# MODELING NEURONAL BIOPHYSICS

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# INTRODUCTION

Models of single neurons span a wide range, with more or less fidelity to biological facts (see PERSPECTIVE ON NEURON MODEL COMPLEXITY and SINGLE-CELL MODELS and MOSAIC NEURON). So-called biophysically-detailed compartmental models of single neurons typically aim to quantitatively reproduce membrane voltages and currents in response to some sort of "synaptic" input. We may think of them as "Hodgkin-Huxley-Rall" models, based on the hypothesis of the neuron as a dynamical system of non-linear membrane channels (e.g. conductances described by Hodgkin-Huxley kinetics; see ION CHANNELS - KEYS TO NEURONAL SPECIALIZATION and AXONAL MODELING) distributed over an electrotonic cable skeleton (e.g. as described by Rall dendritic cable theory; see DENDRITIC PROCESSING).

Such models can incorporate as much biophysical detail as desired (or practical), but in general all include some explicit assortment of voltage-dependent and transmitter-gated (synaptic) membrane channels. Many Hodgkin-Huxley-Rall models also include some system for describing intracellular $Ca^{2+}$ dynamics, for example to account for the gating of $Ca^{2+}$-dependent $K^+$ channels. Modeling these dynamics involves not only $Ca^{2+}$ channels, but often associated buffer systems and membrane pumps as well.

This chapter will summarize the application of the more common mathematical models of these basic biophysical mechanisms (Borg-Graham, 1999, Koch, 1999). The models for each of these mechanisms are at an intermediate level of biophysical detail, appropriate for describing macroscopic variables (e.g. membrane currents, ionic concentrations) on the scale of the entire cell or anatomical compartments thereof.

First, we will discuss general issues regarding model formulations, and data interpretation for contructing models of biophysical mechanisms. We will then describe models for non-linear channel properties, including Hodgkin-Huxley and Markov kinetic descriptions of voltage and second-messenger dependent ion channels. Similar models aimed particularly for synaptic mechanisms are covered in SYNAPTIC INTERACTIONS, KINETIC MODELS (q.v.). We will then discuss concentration systems, including models of membrane pumps and concentration buffers. Finally, examples of model definitions are illustrated using the Surf-Hippo Neuron Simulation System (Graham, 2002), pointing out an essential and minimal syntax that facilitates model documentation and analysis.

# GENERAL ISSUES FOR CONSTRUCTING BIOPHYSICAL MODELS

## Phenomenological and Mechanistic Models

A first consideration for choosing a mathematical model for a given cellular mechanism is whether the model is intended only to capture an empirical relationship between an independent variable (the "input" or "signal") and a dependent variable (the "output" or "response"), or rather the model represents an explicit mechanistic hypothesis. Phenomenological models may be instantiated by a function with few (ref. a low-dimensional polynomial fit) or many (ref. look-up table) degrees of freedom, depending on the nature of the problem. Of course, a mechanistic model can also have few or many parameters, but explanatory power tends to dimish with the number of parameters. The mechanistic and phenomenological model alternatives are not mutually exclusive, since the former may incorporate the latter, and in some ways the distinction between them is rather *ad hoc*.

## Static (Instantaneous) and Dynamic (Kinetic) Models

Another basic consideration is whether the relation between signal and response is instantaneous on the time scale relevant to the entire system at hand. In some cases an instantaneous mechanism may permit analysis by exploiting separation of variables, for example assuming instantaneous activation for $Na^+$ currents relative to $K^+$ currents during spiking (see OSCILLATORY AND BURSTING PROPERTIES OF NEURONS). For cellular models that are solved by explicit integration over time, however, instantaneous relationships between state variables can introduce troublesome numerical instabilities, unless there are intervening kinetics with slow time constants (relative to the time scale of the integration) that serve to "de-couple" element dynamics at the faster time scale.

## Deterministic and Stochastic Models

A stochastic component, or "noise", in experimental measures is ubiquitous, for example in the trial to trial variability of spike responses to deterministic stimuli, or in membrane voltage or membrane current fluctuations (especially *in vivo*). There is accumulating experimental and theoretical evidence

for noise placing an important constraint on information processing under some conditions, while, conversely, serving a useful computational role in others.

Some system noise can be traced to the inherent stochasticity of molecular kinetics at the cellular level, and there is increasing interest in analyzing single neuron models that explicitly consider this contribution. For example, simulations with stochastic Hodgkin-Huxley type channel models can show functional dynamics that would be completely missed by deterministic models. A determinsitic approximation should be valid when the number of channels is very large, the usual assumption, but the actual number in a local region of the neuron membrane may be rather low considering both realistic estimates of channel densities and, especially, the small number of open channels near spike threshold (Schneidman *et al* 1998).

