( N \) into \( p \). Removing rows of \( V \) until it is square (while preserving the first \( n \) and last rows), we can construct an input-output equation by equating entries of \( x \) in the same way as before, and the coefficients of singleton monomials will also be the coefficients of a polynomial with zeros equal to \( \lambda_1, \cdots, \lambda_{2^p-1} \).\]
Hence, the time constants are identifiable, even in the general-
ized case discussed here. This identification can also provide a way to
estimate the time constants from experimental data, discussed
further below.

3.1.3. Power identifiability

**Theorem 3.3.** For a classical two-gate Hodgkin-Huxley model
of the form \( I = g(V - E) m^3 h^2 \), the powers \( p_1 \) and \( p_2 \) are
identifiable.

This can be shown by considering successive derivatives of
\( \log(I(t)) \), specifically \( f(t) = \dot{I}(t)/I(t), f'(t), \) and \( f''(t) \). Computing \( f \) and its derivatives and replacing \( m'(t) \) with \(-m'(t)/\tau_1 \)
yields expressions in terms of the parameters \( p_1 \) and \( p_2 \) and the
ratio of state variables \( m'(t)/m(t) \). Replacing these ratios with
\( a = m_1(t)/m_1(t) \) and \( b = m_2(t)/m_2(t) \) gives the following:
\[
\begin{align*}
  f(t) &= a p_1 + b p_2 \\
  f'(t) &= -a^2 p_1 - (a p_1) \tau_1 - b^2 p_2 - (b p_2) \tau_2 \\
  f''(t) &= 2a p_1 + (a p_1) \tau_1 + (3a^2 p_1) \tau_1 + 2b p_2 + (b p_2) \tau_2 + (3b^2 p_2) \tau_2 
\end{align*}
\]

Using Mathematica to eliminate the variables \( a \) and \( b \) through
a Groebner basis computation yields an input-output equation,
the coefficients of which readily imply the identifiability of \( p_1 \)
and \( p_2 \). We conjecture that a similar result holds for the gener-
alized case discussed here. This proof can also provide a way to
to perfectly for all times). In this case, the additional informa-
tion provided by knowledge of the initial conditions changes
the identifiability structure of the problem.

3.2. Consideration of initial conditions

Thus far we have assumed no knowledge of the initial condi-
tions of the model (although initial conditions for the output
\( I(t) \) and its derivatives are assumed known as \( I(t) \) is measured
perfectly for all times). In this case, the additional informa-
tion provided by knowledge of the initial conditions changes
the identifiability structure of the problem.

**Theorem 3.4.** If initial conditions for the gating variables \( m_{i,0}, n_{i,0} \)
are known, the steady state parameters at a fixed voltage,
\( m_{i,\infty}(V) \), are identifiable from voltage clamp data.

**Proof.** As before, scale the original current trace \( I(t) \) by \( g(V - E) \)
\( \prod_{k=1}^n m_{k,\infty} \) to get \( \hat{I}(t) = \prod_{k=1}^n \hat{m}_{k,\infty} \). The only parameters in
this scaled model are the identifiable \( \tau_i \) values, so by Theo-
rem 2.2 the model is itself identifiable. We can solve for
the initial conditions of the scaled model using the explicit solution
\( \hat{m}_i(t) = 1 - (1 - \hat{m}_{i,0}) \exp(-t/\tau_i) \). Once found, the scaled initial
conditions can be divided into the unscaled initial conditions,
yielding the steady state parameters \( m_{i,\infty}(V) \).

3.2.1. Identifiable combinations in terms of initial conditions

Given the lack of identifiability for HH models unless the
gating variable initial conditions are known, a natural question
arises in whether consideration of the initial conditions—even
when unknown—might yield additional identifiable combinations.
Moreover, when practically fitting the model, the initial
conditions of the gating variables would need to be considered.

**Theorem 3.5.** The pairs \( m_{i,0}/m_{i,\infty} \) are identifiable combina-
tions given voltage clamp data.

**Proof.** Replacing the \( m_i \) in Eq. (1) with their explicit solutions and factoring
yields
\[
I(t) = g(V - E) \left( \prod_{i=1}^n m_{i,\infty} \right) \prod_{i=1}^n \left( 1 - \frac{m_{i,0}}{m_{i,\infty}} \exp(-t/\tau_i) \right)^{p_i}
\]

Dividing the current trace by its steady-state value therefore gives us
\[
\hat{I}(t) = \prod_{i=1}^n \left( 1 - \frac{m_{i,0}}{m_{i,\infty}} \exp(-t/\tau_i) \right)^{p_i}
\]
in which the ratios \( m_{i,0}/m_{i,\infty} \) are identifiable, along the with \( \tau_i \)'s.

We note that this proof also shows that the initial conditions
for the gating variables are identifiable for the scaled model
considered in the proof of Theorem 3.1 wherein we scaled all
\( m_i \) by their steady state values (as in this case, the steady
state values are precisely the \( m_{i,0}/m_{i,\infty} \)).

