Modeling stability in neuron and network function: the role of activity in homeostasis

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Summary
Individual neurons display characteristic firing patterns determined by the number and kind of ion channels in their membranes. We describe experimental and computational studies that suggest that neurons use activity sensors to regulate the number and kind of ion channels and receptors in their membrane to maintain a stable pattern of activity and to compensate for ongoing processes of degradation, synthesis and insertion of ion channels and receptors. We show that similar neuronal and network outputs can be produced by a number of different combinations of ion channels and synapse strengths. This suggests that individual neurons of the same class may each have found an acceptable solution to a genetically determined pattern of activity, and that networks of neurons in different animals may produce similar output patterns by somewhat variable underlying mechanisms. ***BioEssays*** **24:1145–1154, 2002.**

Introduction

The nervous system develops as a consequence of experience and genetically programmed events. The brain of the human adult must retain the capacity to respond to novel challenges by learning while, at the same time, maintaining the essential structure of the networks that allow for sensation and action. This challenge is especially daunting if we remember that neurons can live for up to one hundred years, but the ion channels and receptors that underlie electrical signaling and synaptic transmission turn over in the membrane in minutes, hours, days, or weeks. Thus while the circuits that allow recognition and naming of a tree perform impeccably for scores of years, the components of the networks that do so are constantly rebuilding themselves. It is possible that the nervous system can exploit the same cellular mechanisms to implement plasticity for learning and homeostatic stability, as plastic change must always occur on the background of ongoing control of neuronal stability and synaptic strength.

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The operation of any neuronal circuit depends on the interaction between the intrinsic properties of the individual neurons and the synaptic interactions that connect them into functional ensembles.[1] Therefore, one of the challenges of neuroscience is to explain how system dynamics depend on the properties of individual neurons, the synaptic architecture by which they are connected, and the strength and time course of the synaptic connections. Computational models are invaluable for trying to explain in detail: (a) how individual neuronal properties depend on the number, kind, and distribution of ion channels in each neuron, and (b) how network properties depend on the properties of the component neurons and their connections. Because protein molecules in the membrane are constantly turning over, it becomes critical to ask how sensitively the neuronal activity patterns and network dynamics depend on the densities of channels and strength of synapses. In this article, we will first discuss the construction of semi-realistic model neurons and networks, with particular emphasis on the issue of how tightly controlled the parameters of individual neurons must be for them to produce a given pattern of activity. We will then discuss a class of self-tuning models[2–9] in which activity is used as a feedback signal to allow neurons and networks to maintain optimal activity patterns. We will conclude with a brief discussion of recent work that suggests that synaptic strength is also homeostatically controlled.[10]

Conventional models of neurons show a variety of intrinsic membrane properties

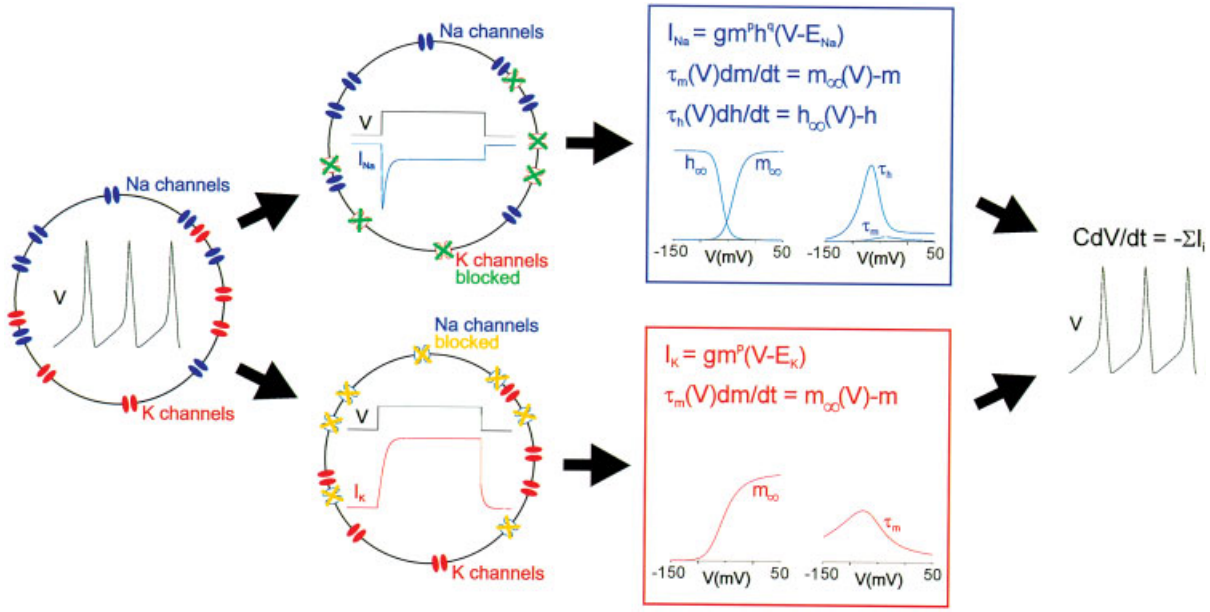
Biological neurons express a large number of different voltage- and time-dependent currents. An individual neuron may have anywhere from four or five different currents to twelve or fifteen, or more. These include the commonly known currents first described by Hodgkin and Huxley,[11] a variety of other Ca^{2+} and K^{+} currents, hyperpolarization activated currents such as I_H, and a leak current.[12] Much of the field of cellular biophysics consists of detailed voltage clamp measurements from one or another cell type in order to determine which currents are expressed in a given cell type, and their current densities and voltage dependencies.[13] Models built from these biophysical data usually have the same form: each current *I* is described by a set of differential equations that captures the voltage and time dependence of activation *m* and