## The Experimenter's Model versus the Theorist's Model

Every model is based on some empirical data set, but an often overlooked point is how the theorist's model relates to, or rather is constrained by, that of the experimentalist. It may be a bit surprising to imagine that there is such a thing as an experimentalist's model (which is not the same thing as an *experimental* model). However, in reality experimental data is never arbitrary, but reflects the experimenter's explicit or implicit notion of what are a phenomena's necessary and sufficient parameters, what are the functionally relevant mappings between signal and response, what is experimentally tractable (no-one is able to do their "dream" experiment!), or some combination of all three. The first issue, in particular, is essentially equivalent to assuming some hypothetical model, but importantly the associated experiments are not normally designed for *testing* that hypothesis (since it is taken as an *a priori*). Examples include electrophysiological reports on whole-cell current kinetics, which usually focus on voltage-dependent activation and inactivation characteristics according to the classical model of Hodgkin and Huxley (described below). However, while practical, this paradigm may miss crucial functional characteristics, basically by not sufficiently characterizing certain important dynamical trajectories. We shall return to this point later in discussing Markov channel models.

# CHANNEL MODELS

Membrane channels underly both intrinsic neuronal excitablility and the direct post-synaptic action

of synaptic transmission. The channel current $I$, assuming some permeant ion $X$, may be expressed as the product of a conduction term $f(V, \Delta[X])$ and a gating term $h(V, t, ...)$:

$$I = f(V, \Delta[X])\ h(V, t, ...)$$

where $V$ is the membrane voltage, $t$ is time and $\Delta[X]$ represents the concentration gradient of $X$ across the cell membrane. The ellipsis in the argument of $h()$ stands for the various ligand-dependent processes, for example $Ca^{2+}$-dependence or the action of synaptic neurotransmitters.

## Ohmic and Permeation Conduction Models

The two common models of the conduction term $f()$ are the ohmic model (thermodynamic equilibrium conduction) and the constant-field permeation model (non-equilibrium conduction). In the ohmic model, current is proportional to the difference of the membrane voltage and the reversal potential for $I$:

$$f(V, \Delta[X]) \ = \ \overline{g}_X\ (V - E_X)$$

where $\overline{g}_X$ is the maximum conductance. The reversal potential $E_X$ for the ion $X$, is given by the Nernst equation:

$$E_X \ = \ \frac{-RT}{zF} Log \frac{[X]_{out}}{[X]_{in}}$$

where $R$ is the gas constant, $F$ is Faraday's constant, and $T$ is temperature in degrees Kelvin. $[X]_{in}$ and $[X]_{out}$ are the intracellular and extracellular concentrations and $z$ is the valence of the permeant ion $X$. For more than permeant ion (all with the same valence) and under some assumptions, the similar Goldman-Hodgkin-Katz (GHK) voltage equation (e.g. Hille, 1992) may be used. Note that if the effect of channel current on $[X]$ is considered (see section on concentration integration), then the ohmic $f()$ is in fact implicitly non-linear.

As the conducting ion moves farther from equilibrium (specifically the case for $Ca^{2+}$), the ohmic model becomes less accurate. A widely used non-equilibrium model is the constant field model, described by the Goldman-Hodgkin-Katz (GHK) current equation. In this equation (Jack, Noble and Tsien, 1983 and Hille, 1992), the non-linearity of permeation is explicit:

$$f(V, \Delta[X]) \ = \ \overline{p}_X\ \frac{V z^2 F^2}{RT}\ \frac{[X]_{in} - [X]_{out} \exp(-zFV/RT)}{1 - \exp(-zFV/RT)}$$

where $\overline{p}_X$ is the permeability (*not* the conductance) of the channel (typically in $cm^3$/second). Note that at membrane potentials far from the reversal point (e.g. < -20mV for $Ca^{2+}$ channels) the GHK current equation becomes linear, and thus the ohmic model may suffice if the model voltages are appropriately bounded.

## Channel Gating *à la* Hodgkin and Huxley: Independent Voltage-Dependent Gating Particles

Hodgkin and Huxley (1952) described channel gating as an interaction between independent two-state (open and closed) elements or "particles", all of which must be in the open state for channel conduction (see ION CHANNELS - KEYS TO NEURONAL SPECIALIZATION and AXONAL MODELING). The state dynamics of each particle are described with first order kinetics:

$$x_C \overset{\alpha(V),\beta(V)}{\rightleftharpoons} x_O \tag{1}$$

where $x_C$ and $x_O$ represent the closed and open states of gating particle $x$, respectively. $\alpha(V)$ and $\beta(V)$ are the forward and backward rate constants of the particle as a function of voltage, respectively.

