Switching Dynamics in the *Aplysia* Bag Cell Neuron

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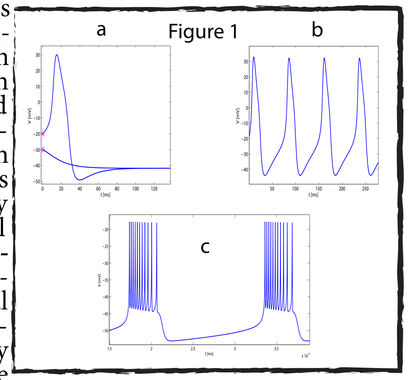
Motivation

In endeavoring to understand the basis of neural function, the field of theoretical neuroscience has gained traction in the last 20 years. This traction has been largely due to the observation and mathematical modeling of the electrochemistry underlying neuron function in the squid giant axon over 60 years ago [1]. Today, there are three widely used classifications of mathematical neuron model: **threshold spiking**, **oscillatory**, and **bursting** neurons (Figures 1a-c), but these prototypical neuron models do not capture the diversity of neuron dynamics as they appear in nature and modifications are often necessary, particularly when second-messenger systems (governed by molecular reaction kinetics) are involved in neuron function. One such example is stimulus-dependent transient bursting.

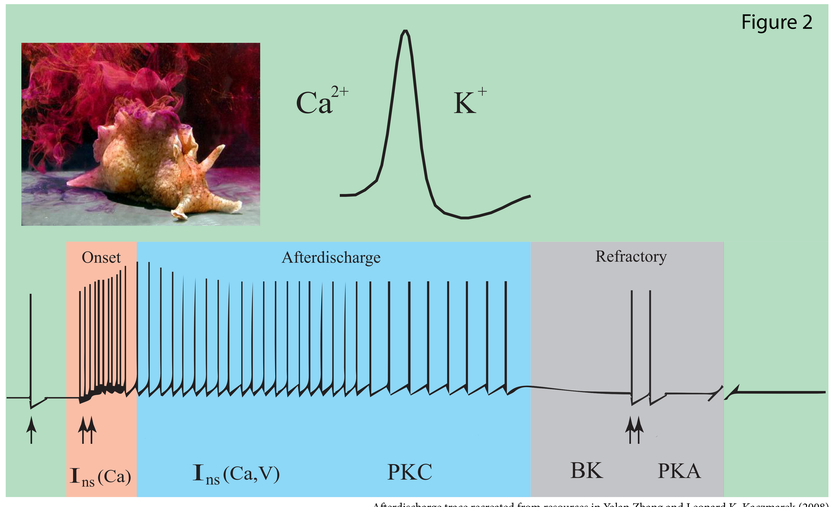
Figure 1



Transient Bursting Cycle

In nature, transient bursting cycles in neurons serves a broad range of functions, including working memory in humans, motor function in turtles, and escape responses in lamprey [2] as well as lactation and birth in mammals [3]. *Aplysia* has emerged as a model organism for this transient behavior, in which the phenomena is referred to as the **afterdischarge** [4,5,6]. As is common of neurons that exhibit transient bursting, the persistent electrical activity of the neuron in an active state is associated with the release of neuropeptides that modulate function downstream [7], making them important high-level signaling neurons.

Figure 2



Afterdischarge trace recreated from resources in Yalan Zhang and Leonard K. Kaczmarek (2008) Bag cell neurons. Scholarpedia, 3(7):4095. http://www.scholarpedia.org/article/Bag_cell_neurons

Aplysia Bag Cell Neuron

In the abdominal ganglia of the seaslug, *Aplysia*, bag cell neurons regulate egg-laying behavior. Thought to be initiated by upstream acetylcholine in nature [7], the afterdischarge is evoked by a pulse-like stimulus in the lab (Figure 2, Onset). Two varieties of calcium-dependent nonselective cation channel are indicated in the transition from the **steady state** to the **limit cycle ruin**. The first is voltage-independent and acts to depolarize the resting potential (Figure 2, Onset) as a function of calcium concentration [8], while the second is voltage dependent [9] and contributes to the repetitive firing of the afterdischarge (Figure 2, Afterdischarge). During the afterdischarge, an additional potassium current and a second-messenger systems are candidates for regulators of a refractory period in the bag cell (Figure 2, Refractory). In addition to afterdischarge behavior, the bag cell neuron also behaves as a typical neuron for a standard brief stimulus (Figure 6, green region). To model these base currents, the Hodgkin-Huxley model [1] is used as a framework. Unlike the canonical Hodgkin-Huxley model (derived from the squid giant axon) the *Aplysia* bag cell neuron relies on calcium for the upstroke of its action potential, which displays some use-dependence, and there are at least two channels involved in the potassium current.

Mathematical Modeling

The task of deriving a system of the form in Figure 2 requires gradual construction, beginning with the base currents that make up the action potential (green region). The key observable of electrical activity in the neuron is the membrane potential and has the form of a leaky capacitor,

$$C\dot{V} = I_A - I_{Ca} - I_K - I_{K2} \qquad (1)$$

Where the change in membrane potential V is governed by the capacitance, C, and the instantaneous value of the applied, calcium, and potassium currents are given, respectively, by the right hand side. With the exception of the constant applied current, I_A, the current have the form,

$$I_x = g_x m(V) h(V)(V - V_x) \qquad (2)$$

That is, the x*th* current is a function of the maximal conductance g_x, the activation function, m(V), the inactivation function $h(V)$, and the driving force, $(V\text{-}V_x)$, where V_x is the reversal potential of the ion current. Experimentalists observe kinetics by isolating currents and performing voltage clamp experiments. We therefore construct each current model independently from raw data provided by **Neil Magoski** [4,5,8,9, Acknowledgements].

