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CHAPTER 12

How tightly tuned are network parameters? Insight from computational and experimental studies in small rhythmic motor networks

Eve Marder, Anne-Elise Tobin* and Rachel Grashow

Volen Center MS 013, Brandeis University, 415 South St., Waltham, MA 02454-9110, USA

Abstract: We describe theoretical and experimental studies that demonstrate that a given pattern of neuronal activity can be produced by variable sets of underlying conductances. Experimental work demonstrates that individual identified neurons in different animals may show variations as large as 2–5 fold in the conductance densities of specific ion channels. Theoretical work shows that models with this range of variation in many of their maximal conductances can produce similar activity. Together, these observations suggest that neurons and networks may be less tightly tuned than previously thought. Consequently, we argue that instead of attempting to construct single canonical models of neuronal function, it might be more useful to construct and analyze large families of models that give similar behavior.

Keywords: neuronal models; conductance-based models; Central Pattern Generators; half-center oscillator; neuronal homeostasis

One of the great challenges in neuroscience is to understand how network dynamics depend on the interaction between the intrinsic membrane properties of the network neurons and their synaptic interactions. We know that most neurons have a large number of different kinds of voltage and time dependent ion channels (Marder, 1998). Additionally, synaptic potentials are quite diverse, and can show complex time- and voltage-dependent properties (Zucker and Regehr, 2002). The widespread implementation of synaptic learning rules in neural networks has led to an implicit, almost unconscious, assumption among many neuroscientists that in order for a network to perform well all of its parameters must be quite tightly tuned. This assumption was buttressed by the historical difficulty of tuning complex models to give a desired output. In this chapter we will present a combination of both experimental and computational work that suggests that many solutions can produce similar network performance.

*Corresponding author. Tel.: +1 781 736 3141;
Fax: +1 781 736 3142; E-mail: atobin@brandeis.edu

Compensating conductances in a two-cell network

Two-cell, reciprocally inhibitory networks have been studied for almost 100 years. Early work in motor control defined the concept of a half-center oscillator in which rhythmic bursts of activity would drive alternations in flexor-extensor activity in the spinal cord (Brown, 1911, 1914). Subsequently, this generic circuit has been richly studied computationally (Perkel and Mulloney, 1974;

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Wang and Rinzel, 1992; Cymbalyuk et al., 1994; Skinner et al., 1994; Van Vreeswijk et al., 1994; Nadim et al., 1995, 1999; Olsen et al., 1995; White et al., 1998) and experimentally (Friesen, 1994; Sharp et al., 1996; Cymbalyuk et al., 2002; Sorensen et al., 2004).

Reciprocally inhibitory circuits can produce a wide variety of outputs, including alternating spiking, alternating bursting, in-phase spiking, and in-phase bursting (Sharp et al., 1996), depending on a variety of parameters, including the time course of the reciprocal inhibition (Van Vreeswijk et al., 1994). Sharp et al. (1996) used the dynamic clamp (Sharp et al., 1993a, b; Prinz et al., 2004) to construct reciprocally inhibitory networks using two Gastric Mill (GM) neurons from the crab stomatogastric ganglion. They were able to produce alternating bursting in two-cell networks by adding an I_h conductance (also with the dynamic clamp) to each neuron, which provided a slowly activating inward current that sustained slow alternating bursts. The period of the alternating bursts increased as the conductance of the inhibitory synapse was increased and also when the I_h conductance was decreased. In this study, the two conductances were varied individually.

To understand how intrinsic and synaptic parameters may interact, we replicated the essential paradigm used by Sharp et al. (1996); however, we varied the conductances of the inhibitory synapses and I_h simultaneously to construct a 9×9 matrix of 81 different versions of the two-neuron network (Fig. 1). This allows us to examine the behavior of