## An Extended Hodgkin and Huxley Model

While Hodgkin and Huxley hypothesized that the steady state behaviour of each particle fit a Boltzman distribution, their underlying rate equations were essentially *ad hoc* fits to the experimental data. Although taken as a canonical form by countless cell models, one consequence is that there is not an obvious relationship between the equations' parameters and the more "observable" steady state, $x_\infty(V)$, and time constant, $\tau_x(V)$, functions associated with Equation 1.

The Hodgkin and Huxley model can be recast in more explicit form by considering parameters of a single-barrier kinetic model for each particle (Jack, Noble and Tsien, 1983, Borg-Graham, 1991, 1999). In its basic form this formulation has five parameters for each particle, compared to six parameters of the Hodgkin-Huxley model. Nevertheless, this formulation may be readily fitted to the original Hodgkin-Huxley equations of squid axon $I_{Na}$ and $I_K$; the error is comparable to the error between the original equations and the data to which they were fit (cf. figures 4, 7, and 9 in Hodgkin and Huxley, 1952).

We first derive the expressions the forward, $\alpha'_x(V)$, and backward, $\beta'_x(V)$, rate constants of the

single barrier transition. The parameter $z$ (dimensionless) is the *effective* valence of the gating particle: when positive (negative), the particle opens (closes) with depolarization, thus it is an "activation" ("inactivation") particle. The effective valence is the product of the actual valence of the particle and the proportion of the membrane thickness that the particle moves through during state transitions. $\gamma$ (dimensionless, between 0 and 1) is the asymmetry of the gating particle voltage sensor within the membrane (symmetric when $\gamma = 0.5$). $K$ is the leading rate coefficient of both $\alpha'_x(V)$ and $\beta'_x(V)$. This term can be described in terms of Eyring rate theory, but here we just take $K$ as a constant. $V_{1/2}$ is the voltage for which $\alpha'_x(V)$ and $\beta'_x(V)$ are equal. The final equations for $\alpha'_x(V)$ and $\beta'_x(V)$ are then:

$$\alpha'_x(V) = K \exp\left(\frac{z\ \gamma\ (V - V_{1/2})\ F}{R\ T}\right)$$

$$\beta'_x(V) = K \exp\left(\frac{-z\ (1-\gamma)\ (V - V_{1/2})\ F}{R\ T}\right)$$

An additional parameter, $\tau_0$ (*not* the passive membrane time constant), is crucial for fitting the expressions to the original Hodgkin-Huxley equations. $\tau_0$ represents a rate-limiting step in the state transition, for example "drag" on the particle conformation change (similar considerations have been explored for other, more general, kinetic schemes, e.g. Patlak, 1991), and may be incorporated directly in the expression for the time constant $\tau_x(V)$. $x_\infty(V)$, however, is not effected by $\tau_0$:

$$\begin{aligned} \tau_x(V) &= \frac{1}{\alpha'_x(V)\ +\ \beta'_x(V)}\ +\ \tau_0 \\ x_\infty(V) &= \frac{\alpha'_x(V)}{\alpha'_x(V)\ +\ \beta'_x(V)} \end{aligned}$$

Two additional parameters, $\alpha_0$ and $\beta_0$, may be considered in some cases, though they are not necessary in reproducing the original Hodgkin-Huxley equations. These parameters are voltage-independent forward and backward rate constants, respectively, of parallel state transitions. If considered, these transitions will change the final forms of $\tau_x(V)$ and $x_\infty(V)$.

The parameters of this form have clear relationships to the corresponding $x_\infty(V)$ and $\tau_x(V)$ functions. Thus, the $V_{1/2}$ parameter gives the midpoint and $z$ sets the steepness of the $x_\infty(V)$ sigmoid. The symmetry parameter $\gamma$ determines the skew of $\tau_x(V)$: $\gamma = 0.5$ gives a symmetrical bell-shaped curve for $\tau_x(V)$, which otherwise bends to one side or the other as $\gamma$ approaches 0 or 1. $z$ sets the width of $\tau_x(V)$,

unless $\gamma$ is equal to either 0 or 1, in which case $\tau_x(V)$ becomes sigmoidal and thus $z$ sets the steepness as for $x_\infty(V)$.

With this scheme a particle with a voltage-independent rate constant can be represented by setting $1/K << \tau_0$ (and $\alpha_0 = \beta_0 = 0$), thus making $\tau_0$ the effective time constant. Likewise, both the time constant and steady-state become voltage-independent by setting $K = 0$ and choosing the appropriate $\alpha_0$ and $\beta_0$.