inactivation *h* of the current, the reversal potential *E* of the open channels, and the maximal conductance, or the number of channels, *g* (see Box). With the hope of replicating the electrophysiological properties of the neuron in question, these are then incorporated into either a single-compartment model or a multicompartment model of the neuron in which the voltage in each of the electrically connected compartments is described by

$$C\frac{dV}{dt} = -\sum_i I_i - I_{neighbors}$$

where C is the membrane capacitance of the compartment and $I_{neighbors}$ is the net current flowing into the neighboring compartments.[14–23] In a single compartment model, the

Box 1



Most model neurons in this review are so-called Hodgkin–Huxley type models because their ion currents are described by differential equations similar to those first proposed by Hodgkin and Huxley in their seminal work on the squid giant axon[11]. This box explains how such a model neuron is constructed from experimental data and how it can be used to simulate neuronal activity.

The left part of the figure shows a cartoon of a biological neuron with only two types of ion channels in its membrane. To characterize the currents flowing through these channels, each current can be isolated by pharmacologically blocking the other current. The remaining current can then be studied by itself, typically by applying voltage steps to the neuron and recording the resulting membrane currents as shown in the figure. The voltage-dependence and dynamics of every individual membrane conductance are described by a set of differential equations whose parameters can be determined by fitting them to families of such current traces in response to voltage steps of different amplitudes.

Ion channels are membrane proteins that can be either in an open state that permits ion flow or in a closed state that prevents it. The probability that a channel is open is m^ph^q, where m and h are so-called gating variables whose value depends on the membrane potential, and p and q are integer numbers. Because every channel of a given type is open with probability m^ph^q, the current flowing through a large number of channels of this type is $I = gm^ph^q(V-E)$, where g is the conductance if all channels are open, V is the membrane potential and E is the reversal potential of the current.

The voltage-dependent dynamics of the gating variables m and h are given by the differential equations in the blue and red boxes, where $m_\infty(V)$ and $h_\infty(V)$ are steady state values for the two variables and $\tau_m(V)$ and $\tau_h(V)$ are the time constants with which the steady state is approached.

Once all the parameters in these differential equations are known from fits to experimental current traces, the set of equations completely characterizes the membrane currents in the neuron. The equation $CdV/dt = -\Sigma I_i$ describes how the membrane potential changes due to the sum of all currents in a neuron and the membrane capacitance C. This set of differential equations describes the electrical activity of the biological neuron–it constitutes the model neuron.

Simulating the activity of the model neuron involves solving the set of differential equations given in the figure to obtain the time course of the membrane potential V. Because the differential equations are non-linear, this can usually not be done analytically–instead, the equations are integrated numerically by a computer.

entire neuron is represented as an isopotential sphere, so all spatial localization of ion channels and receptors is lost. In contrast, multicompartment models couple together individual compartments that can differ in the density and kind of ion channels and receptors, thus capturing loosely the complex spatial segregation of membrane proteins seen in biological neurons. Both kinds of models are widely used in neuroscience, as some problems require the detail possible with multicompartment models, while others benefit from the relative simplicity of single compartment models.

