



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.

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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 [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 [3–12].

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 [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

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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

$$I(t) = g(V - E)m_1^{p_1} \dots m_n^{p_n} \quad (1)$$

where g is the conductance associated with the ion channel (also commonly denoted \bar{g} or g_{max}), 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

$$m_i'(t) = \frac{m_{i,\infty}(V) - m_i}{\tau_i(V)} \quad (2)$$

in which $m_{i,\infty}(V)$ 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 $m^{p_1}h^{p_2}$ may be used instead of $m_1^{p_1}m_2^{p_2}$.

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, $m_{i,\infty}$ and τ_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 found, the values for $m_{i,\infty}$ and τ_i across all the fixed voltages are considered together and fit so that the two parameters are then described by functions of voltage, $m_{i,\infty}(V)$ and $\tau_i(V)$. These functions often follow standard forms, e.g. Boltzmann equations, although these are not necessarily completely physically accurate [6].

Much other work has concerned the process of parameter estimation for HH-type models [3], but only a few sources have addressed the issue of identifiability. In [5], the identifiability of the parameters $\{g, m_{1,\infty}, m_{2,\infty}\}$ was evaluated in currents of the form $I(t) = g m_1^{p_1} m_2^{p_2} (V - E)$. Cserecsik and colleagues show that these parameters are unidentifiable, and moreover, no pair of them is identifiable, although the precise form of any identifiable combinations is not determined. Here, we repeat and extend that analysis in the generalized case for an arbitrary number of gates, using a scaling argument, and then additionally show that the time constants τ_i are identifiable. We also examine the identifiability of powers p_i 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 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 [13–15]. The importance of identifiability and its place as a necessary precursor to fitting data are discussed further in [5,15,16].

Methods for determining structural identifiability have been developed in detail elsewhere [13–15,17–20], so we provide only brief overview here. Consider a model of the form:

$$\mathbf{x}'(t, \mathbf{p}) = f(\mathbf{x}(t, \mathbf{p}), \mathbf{u}(t), t; \mathbf{p}),$$

$$\mathbf{y}(t, \mathbf{p}) = g(\mathbf{x}(t, \mathbf{p}); \mathbf{p}),$$

where \mathbf{p} represents the (vector of) parameters, \mathbf{x} is the unobserved state variable vector, $\mathbf{u}(t)$ are the known experimental input(s) into the system, if any, and $\mathbf{y}(t)$ represents the observed (measured) output (s). We also let \mathbf{x}_0 represent the vector of initial conditions for $\mathbf{x}(t)$. A model is said to be *identifiable* if \mathbf{p} can be recovered uniquely from \mathbf{y} and \mathbf{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 [13,14,21]:

Definition 2.1. For a given ODE model $\mathbf{x}'(t, \mathbf{p}) = f(\mathbf{x}, t, \mathbf{u}, \mathbf{p})$ and output \mathbf{y} , an individual parameter p is *uniquely (globally) structurally identifiable* if for almost every value \mathbf{p}^* and almost all initial conditions, the equation $\mathbf{y}(\mathbf{x}, t, \mathbf{p}^*) = \mathbf{y}(\mathbf{x}, t, \mathbf{p})$ implies $p = p^*$. A parameter p is said to be *non-uniquely (locally) structurally identifiable* if for almost any \mathbf{p}^* and almost all initial conditions, the equation $\mathbf{y}(\mathbf{x}, t, \mathbf{p}^*) = \mathbf{y}(\mathbf{x}, t, \mathbf{p})$ implies that p has a finite number of solutions.

Definition 2.2. Similarly, a model $\mathbf{x}'(t, \mathbf{p}) = f(\mathbf{x}, t, \mathbf{u}, \mathbf{p})$ is said to be *uniquely (respectively non-uniquely) structurally identifiable* for a given choice of output \mathbf{y} if every parameter is uniquely (respectively non-uniquely) structurally identifiable, i.e. the equation $\mathbf{y}(\mathbf{x}, t, \mathbf{p}^*) = \mathbf{y}(\mathbf{x}, t, \mathbf{p})$ has only one solution, $\mathbf{p} = \mathbf{p}^*$ (respectively finitely many solutions).

There are a number of approaches to determining identifiability; here, we use the differential algebra approach [13,15,22] 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 \mathbf{p} (i.e. with the state variables \mathbf{x} and all of their derivatives eliminated from the equations). These can be generated in many ways, including using Ritt's pseudodivision or Groebner bases, among others [13,15,20,22–24]. The coefficients (rational in \mathbf{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

$$\frac{I'(t)}{g(V - E)} = \frac{m_{1,\infty} - \frac{I(t)}{g(V - E)}}{\tau_1}.$$

To make this equation monic, we simply clear the coefficient for

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