## Determining the Number of Particles in Hodgkin-Huxley Models

The Hodgkin-Huxley paradigm includes the possibility of multiple gating particles of a given type associated with a given channel. Some experimental papers report fitting integer powers of hypothetical gating particles to the observed kinetics, but more typically steady-state activation or inactivation data is simply the observed macroscopic behaviour (that is, reflecting the steady-state of the ensemble of particles). Thus, gating particle powers for channel models can often be considered as a free parameter.

Gating particle powers greater than one have several kinetic consequences, including a sigmoidal "delayed" timecourse of activation (Hodgkin and Huxley, 1952), a more rapid approach to zero in the steady-state characteristic as a function of voltage, and a shift in either the peak (when $0 < \gamma < 1$) or inflection point (when $\gamma = 0$ or 1) of $\tau_x(V)$ in the direction of voltage for which $x_\infty(V)$ tends to 0.

## Channel Gating as Dynamical Systems *à la* Markov Models

The independence and simplicity of the Hodgkin-Huxley gating particle models have at least two advantages: model kinetics can be predicted in an intuitive way, and their numerical evaluation is efficient (Hines, 1984). In addition, as mentioned electrophysiological measures of whole cell currents are often guided by this model. The two-state gating model can also be readily adapted to include factors such as intracellular $[Ca^{2+}]$, by using the appropriate functions for $\alpha$ and $\beta$ (see below).

On the other hand, the independence of the two-state Hodgkin-Huxley particles constrains the equivalent state space description (e.g. allowed state transitions) given by the more general Markovian model (see SYNAPTIC INTERACTIONS, KINETIC MODELS). General Markov kinetic models are standard for detailed biophysical analysis of single channel kinetics, but there have been relatively few

applications in the neural modeling literature. One practical limitation is that Markov models are often much more computationally expensive than the Hodgkin-Huxley model. Nevertheless, the richer dynamics of Markov models may prove necessary for capturing functional properties of some channel types, including subthreshold steady-state $Na^+$ channel rectification (Figure 4), delay of activation for $Na^+$ and $K^+$ currents, and the coupling between opening of $K^+$ channels by $Ca^{2+}$ entering during the action potential and subsequent inactivation (Borg-Graham, 1999).

Although the Markovian framework puts no restrictions on the functions that define state transitions (other than the no-memory condition), the form presented above of the $\alpha(V)$ and $\beta(V)$ functions for the extended Hodgkin-Huxley model is convenient and very general. Another form is the following squeezed exponential formula for the transition rate $\alpha_{ij}(V)$ from state $i$ to state $j$:

$$\alpha_{ij}(V) \;=\; \left(\tau_{min} \;+\; \left((\tau_{max}-\tau_{min})^{-1} + \;\exp\left(\frac{(V-V_{1/2})}{k}\right)\right)^{-1}\right)^{-1} \tag{2}$$

where the inverse of $\tau_{min}$ (analogous to $\tau_0$ in the extended Hodgkin-Huxley model) and $\tau_{max}$ put upper and lower bounds, respectively, on the rate constant $\alpha_{ij}(V)$. Note that there is an implicit coefficient of the exponential term of 1/ms (same units as either $1/\tau_{min}$ or $1/\tau_{max}$) in this equation.

## $Ca^{2+}$-Dependent Gating

Neural models have used a variety of explicit relationships between the concentration of some second messenger and the activation state of the target mechanism. Here we consider a range of examples that have been used to describe $Ca^{2+}$-dependent $K^+$channels.

A simple instantaneous model for $Ca^{2+}$-dependent gating is given by a static rectified power function of concentration with some threshold $\theta_{Ca}$, reminiscent of firing rate models:

$$K \times \sigma([Ca^{2+}]^n - \theta_{Ca})$$

where $\sigma(x) = 0$ for $x < 0$, and $\sigma(x) = x$ otherwise.