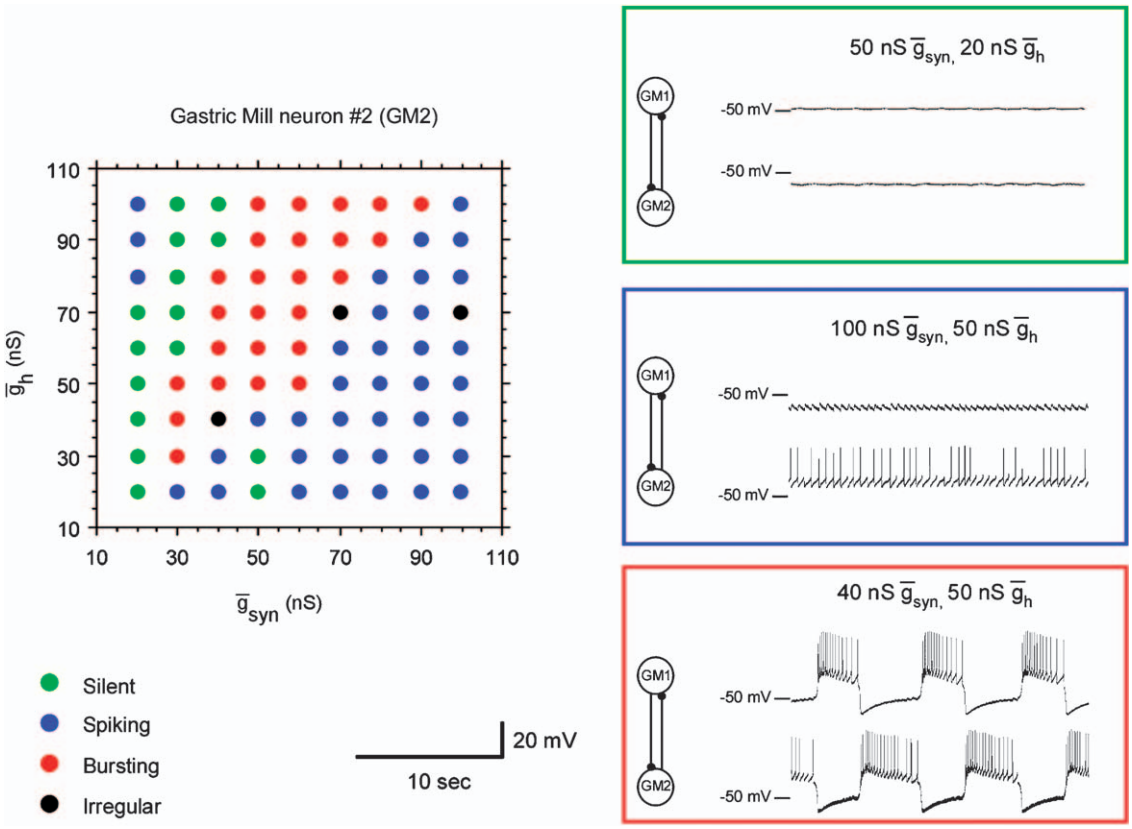

Fig. 1. A range of parameter values can produce similar network output in an artificial reciprocally inhibitory two-cell network. *Left*, map of parameter space (synaptic conductance g_{syn}, and h-conductance g_h) for one GM neuron (GM2) in the network. Green, blue, red, and black mark the parameter values for which GM2 was quiescent, spiking tonically, bursting rhythmically, and exhibiting irregular activity, respectively. *Right*, intracellular recordings exemplifying three characteristic activity patterns of the network for different parameter values. Box colors correspond to activity of GM2 as symbolized in the parameter map legend.

the network as a function of these two conductances. At the top left of the matrix, the green points mark parameter combinations in which GM2 was silent (see recordings shown in the green inset box). The blue points in the lower right of the plot mark the parameter regime that led to tonic spiking in GM2 (inset shown in blue). The points shown in red mark the parameters that gave rise to alternating bursts of activity (recordings shown in red inset box).

It is clear from this experiment that there is a wedge in parameter space in which stable rhythmic alternating bursts were found. The shape and size of the wedge demonstrates that, in this experiment, stable half-center activity was produced over a 3-fold range of both I_h and synaptic conductances, as long as they were covaried (Fig. 1). That is to say, both conductances had to be either large or small, but that within that constraint, they could vary considerably.

Figure 2 shows the frequency of the alternating bursts produced in the same experiment as shown in Fig. 1. The same color code is used: the red points and the recordings show that similar burst frequencies can result from quite different sets of parameters. These dynamic clamp experiments illustrate that a given network output can be produced over an extensive range of parameters, as long as appropriate relationships among some of those parameters are maintained.

Modeling studies of leech heart interneurons have demonstrated similar findings (Cymbalyuk et al., 2002). The leak parameters, E_{leak} and g_{leak} could vary up to 3-fold, as long as the parameters covaried. Within that range, many parameter combinations could produce similar burst frequency, duty cycle, and interburst spike frequency.