Calcium Channel

The primary component of the upstroke is a calcium channel that exhibits **use-dependence**. A series of pulses to a channel with use-dependence will return a successively lower peak current with each subsequent pulse (Figure 3, left). To model this phenomena, the calcium channel's activation kinetics are first fit to model, using the standard Hodgkin-Huxley framework,

$$\dot{m} = \frac{m_{ss} - m}{\tau_m} \qquad (3)$$

The functions, m_{ss} and τ_m, are function fit directly from experimental data. To model the use-dependence, a differential equation is added to the system to keep track of calcium concentration in a small intracellular domain near the calcium channels:

$$\dot{s} = \frac{I_{Ca}(1 - P_b)}{-2Fv} - Ds \qquad (4)$$

where s is the calcium concentration in the internal domain, I_{Ca} is the calcium current, P_b is the probability of a single ion channel being bound to a buffer (presumably calmodulin), F is Faraday's constant, b is the rate of calcium dissipation, v is the volume of the internal calcium domain, D describes the rate of diffusion of calcium out of the internal domain. The calcium-dependent inactivation is then

$$I_{Ca} = g_{Ca} m \frac{V - V_{Ca}}{1 + Ks} \qquad (5)$$

Together, Equations (3)-(5) describe the evolution of the calcium current as a function of membrane potential and calcium concentration. For some parameters, the system exhibits use dependence (Figure 3, left) comparable to the experimental result (Figure 3, right).

Figure 3

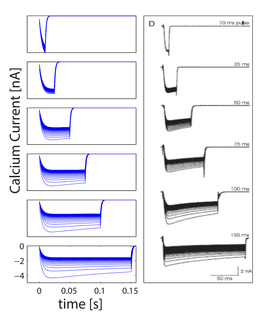
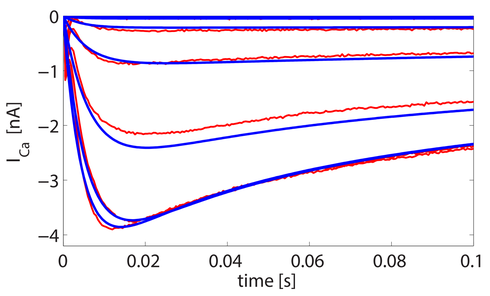


Figure 4



In addition to reproducing use-dependence experiments in bagt cell neurons, the same parameter regime can also reproduce the standard activation experiments, at least over time courses relevant to the action potential (Figure 4). The model used here originated from a formulation of use dependence in Aplysia abdominal ganglion [10].

Potassium Channels

Little ground has been made in separating the kinetics of the two potassium channels because ambiguities lie in fitting procedures. Four equations of the form in Equation 3 must be fit to a summation of two equations of the definition of the current (Equation 2). The fitting program is applied to each voltage clamp trace independently, and therefore has no information about other voltage-dependent traces. Often, the resulting kinetics are noisy (Figure 5, bottom) despite a well-approximated fit (Figure 5, top). In order to gain some control over the result in the kinetics, **paramater forcing** is used. The upper and lower bounds of the fit are determined as a deviation from the expected Botlzmann kinetics (Figure 6, bottom). The resulting fit loses some specificity in favor of generality, but maintains the important qualitative properties of current response.

Figure 5

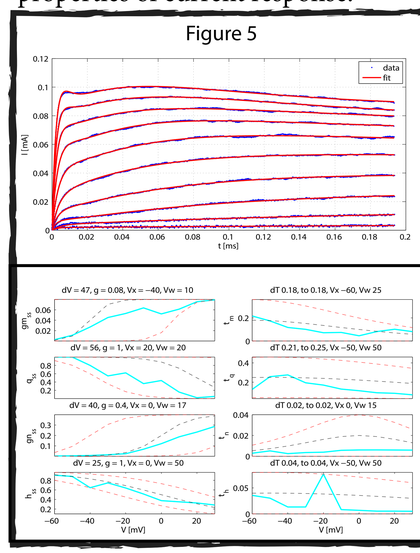
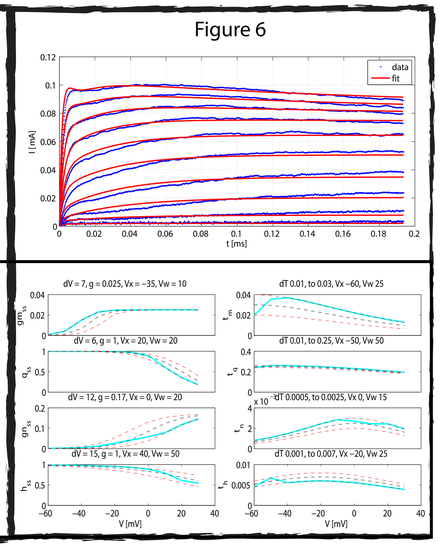
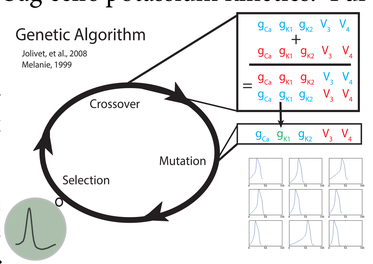


Figure 6



Whole Bag Cell Neuron Synthesis

Having derived parameters for potassium and calcium is not enough to construct the action potential of a whole bag cell neuron. Variability between neurons is significant enough that one bag cell's calcium kinetics may not produce an action potential with another bag cell's potassium kinetics. Further, the maximal conductances in Equation 2 for each current depends on properties that vary from experiment to experiment (such as the patch size, amplifier settings, and concentration of channels at the detection electrode). To find a parameter space in a region consistent with experimental results, a genetic algorithm will be employed (right), having yielded successful results in the past (right, inset).



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Acknowledgements
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