A simple kinetic model for $Ca^{2+}$-dependent gating can be described by the following reaction. Assume that $w_C$ and $w_O$ represents the closed and open probabilities, respectively, of a $Ca^{2+}$-dependent gating particle $w$ with forward and backward rate constants $\alpha$ and $\beta$, respectively:

$$w_C + nCa^{++} \;\overset{\alpha,\beta}{\rightleftharpoons}\; w_O$$

Note that the open state $w_O$ is bound to $n$ $Ca^{2+}$ ions. One can also imagine a similar but reverse reaction for the description of $Ca^{2+}$-dependent inactivation, as has been reported for some $Ca^{2+}$ channels. In the more general Markovian framework, $w_C$ and $w_O$ refer to two adjacent states out of the entire state space. This scheme assumes that binding with $Ca^{2+}$ ions is cooperative - either all binding sites are occupied or none are. We may also consider a $\tau_0$ parameter as in the extended Hodgkin-Huxley model. If we assume that the binding of $Ca^{2+}$ in this reaction does not appreciably change $[Ca^{2+}]$, then the steady state value for $w$, $w_\infty$, and the time constant for the kinetics, $\tau_w$, are given by:

$$w_\infty \;=\; \frac{\alpha}{\alpha \;+\; \beta[Ca^{2+}]_{in}{}^{-n}}$$

$$\tau_w \;=\; \frac{1}{\alpha[Ca^{2+}]_{in}{}^{n} \;+\; \beta} \;+\; \tau_0$$

An important distinction is whether or not a $Ca^{2+}$-dependent channel is also dependent on voltage. For example, in recordings of the large-conductance $Ca^{2+}$-dependent $K^+$ (BK) channel, Barrett et al. (1982) found an approximate third power relationship between channel open times and $[Ca^{2+}]$ that was strongly facilitated by depolarization. At a membrane voltage of 10 millivolts, channels became open with a $[Ca^{2+}]$ threshold of about $1\mu$M.

If the dependences are separable, it may be convenient to consider a product of voltage-only and $Ca^{2+}$-only gating terms, for example according to the formulations presented earlier. Otherwise, a single gating "particle" must take into account both voltage and $Ca^{2+}$. A direct voltage dependence of the simple kinetic scheme above can be added in a number of ways, for example by adding a voltage-dependent term to the forward rate constant, now defined as $\alpha(V, [Ca^{2+}]_{in})$:

$$\alpha(V, [Ca^{2+}]_{in}) \;\;=\;\; \alpha_V(V) \;\times\; \alpha[Ca^{2+}]_{in}{}^{n}$$

where, e.g. $\alpha_V(V)$ is the squeezed exponential function of voltage in Equation 2, such that the forward reaction speeds up with depolarization.

Moczydlowski and Latorre (1983) proposed a detailed Markovian kinetic scheme for the $Ca^{2+}$ and voltage-dependent gating of the BK channel, which has been interpreted in several neuron models. The

essential dynamics are captured by a two-state scheme as in Equation 1, with rate constants dependent on both voltage and $Ca^{2+}$-dependent, thus:

$$\begin{aligned}\beta(V,[Ca^{2+}]_{in}) &= \beta_0\left(1+\frac{k_1(V)}{[Ca^{2+}]_{in}}\right)^{-1}\\ \alpha(V,[Ca^{2+}]_{in}) &= \alpha_0\left(1+\frac{[Ca^{2+}]_{in}}{k_4(V)}\right)^{-1}\end{aligned}$$

where

$$k_i(V) = k_i(0)\times\exp\left(\frac{-V\delta_i FZ}{RT}\right)$$

# IONIC CONCENTRATION DYNAMICS

An inevitable consequence of channel currents is that the concentrations on either side of the membrane will change as a function of electrical activity. In addition to the negative feedback on channel currents already mentioned (due to reduction in driving force), such changes can have a variety of other functional consequences. These include the activation of intracellular or extracellular receptors, the most important being those that underly the myriad of $Ca^{2+}$-dependent pathways (including the $Ca^{2+}$-dependent channel gating just described). We may also consider the role of the membrane pumps which tend to maintain ionic gradients (see MOSAIC NEURON), and intracellular buffer systems. In the following discussion, we emphasize $Ca^{2+}$ dynamics, but similar considerations are relevant for other ions.

## Concentration Integrators

Most neuron models which consider concentration changes rely on some partition of the extracellular and intracellular space into a set of well-mixed compartments (e.g. "shells"), with or without an "inifinite" compartment with a fixed concentration. Simple diffusion is normally assumed between compartments, according to the geometry of the partitioning and assumptions about the diffusion coefficient for the free ion, $D$. Compartments adjacent the cell membrane also take into account ion flow across

the membrane, e.g. due to channels and pumps. The physical partitioning into compartments depends on the question being addressed, with the simplest system being a single intracellular compartment (extracellular concentration being assumed constant).

Any model of $[Ca^{2+}]$ must take into account not only the influx of $Ca^{2+}$, but also some mechanism for the removal of $Ca^{2+}$. The simplest method is to include a steady-state term in the differential equation(s) describing $[Ca^{2+}]$. In the general case this value is associated with a second parameter corresponding to the time constant for concentration decay.