Building models to capture the dynamics of real neurons

For many years most researchers wishing to build a conductance-based model of a specific neuron or

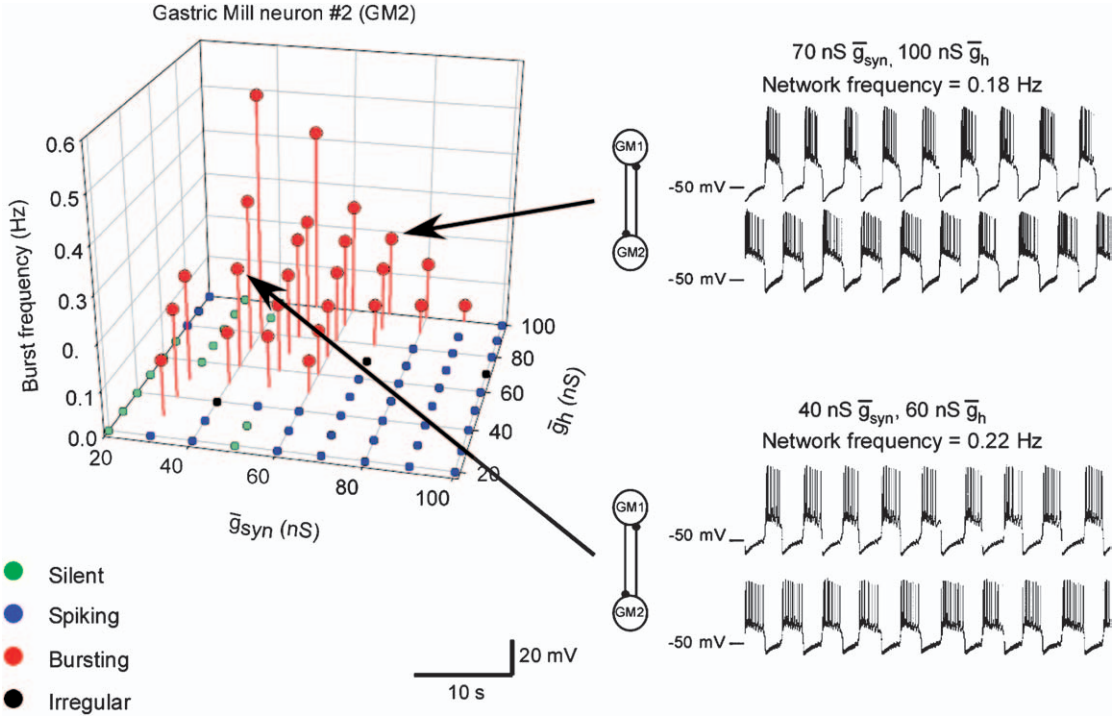

Fig. 2. Similar network frequencies result from different network parameters. *Left*, burst frequency for the artificial half-center network when the values of g_{syn} and g_h are varied. *Right*, intracellular recordings from two half-center networks with different parameter values.

neuron type followed the same general strategy. First, all available biophysical data describing the voltage- and time-dependent currents in the neuron were fit with appropriate differential equations (Hodgkin and Huxley, 1952; Buchholtz et al., 1992; Traub et al., 1994). Second, values for currents not measured in the neuron in question were pulled from the literature, either from other cell types in the same species, or from different species. Third, a decision was made to build either a single-compartment model or a multicompartmental model (De Schutter et al., 2005). Fourth, the model was hand-tuned, using some set of measurements of the neuron's firing properties as a criterion for the tuning process (De Schutter et al., 2005).

Inherent in this program are two fundamental assumptions: (a) that all neurons of the same class or type are virtually identical, and (b) that the end-result of the hand-tuning would produce an optimal solution that would capture in detail the parameters of the ideal neuron, and therefore could be used to extract insights into the mechanisms by which interacting currents give rise to specific dynamics. Recent experimental and theoretical work summarized below challenges the validity of both of these assumptions. We now argue that the process of building semi-realistic or realistic model neurons in the future will involve the construction of a family of models that may equally well capture the dynamics and variability of the neurons that are to be modeled.