Figure 1A shows an example of a single compartment model with five voltage-dependent membrane currents. As the values of the maximal conductances for these currents are varied (not shown), the behavior of the model changes, from silence (top panel), to firing action potentials tonically (middle panel), or to firing bursts of action potentials separated by a hyperpolarized interburst interval (bottom panel). Studies of these kinds of models have led to useful intuitions about how individual currents shape neuronal firing. For example, I_A is a K^+ current that transiently activates and rapidly inactivates.[24] Early models incorporating this current into a Hodgkin-Huxley spiking axon revealed that this current could slow the rate of spiking and control the latency to firing after a hyperpolarization.[14,15]

The approach of building a model and then varying the properties of one of its currents at a time to understand the possible role of that current in shaping the firing properties of a neuron has obvious value when the initial model contains relatively few currents, but becomes less useful when the initial model contains a number of currents. This is because in more complex models similar firing properties can be produced by widely different combinations of currents[25] and, consequently, the effect of varying the number of channels of one current can differ considerably depending on the numbers of each of the other kinds of channels in the neuron.[25] Figure 1B shows data plotted from a study in which the authors constructed a model neuron with five different voltage-dependent currents, and then varied the maximal conductances of each of them separately. The thousands of model neurons were then classified as silent, tonically firing, or bursting (Fig. 1A). The plot in Fig. 1B shows that there were model neurons of each activity pattern with both high and low values of each of the five conductances, illustrating that no single conductance uniquely determines the activity state of the neuron.[25] Figure 1C

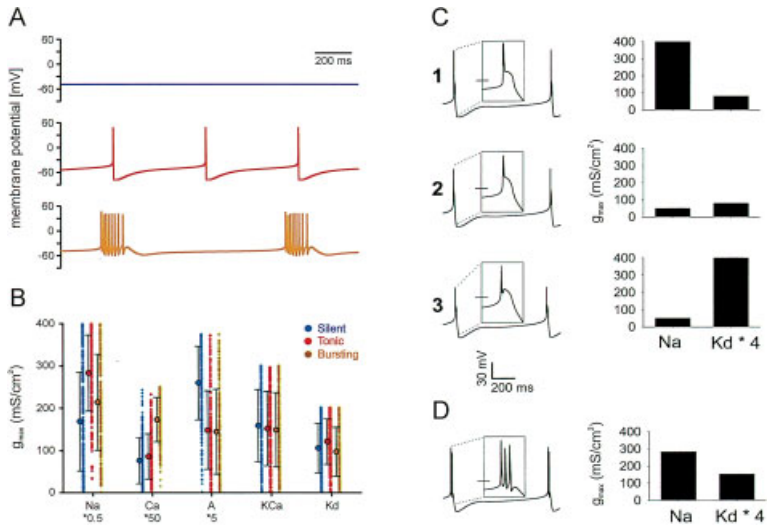


Figure 1. Dependence of model neuron activity on the underlying membrane conductances. **A:** Three examples of model neuron activity patterns. Different combinations of maximal conductances of five voltage-dependent currents produced a silent model neuron (top panel), a tonically spiking (middle panel), and a bursting model neuron (bottom panel). **B:** Activity states observed when all five conductances were varied independently. For each conductance, the values that led to silent, spiking or bursting behavior are reported as blue, red or yellow dots and the mean values and standard deviations are indicated as circles and error bars. For almost any value of any of the five conductances, all three activity states were observed, thus no single conductance predicts the activity pattern. Modified from Goldman MS, Golowasch J, Marder E, Abbott LF. J Neurosci 2001;21:5229–5238 with permission of the Society of Neuroscience. **C:** Voltage traces (left) and sodium and delayed rectifier conductances (right) for three 1-spike-bursters show that similar activity can result from very different conductance combinations. **D:** Sodium and delayed rectifier conductances obtained by averaging the conductances of 160 one-spike bursters with similar activity patterns (right). The voltage trace produced by the average conductances (left) has three spikes per burst, showing that pooling conductance measurements from biological neurons does not necessarily result in a model neuron that reproduces their behavior. Modified from Golowasch J, Goldman MS, Abbott LF, Marder E. J Neurophysiol 2002;87:1129–1131, with permission of the American Physiological Society.

shows three examples of so-called one-spike bursters, that is, neurons that are generating single spikes followed by a sustained plateau phase. Although the voltage trajectories of these three model neurons are quite similar, they vary dramatically in their conductance densities: neuron 1 has a high Na^+ conductance and a low delayed rectifier K^+ conductance, neuron 2 has low values of both conductances, and neuron 3 has a low Na^+ conductance and a high delayed rectifier K^+ conductance.[26] Thus together, the data in Fig. 1B,C indicate that different combinations of conductances can produce similar activity patterns, and that no single current individually determines the firing properties of a neuron. Consequently, variation of the conductance density of a given current may produce qualitatively different effects on neuronal firing properties, depending on the densities of all the other currents in the cell.[25]