## Membrane Pump Models

More explicit models of ion removal includes mechanisms such as membrane-bound pumps, that transport $Ca^{2+}$, $K^+$, $Na^+$ and other ions against their respective concentration gradients. A general pump model may be described with a Michaelis-Menton mechanism, assuming no appreciable change in the extracellular $[Ca^{2+}]$:

$$J_{Ca^{2+}} = V_{max} \frac{[Ca^{2+}]_{in}}{K_d + [Ca^{2+}]_{in}} - J_{leak}$$

where $J_{Ca^{2+}}$ is the removal rate of $Ca^{2+}$ per unit area, $V_{max}$ is the maximum flux rate per unit area, $K_d$ is the half-maximal $[Ca^{2+}]_{in}$. $J_{leak}$ compensates for the resting pump rate, and is typically adjusted so that there is no net pump current at rest, given some resting activation of $Ca^{2+}$ channels.

For example, the spine model by Zador, Koch and Brown (1990) included two $Ca^{2+}$ pumps with Michaelis-Menton kinetics: one high-affinity, low-capacity, corresponding to a CaATPase-driven mechanism, and the other low-affinity, high-capacity, corresponding to a $Ca^{2+}/Na^+$ exchange mechanism (see also Koch, 1999). These pumps were treated as a separate currents in the $[Ca^{2+}]$ differential equation. Other models have incorporated a pump which binds to intra and extracellular $Ca^{2+}$ with various rate constants. These reactions are then solved simultaneously with another binding reaction between $[Ca^{2+}]_{in}$ and a buffer.

## Buffer Models

Endogenous intracellular $Ca^{2+}$ buffers have a strong effect on the free intracellular $[Ca^{2+}]_{in}$. Cell models that consider $Ca^{2+}$ dynamics have incorporated buffer mechanisms of varying complexities, in-

cluding solving the dynamical equations for the buffer-$Ca^{2+}$ reaction during the course of the simulation. Note that in some models an explicit (instantaneous) buffer mechanism is replaced by adjusting $Ca^{2+}$ sensitivities of $Ca^{2+}$-dependent mechanisms, such as $Ca^{2+}$-dependent $K^+$ channels.

A simple way to treat intracellular buffering of $Ca^{2+}$ is to assume a non-saturated buffer (i.e. $[Bu] >> [Ca^{2+}]_{in}$, where $[Bu]$ is the concentration of buffer binding sites) with instantaneous kinetics. The key parameter, $\beta_{Bu}$, in this mechanism equals the ratio of the concentration of bound $Ca^{2+}$ and free $Ca^{2+}$:

$$\beta_{Bu} \;=\; \frac{[Ca^{2+}]_{in}^{bound}}{[Ca^{2+}]_{in}^{free}}$$

and thus is a function of $[Bu]$. This mechanism implies that the *measured* $[Ca^{2+}]_{in}$ is equal to the total $[Ca^{2+}]_{in}$ divided by $(\beta_{Bu} + 1)$. For non-diffusional models of $[Ca^{2+}]_{in}$, e.g. where there is one $Ca^{2+}$ compartment per electrical compartment, this is the only role of the instantaneous buffer. For multiple compartment systems, the effective diffusion constant $D'$ applied to the difference in $[Ca^{2+}]$ between compartments must also be adjusted to take into account the instantaneous buffer, by setting $D'$ equal to $D/(\beta_{Bu}+1)$. A variation on this scheme would be to assume that $\beta_{Bu}$ is a function of each compartment - in this case the diffusion equation between compartments would reference the original $D$, with the concentration difference between any two compartments determined by the difference of the total concentrations, weighted by the appropriate $\beta_{Bu}$s.

## PRACTICAL ASPECTS OF CODING BIOPHYSICAL MODELS

The translation of experimental data on some biophysical mechanism into simulator code, within the framework of a given mathematical model, and the reverse process (which is a necessary step in formulating experimental predictions from a model), have received little attention. However, these steps have many practical aspects, not the least of which is that as models become more and more complex, the opportunity for errors becomes more and more serious. For this reason it is useful to consider model *syntax* (see NEUROSIMULATION: TOOLS AND RESOURCES and GENESIS SIMULATION SYSTEM and NEURON SIMULATION ENVIRONMENT and NSL NEURAL SIMULATION LANGUAGE).

In most situations, it is desirable that a simulator program act essentially as a "black-box", so that model analysis concerns only the input (some collection of model definition files) and the output (numerical data, usually time sequences). Thus, when composing the model definition, one should ideally be able to focus on the model algorithms and their parameters, rather than on their implementation.