Biological variability in synaptic and intrinsic conductances

Biophysical measurements of synaptic and intrinsic conductances are conventionally reported as means and standard errors, leading to the assumption that the mean is the "true value." However, we now argue that reporting the range of the underlying data may be as important as reporting means alone. For example, it is now becoming clear that 2–5 fold ranges of both intrinsic and synaptic conductances may be common in many systems (Golowasch et al., 1999a; Swensen and Bean, 2005; Marder and Goaillard, 2006; Schulz et al., 2006). Figure 3a shows electrophysiological recordings from two LP neurons from two different crab stomatogastric ganglia during ongoing activity, and the voltage-clamp measurements of three K currents from those same neurons. Note that while the overall activity pattern is quite similar in the two cases, the outward currents were quite different in the recordings from the two preparations (Schulz et al., 2006). Figure 3b shows data from a larger population of neurons (Schulz et al., 2006) and shows the spread of conductance densities measured in different LP neurons, a result similar to that reported earlier (Golowasch et al., 1999a). Interestingly, the same kind of variability is seen at the level of mRNA expression for these channel genes (Fig. 3c). Note that the mRNA expression and measured conductance are correlated in the same neuron, demonstrating that this variability is not a result of experimental error (Fig. 3d). Thus, the parameter range that we see in the half-center examples in Figs. 1 and 2 may be similar to the parameter ranges found in biological preparations.

This conclusion, that 2–5 fold ranges in conductances can underlie similar activity, flies in the face of years of intuitions we have developed from pharmacological studies in which currents and synapses are modified. These studies often show dramatic alterations in activity from changes in a synaptic or intrinsic conductance of 20–50%. Figure 4A shows the effects of the application of the neuromodulator, dopamine, on the transient outward current, I_A, recorded from the PD neuron of the lobster stomatogastric ganglion (Harris-Warrick et al., 1995a, b; Szucs and Selverston, 2006). Note that while dopamine increased the outward current by ~25%, the PD neuron dramatically changed its firing patterns – much of this change presumably attributable to the effects of dopamine on I_A (Fig. 4B).

While such neuromodulator studies indicate that even moderate changes in a conductance can greatly alter activity, it is extremely important to distinguish between changing one parameter in a neuron or a network at one moment in time and the variance that can occur in a population, when compensatory mechanisms act throughout the lifetime of each animal (Swensen and Bean, 2005; Marder and Goaillard, 2006). This is illustrated by

