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Research Report

Modeling neuronal activity in relation to experimental voltage-/patch-clamp recordings

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A B S T R A C T

A mechanism-based, Hodgkin–Huxley-type modeling approach is proposed that allows connecting the key parameters of experimental voltage-/patch-clamp data directly to the major control values of the model. The objective of this paper is to facilitate the use of mathematical modeling in supplement to electrophysiological recordings. Typical recordings from current-clamp, whole-cell voltage-clamp, and single-channel patch-clamp experiments are illustrated by means of a simplified computer model designed for life science education. These examples demonstrate that the "rate constants", on which the original Hodgkin–Huxley equations are built up, are difficult, in most experiments even impossible, to extract from experimental data. As the combination of the two exponential rate constants leads to sigmoid activation curves, they can be replaced by sigmoid voltage dependencies, mostly presented in form of Boltzmann functions. Conversely, connecting whole-cell and single-channel patch-clamp simulations, the Boltzmann functions, can be related to exponentially voltage dependent probability factors of ion channel transition rates. The thereby introduced small variability of the activation values suggests that the power functions of the activation variables in the current equations can be neglected. Eliminating the rate constants and the power functions can be physiologically justified and

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makes the model easier to handle, especially in context with experimental data. Further possibilities of dimension reduction as well as model extensions are discussed.

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1. Introduction: experiments and models

Mathematical models are very useful tools for understanding of experimentally recorded data. This has been demonstrated perfectly well already in the 1950s by Hodgkin and Huxley (1952) with an exceptionally successful combination of experimental and modeling studies. Based on experimental recordings of action potentials and ion currents, they designed a mathematical model of action potential generation and conduction explaining the underlying mechanisms by voltage- and time-dependent alterations of ionic membrane conductances. Their major assumptions have been fully confirmed in numerous experiments and their modeling concept set standards in neurophysiology and beyond. Since then this so-called conductance-based modeling strategy has been used not only for the examination of neurons, but for all kind of excitable cells, e.g. heart cells (Noble, 1962) or pancreatic beta-cells (Mosekilde et al., 2001).

Unfortunately, when facing larger scale problems such as interactions between neuronal networks in different brain areas, the classical Hodgkin–Huxley (HH)-type algorithms soon become unwieldy and even have been considered as "computationally prohibitive" (Izhikevich, 2003). Accordingly, a diversity of simplified approaches has been developed, like the widely used Fitzhugh–Nagumo model (Fitzhugh, 1961) or its modifications and extensions, e.g. by Hindmarsh and Rose (1984) or Izhikevich (Izhikevich, 2003) models. However, this type of model was never fully accepted in experimental and clinical research. The reasons are obvious. Even when specific phenomena are simulated sufficiently well, the direct relation of the models' variables and parameters to physiological mechanisms are often sacrificed. Others, like the Morris–Lecar model (Morris and Lecar, 1981), keep relations to the physiological processes, even despite significant simplifications and dimension reduction, but mostly have their limitations in being designed for modeling of specific characteristics.

In this paper we present a modeling strategy, which is significantly simplified compared to the original HH equations but, nevertheless, keeps connections to physiological mechanisms. As a major point, we will eliminate the rate constants of the original HH-equations directly referring to the experimentally easier accessible parameters of ion current activation. We will demonstrate that these simplifications are physiologically justified and that the resulting equations simulate experimental recordings even better than the HH model. The goal is to provide a modeling framework where variables and parameters are directly connected to actual experimental measures, which will enable and facilitate the use of models by experimentalists.

Irrespective of the specific type of a neuron, knowledge about its electrophysiological properties is essentially based on a few major types of experimental recordings: (1) current-clamp experiments, which record action potentials, (2) voltage-clamp or whole-cell patch-clamp recordings of ion-currents, and (3) single-channel patch-clamp recordings. Simulation examples of these types of recordings and their interrelations are summarized in Fig. 1 with the plots obtained from the educational software SimNeuron (accessible via http://www.virtual-physiology.com/). The model neuron only includes a leak current and the voltage-dependent Na^+ and K^+ currents for spike generation. In experimental studies it is very rare for all these recordings to be done in parallel due to technical difficulties. Nevertheless, for the understanding of the neural dynamics, and especially for an appropriate modeling strategy related to experimental data, it is important to be aware of their interdependencies.

The graphs in the upper row in Fig. 1 represent the most typical experimental recordings. They can be obtained with the so-called current-clamp experiments (Fig. 1A1) and voltage-clamp or whole cell patch-clamp experiments (Fig. 1B1). Simulations of single-channel patch-clamp experiments are given in Fig. 2. Below we describe each of these methods in more detail.

1.1. Current-clamp recordings of membrane potentials

Current-clamp is a technical term that occasionally leads to misunderstandings in the engineering and biophysics community. Technically it is equivalent to using a constant current source delivering an adjustable current strength that is independent from a varying membrane resistance.

The recording example from the current clamp mode in the left upper diagram (Fig. 1A1) shows a neuron that is in the steady state (constant membrane potential) but exhibits repetitive spiking upon current injection. The diagrams below (Fig. 1A2) show a single current-induced spike on an expanded time scale together with the underlying alterations of the spike-generating Na^+ and K^+ currents and their ionic conductances. The alterations of ion currents and conductances cannot directly be recorded in the current clamp mode but can be reconstructed computationally on the basis of voltage-clamp data.

1.2. Voltage-clamp recordings of ion currents

The most widely used approach is the whole-cell patch-clamp technique with numerous publications illustrating voltage-dependent ion currents mostly in response to step-like voltage changes, often combined with alterations of ion concentrations or application of neuromodulators or drugs. Fig. 1B1 illustrates how the Na^+ and K^+ currents that are underlying the action potentials in Fig. 1A would look like if recorded separately, e.g. with blockade of all other currents. In these experiments, a manifold of different ion channels was discovered beyond the initially described channels of the