Model syntax should therefore allow the expression of mathematical (and symbolic, if appropriate) relationships in as close to a "natural" syntax as possible, i.e. one should be able to simply "write down the equations" defining the model. Certainly a practical consequence of such a syntax is that the learning curve for the simulator is reduced, but more important over the long term is simply that if model definitions are easier to read, they are also easier to verify, document and change.

To illustrate these ideas, here we present examples of biophysical model definitions taken from the Surf-Hippo Neuron Simulation System (Graham, 2002). This system is written in Lisp, an important point since the system exploits many advantages of this truly high-level language that are well-known to the AI community, while at the same time having a numerical performance on par with languages such as C.

In particular, Lisp supports an emphasis on more declarative descriptions (emphasizing *what* kind of model is desired), rather than imperative ones (emphasizing *how* to construct a model). Thus, model syntax in Surf-Hippo is designed to minimize the actual code for mechanism specification: correspondingly, these examples illustrate the necessary and sufficient parameters for each mechanism, avoiding "overhead" code that would be simulator-specific. Surf-Hippo also includes automatic generation of mechanism definition code, for example allowing to capture the "state" of a given mechanism model that has been modified on-line during automatic or manual parameter exploration. This capability, which is facilitated by both the minimal requirements for model specification and the relative ease by which Lisp programs may be able to write Lisp code, is important for avoiding errors when documenting model results.

Figure 1 illustrates the definitions of the classical Hodgkin-Huxley model of the squid axon $Na^+$ channel and the associated "M" activation gating particle, showing in particular how arbitary functions are represented. Once the basic syntax of Lisp is grasped, the human readability of this format is enhanced because it includes only the essential kinetic parameters. As a comparison, the equivalent source code in similar simulation systems such as GENESIS and NEURON is about two to three times larger.

Several parameterized models of biophysical mechanisms are included in Surf-Hippo, including those discussed in this chapter. For example, Figure 2 shows the definition for the extended Hodgkin-Huxley model of the $Na^+$ channel "M" gating particle. Markov models for particle gating are also readily represented in this system. As an example, Figure 3 illustrates the definition of a Markovian gating particle for a hippocampal pyramidal cell $Na^+$ channel model (Borg-Graham, 1999; state diagram in

Figure 4).

# DISCUSSION

Biophysical details are likely to be crucial for understanding neural computation (see MOSAIC NEURON). This process entails an informed tradeoff between incorporating every known experimental nuance of a given cellular mechanism, and the practical application of abstractions and simplifications which capture essential dynamic relationships between biological molecules and various neuronal signals. In this chapter we have presented some of the more commonly used mathematical descriptions for these relationships. We may note in closing that an increasingly important (and unavoidable) problem with complicated neural models that rely on these sorts of mechanisms is the lack of formal or analytic verification. This situation calls for alternative methods, in particular the cross-validation of numerical results using several tools of similar capability (e.g. NEURON, GENESIS, Surf-Hippo). Practical aspects of coding biophysical models, such as the minimal model syntax discussed here, should facilitate such efforts.

**Road Map:** Biological Neurons and Synapses, Implementations and Analysis

**Related Reading:** Perspective on Neuron Model Complexity, Single-Cell Models, Mosaic Neuron, Oscillatory and Bursting Properties of Neurons, Ion Channels - Keys to Neuronal Specialization, Axonal Modeling, Synaptic Interactions, Kinetic Models, Neurosimulation: Tools and Resources, GENESIS Simulation System, NEURON Simulation Environment, NSL Neural Simulation Language

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**Figure 1:** The Surf-Hippo definitions of the classical Hodgkin-Huxley model of the squid axon $Na^+$ channel and the associated "M" activation gating particle. The plethora of parentheses may seem daunting, however all formatting (including indentation) is done automatically by Lisp-savvy editors (such as Emacs). The last line in the `CHANNEL-TYPE-DEF` form specifies three `M-HH` and one `H-HH` gating particles. Surf-Hippo model definitions allow concise inclusion of arbitrary functions, in this case for the `ALPHA` and `BETA` rate constants (ref. equations of the Hodgkin-Huxley $Na^+$ channel in AXONAL MODELING, q.v.) in the `PARTICLE-TYPE-DEF` form. The `LAMBDA` symbol denotes the beginning of a function definition. In the context of gating particle definitions, Surf-Hippo assumes only that the rate functions take a single `VOLTAGE` argument (in millivolts), and return a rate value (in $\text{ms}^{-1}$). Comments are indicated with a semicolon. Expression precedence is unambiguous with the infix notation of Lisp. The first element of each (parenthesized) list defines the operation applied to the rest of the list, and in nested lists everything is evaluated from the inside out: e.g. `(+ A (* B C) D)` is $A + BC + D$.