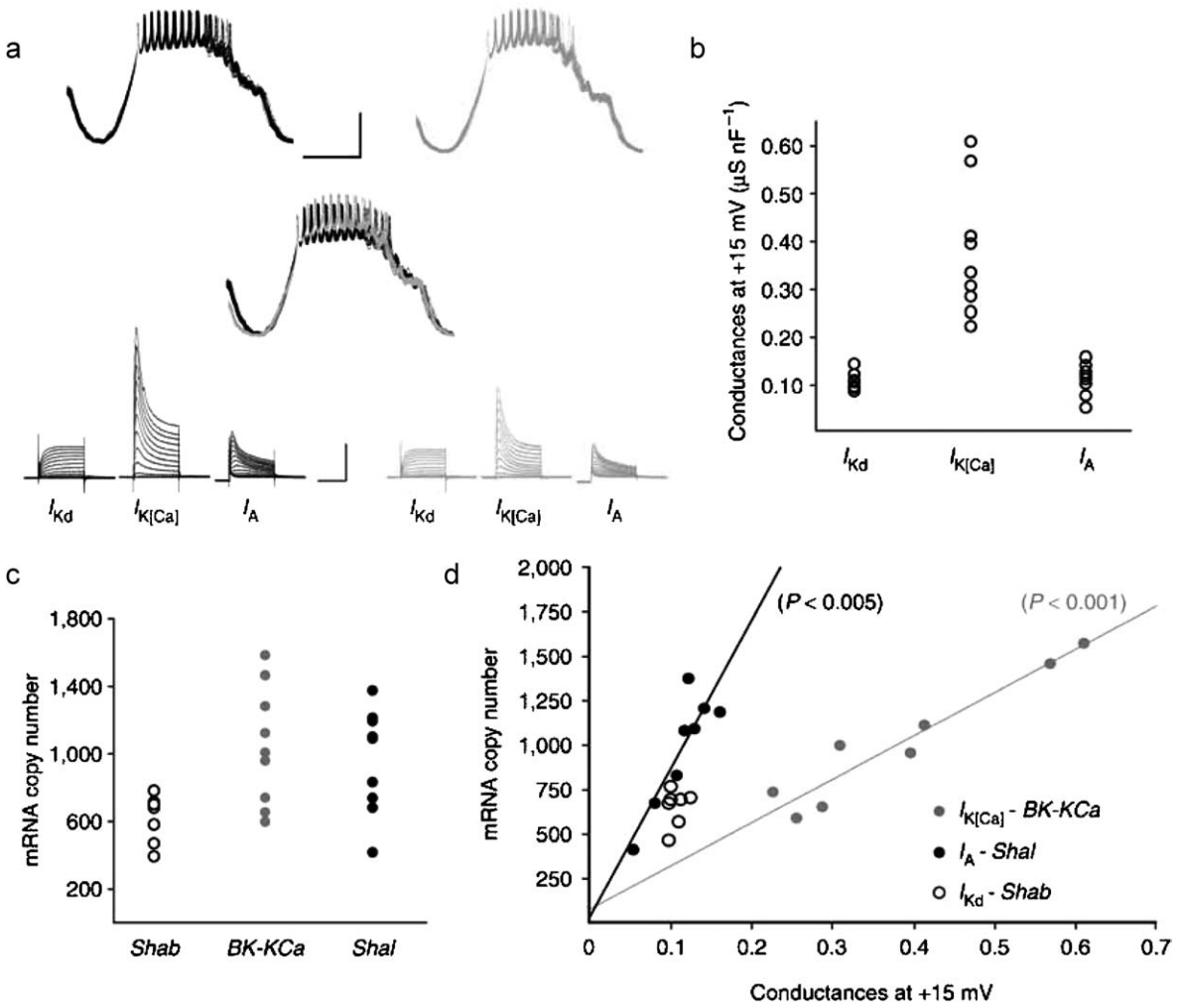

Fig. 3. Variable conductances underlie stereotyped activity in identified neurons. (a) *Top*, 20 burst cycles are overlaid for each of two LP neurons from two different animals, black and gray. Vertical scale is −60 to −50 mV; horizontal scale, 200 ms. *Middle*, traces from the two neurons are overlaid to demonstrate similarity. *Bottom*, voltage-clamp recordings from each neuron of 3 K currents: I_{Kd}, delayed rectifier, $I_{K[Ca]}$, calcium-dependent K, and I_A, fast transient K. Vertical scale is 50 nA; horizontal scale, 100 ms. (b) Normalized conductances for the 3 K currents as measured in voltage clamp. (c) Normalized levels of mRNA of *Shab*, *BK-KCa*, and *Shal* corresponding to the 3 K currents, I_{Kd}, $I_{K[Ca]}$, and I_A, respectively. The mRNA levels are measured in the same neurons for which voltage-clamp measurements are taken. (d) mRNA levels significantly correlate with the conductance measurements for $I_{K[Ca]}$ and I_A. Adapted with permission from Schulz et al. (2006).

the recent experiments from the Harris-Warrick laboratory in which mRNA encoding I_A was injected into single PD neurons. This resulted in 2–3 fold changes in the measured outward current (Fig. 4C), but no change in the neuron's activity (Fig. 4D) because a compensatory upregulation of I_h occurred (MacLean et al., 2003, 2005).

Constructing model families

Hand-tuning detailed conductance-based models is tedious, frustrating, and intellectually unsatisfying. It is intellectually unsatisfying because at the end of a hand-tuning process the modeler has no assurance that the solution is in any way "correct"