In applying these results to experimental data, we also note
that it is reasonable to assume that the initial conditions of the
gating variables \( m_{i,0} \) are the same for all experimental voltage
steps \( V \) because of the pre-step fixed holding potential \( V_{hold} \).
As a result, the shape of the \( m_{i,\infty}(V) \) curve up to scaling by
the constant \( m_{i,0} \) can be found from the data in this way, and a
concrete value of \( m_{i,0} \) can be chosen so that \( \frac{m_{i,0}}{m_{i,\infty}(V_{hold})} = 1 \). If the
curve isn’t smooth at a certain value of \( V \), it is possible that \( m_{i,0} \)
differed from the other trials at that point (e.g. the system may
not have fully equilibrated before the next clamp experiment
was run).

3.3. Applications

3.3.1. Rescaling the Sim-Forger model

To demonstrate the unidentifiability and identifiable combina-
tions determined in Theorem 3.2.1 using an HH-model applied
in practice, we consider the Sim-Forger model of a suprachri-
asmatic nucleus (SCN) neuron \[23\]. Extensions of this model
have used the HH model to gain insight into the underlying
mechanisms of timekeeping in the SCN \[24\] \[25\]. The non-
uniqueness of the steady-state parameters when the initial con-
ditions are not known allows us to generate the same output
from two different Hodgkin-Huxley style models using two differ-
ent sets of initial conditions. The sodium current equation in
this model is given by: \( I_Na = g_{Na}(V - E_{Na})m^3 h \). The steady-
state parameters \( m_{\infty} \) and \( h_{\infty} \) are given by the equations
\[
\begin{align*}
  m_{\infty} &= \frac{1}{1 + \exp(-(V + 35.2)/7.9)} \\
  h_{\infty} &= \frac{1}{1 + \exp((V + 62)/5.5)}
\end{align*}
\]
with initial conditions \( m_{0} = 0.34 \) and \( h_{0} = 0.045 \). If we rescale
so that \( \hat{m}_{\infty} = am_{\infty}, \hat{h}_{\infty} = \frac{h_{\infty}}{a^2}, m_{0} = 0.34a \) and \( h_{0} = \frac{0.045}{a^2} \), the
model will produce identical output for \( a \neq 0 \). This is shown in Figure [13], where the solid line shows the output for \( a = 1 \) while the open circles shows the same output for \( a = 2 \). The two traces are identical.

3.3.2. Fitting the time constants through a least squares approach

Finally, while the proof of time constant identifiability in Theorem 3.1.2 does not immediately appear useful for parameter estimation, we next illustrate how the input-output equations obtained in the proof of Theorem 3.1.2 can be used to estimate the identifiable \( \tau_i \)'s. We demonstrate this using the two-gate HH model, with each gate appearing once: \( I = g(V - E) mh \). We generated simulated voltage clamp data, \( I(t) \) (with a timestep of 0.1 milliseconds), and the first and second derivatives \((I', I'')\) were estimated numerically from the data in MATLAB (from the slope of the line between first two data points).

The resulting current trace and its derivatives were concatenated into a \( T \)-by-9 matrix, where \( T \) is the number of time points composing \( I \) and 9 is the number of distinct monomials in \((I - 1), I', \) and \( I'' \), of maximum degree two:

\[
A = \begin{pmatrix}
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
I - 1 & I' & I'' & (I - 1)^2 & I'^2 & (I - 1)I' & I'I' & (I - 1)I'' & \vdots \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
\end{pmatrix}
\]

These monomials should form an input-output equation with the appropriate coefficients; hence, the vector \( x \) making up the null space of \( A \) will give us these coefficients.

To ensure that \( A \) has a null space, we took its singular value decomposition and made the least singular value equal to zero. This corrected for any errors in the derivative computation and enforced the rank deficiency requirement. We then solved for \( x \) from \( Ax = 0 \). From the theorem proving the identifiability of the time constants, the first three entries of \( x \) should be the coefficients of the degree 2 polynomial with roots \(-1/\tau_m \) and \(-1/\tau_h \). We then found the roots of this polynomial using the aptly-named MATLAB function ‘roots’.

Indeed, the roots did agree with the prescribed time constants. For preset \( \tau_h = 4 \) and \( \tau_m = 22 \), the time constants recovered in this way were \( \tau_h = 3.9928 \) and \( \tau_m = 22.0072 \). While noise will likely confound this process in real data, it nonetheless provides an interesting and novel way of fitting HH-style equations. As the other identifiability results predict, the steady-state parameters do not need to be known to estimate the time-constants. In addition, no initial guess of where the time constants lie in parameter space is needed to arrive at this estimate. Thus, even given the issues that may come with estimating the derivatives of \( I(t) \) in the presence of noise, this approach may also be a useful way to obtain initial estimates of the \( \tau_i \)'s which are ‘in the ballpark’, and then more conventional optimization approaches can be used.

4. Conclusions

In this work, we have shown that the time constants for the gating variables of a generalized HH-type model are identifi-
process, the idea behind it could prove useful in later work, perhaps in suggesting a starting point in parameter space for error-minimizing parameter searches.

This analysis has focused only on the identifiability of the Hodgkin-Huxley model from data obtained through voltage clamp; a natural extension for future work is to consider data taken from current clamp experiments, in which a current is applied and changes in voltage are recorded, and action potential clamp experiments, which are similar to voltage clamp except that instead of a constant voltage being maintained via a feedback loop, the voltage is instead fixed to match an action potential. Finally, the extensions of Hodgkin-Huxley are wide and varied and encompass much more than voltage-dependent gates acting independently. There is a broad literature of ion channel models out there that could likely benefit from inspection similar to this.

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