**Figure 2:** The Surf-Hippo definition for the extended Hodgkin-Huxley model for the "M" activation particle type of the squid axon $Na^+$ channel.

**Figure 3:** The Surf-Hippo definition of a Markovian gating particle for a hippocampal pyramidal cell $Na^+$ channel model (Borg-Graham, 1999). Transition rates between states, in $\text{ms}^{-1}$, are defined with either constants (for example, 3 $\text{ms}^{-1}$ for the transition from state `O` to state `I`) or functions of voltage (as indicated by the "dummy" variable `VOLTAGE`). The `SQUEEZED-EXPONENTIAL` function (Equation 2) is built in to Surf-Hippo (when :TAU-MAX is not specified, then the mininum rate is 0).

**Figure 4:** State diagram of a hypothetical Markov gating model used for $I_{Na}$ in a model of hippocampal pyramidal cells (Borg-Graham, 1999). From the single inactivated state $I$, the two closed states $C_i$ are reached with increasing hyperpolarization. The $C_i \rightarrow O$ transitions implement in effect distinct thresholds, occuring at progressively lower potentials with increasing $i$. Likewise, the $I \rightarrow C_1$ and $C_1 \rightarrow C_2$ transitions occur at voltages hyperpolarized to the associated $C_1 \rightarrow O$ and $C_2 \rightarrow O$ transitions, respectively, somewhat like a rachet mechanism. The $O \rightarrow I$ transition is voltage-independent. The arrows denote the dominant transitions during spike depolarization/repolarization. One important

aspect of this model is that the inactivation state is reached only after channel opening, as reported from studies of single $Na^+$ channels (Patlak, 1991, Hille, 1992). Such coupling contradicts the central assumption of independent activation and inactivation kinetics in the Hodgkin-Huxley model.

```
(CHANNEL-TYPE-DEF
 `(NA-HH
   (GBAR-DENSITY . 1200) ; pS/um2
   (E-REV . 50)          ; mV
   (V-PARTICLES . ((M-HH 3) (H-HH 1)))))

(PARTICLE-TYPE-DEF
 `(M-HH
   (CLASS . :HH)
   (ALPHA . (LAMBDA (VOLTAGE)
              (/ (* -0.1 (- VOLTAGE -40))
                 (1- (EXP (/ (- VOLTAGE -40) -10)))))))
   (BETA . (LAMBDA (VOLTAGE)
             (* 4 (EXP (/ (- VOLTAGE -65) -18)))))))
```

Figure 1

```
(PARTICLE-TYPE-DEF
 `(M-HH-FIT
   (CLASS . :HH-EXT)
   (VALENCE . 2.7)
   (GAMMA . 0.4)
   (BASE-RATE . 1.2)  ; 1/ms
   (V-HALF . -40)     ; mV
   (TAU-0 . 0.07)))   ; ms
```

Figure 2

```
(PARTICLE-TYPE-DEF
 '(NA-X-HPC
   (CLASS . :MARKOV)
   (STATES . (O I C1 C2))
   (OPEN-STATES . (O))
   (STATE-TRANSITIONS .
    ((O  I  3)
     (O  C1 (SQUEEZED-EXPONENTIAL VOLTAGE :V-HALF -51 :K -2 :TAU-MIN 1/3))
     (C1 O  (SQUEEZED-EXPONENTIAL VOLTAGE :V-HALF -42 :K  1 :TAU-MIN 1/3))
     (O  C2 (SQUEEZED-EXPONENTIAL VOLTAGE :V-HALF -57 :K -2 :TAU-MIN 1/3))
     (C2 O  (SQUEEZED-EXPONENTIAL VOLTAGE :V-HALF -51 :K  1 :TAU-MIN 1/3))
     (I  C1 (SQUEEZED-EXPONENTIAL VOLTAGE :V-HALF -53 :K -1 :TAU-MAX 100 :TAU-MIN 1))
     (C1 C2 (SQUEEZED-EXPONENTIAL VOLTAGE :V-HALF -60 :K -1 :TAU-MAX 100 :TAU-MIN 1)))))
```

Figure 3

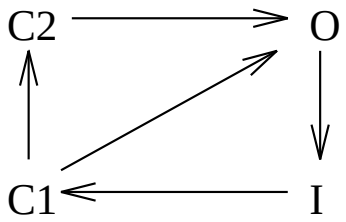


Figure 4