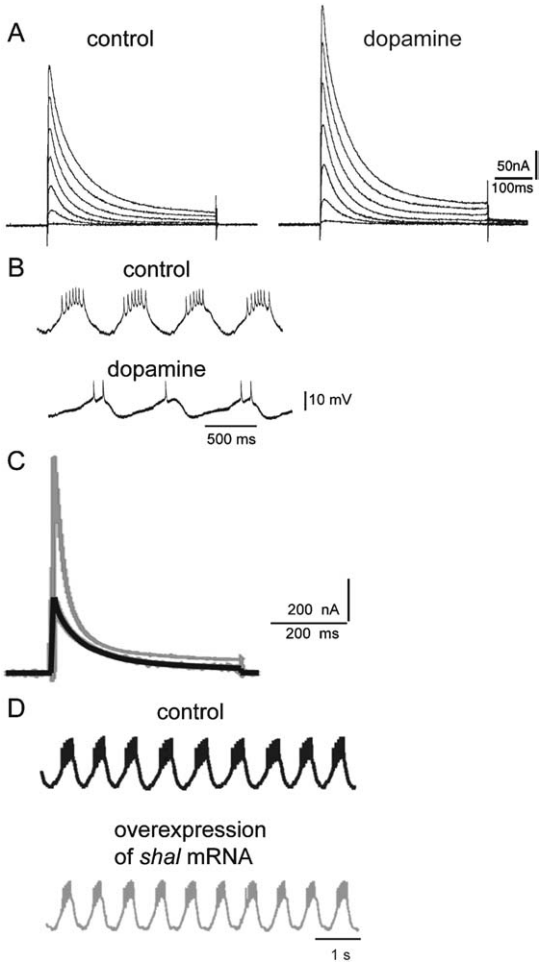

Fig. 4. Effect on PD neuron activity differs whether the K current, I_A, is increased by a modulator or by overexpression of *Shal* mRNA, with a compensatory increase in I_h. (A) Increase in I_A, as measured by a series of voltage-clamp steps, in PD neurons due to dopamine application. (B) Change in PD activity due to dopamine application. (C) I_A is considerably larger, as measured by a single voltage-clamp step, in PD neurons injected with *Shal* mRNA (gray) than in control PD neurons (black). (D) Activity is similar between control PD neurons (black) and those injected with *Shal* mRNA (gray). No vertical scale bar provided. (A) and (B) adapted with permission from Kloppenburg et al. (1999), Figs. 1A and 4A, respectively. (C) and (D) adapted with permission from MacLean et al. (2005), Figs. 1A and 4B, respectively.

or even representative of all of the possible solutions that might be present in a complex, multidimensional parameter space. As computational power has increased, we are seeing the development of multiple strategies to replace hand-tuning. These include randomly generating many potential solutions, and then selecting among them for candidate models (Goldman et al., 2001; Prinz et al., 2003), and using parameter optimization algorithms multiple times to produce multiple solutions (Achard and De Schutter, 2006; Tobin and Calabrese, 2006).

Interestingly, in several recent studies, multiple models that show similar electrophysiological phenotypes are found in connected regions of parameter space (Achard and De Schutter, 2006; Taylor et al., 2006). This latter observation is not to be taken for granted, as there easily could be disconnected islands in multidimensional parameter space that give similar behavior. Nonetheless, if neurons with similar behavior are connected in multidimensional parameter space, a neuron could maintain its overall physiological properties while adjusting ion channel number and distribution using homeostatic tuning rules. More specifically, if activity or other feedback mechanisms are used to control the insertion and deletion of ion channels, then neurons may continuously self-tune to maintain constant activity despite ongoing channel turnover (LeMasson et al., 1993; Liu et al., 1998; Golowasch et al., 1999b). In other words, individual neurons may be "wandering around" in parameter space throughout their lifetime, as long as they stay within the connected region of multidimensional parameter space consistent with a given output pattern of activity. This could then help explain the 2–4 fold range of conductances measured in identified neurons of the same cell type (Fig. 3b).

What can be learned from a population of model neurons with similar behavior that cannot be learned from studying a canonical model? Classically, sensitivity analyses are performed to determine how a model's behavior depends on one or more of its parameters (Guckenheimer et al., 1993, 1997; Nadim et al., 1995; Olsen et al., 1995). These methods are very good at finding the precise location of bifurcations or transitions between states in a model's output. Different information can be obtained by generating a large population of models, all of which mimic well the biological neurons to be studied (Taylor et al., 2006). By looking at the ranges of the values for each of the parameters in the population and at correlations among

these parameters, one can begin to discover which combinations of parameters may compensate for each other to maintain a desired output pattern.

Moreover, using a single canonical model to study neuron function is as dangerous as using measurements from a single neuron to represent the neuron population as a whole. Just as the maximal conductances vary from neuron to neuron, neuronal morphology, responses to synaptic inputs, and neuromodulators also vary across preparations. Studies of a single-model neuron run the risk of sampling only a small region of the set of biologically possible examples, and may lead to conclusions that are idiosyncratic to that particular model. In contrast, by studying a population of models, one can look for results that are general, in much the same way that experimentalists look for results that are common to all examples of a single neuron type.

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