Because the brain is composed of numerous neuron types, with disparate electrophysiological firing properties, there is great interest in characterizing each of these in terms of the currents that give rise to those properties. The diversity of channel subtypes with their consequently different biophysical properties requires the collection of detailed biophysical data from each cell type of interest.[12] Therefore, the enterprise of building a biophysically realistic model of a given cell type is fraught with several difficulties. (1) The usual methods of fitting biophysical data may not always accurately capture the full voltage and time dependence of the currents.[13] (2) It is almost impossible to separate adequately all of the currents expressed in a given cell type to accurately and completely characterize all of the cell's currents. Consequently, almost all biophysically realistic model neurons include some data directly measured from the actual neurons to be modeled, and other data from other cell types from the same animal, or even from other species. Although the reason that forces this is clear, nonetheless, it is possible that the properties of the currents not measured directly from the neuron to be modeled may significantly compromise the conclusions that can be drawn from studying the model. (3) It is impossible to measure all of the currents in an individual neuron, and therefore pooled data from multiple neurons are used to constrain models.

An underlying assumption of using mean values from pooled data is that all of the individual neurons of a given type have essentially the same set of conductances, and that any measured variance in conductance densities is produced by measurement error, rather than true differences in conductance densities. Recent work calls this assumption into question. The crab stomatogastric ganglion (STG) contains one lateral pyloric (LP) and one inferior cardiac (IC) neuron. These neurons are identifiable in every preparation, and therefore one can ask how much variance in measured conductance densities is found in these neurons from animal to animal. Measurements of three different K^+ currents in multiple LP and IC neurons showed variations in maximal conductance densities of 2- to 4-fold, although there was no systematic relationship among these measured current densities.[4,25] Moreover, the measured K^+ current densities in IC neurons changed as a function of activity over several hours.[27] This demonstrates that a cell's recent history of activity may alter the conductances that are measured in a typical voltage clamp experiment. Consequently, it is likely that the values that are measured from slice and culture experiments in which the natural patterns of activity of a network are altered prior to measurement will differ from those that contribute to network dynamics during behavior.

Building models from measured means of a population of neurons with variable underlying conductances can lead to a model that fails to replicate the behavior of the neurons used to construct the model.[26] As previously described, Fig. 1C shows voltage traces from three individual neurons with similar waveforms but with quite different Na^+ and delayed rectifier K^+ conductances. When a model was built using the mean Na^+ and delayed rectifier K^+ conductances of 160 neurons with similar waveforms, the model neuron was not a single spike burster, but rather fired three spikes per burst.[26] In this case, averaging fails because the phenotype depends not on one single conductance, but on the correlated levels of several and illustrates that, although building models from average data is often reliable, it is not necessarily so. Unfortunately for experimentalists, it is usually impossible to predict when averaging will fail, and also usually impossible to predict which combinations of currents will together predict the behavior of a neuron.

Dynamically regulating model neurons can "self-tune" their intrinsic properties

The underlying assumption of building models in which the maximal conductance of each current is a fixed parameter is that each neuron has a fixed number of each of its ion channels, and that a neuron's activity is a consequence of the number and distribution of its ion channels. This assumption presumes that the number of each kind of membrane channel is tightly controlled by transcriptional and translational processes. An alternative paradigm is to assume that, early in development, as part of setting a neuron's identity, its target activity levels are specified. These target activity levels are then used to regulate the number of each kind of channel found in the membrane. Thus, according to this way of thinking, it is the final activity of a neuron that is tightly controlled, rather than the number of each kind of ion channel individually.

A number of models have been built using these ideas. These model neurons can self-tune to find a combination of conductance densities consistent with a target activity pattern. These models were initially designed to account for stability in the face of ongoing channel turnover, but also have some additional interesting attributes. The underlying premise in this class of models is that, when the activity level drifts away from an equilibrium state, intracellular sensors detect these

changed activity levels, and trigger changes in the number and/or distribution of ion channels.[3–5] In the early generation of these models,[2,3] the activity sensor was a simple measure of the bulk intracellular Ca^{2+} as a great deal of experimental data indicates that intracellular Ca^{2+} concentrations fluctuate as a function of activity.[28,29] In these models, the stipulation was that excess activity, as detected by the sensor, would trigger a slow decrease in the inward currents and a slow increase in the outward currents, according to a simple negative feedback rule of the form

$$\tau \frac{dg}{dt} = \sigma([Ca^{2+}]) - g$$

where the sensor $\sigma([Ca^{2+}])$ is a sigmoidal function of the Ca^{2+} concentration with a different midpoint and slope for each conductance and the regulation time constant τ can also be different for different conductances (Fig. 2). In later models, multiple sensors were used: a fast, slow and DC filter of the Ca^{2+} current.[4] In this class of models, each membrane current was individually controlled to a greater or lesser degree by these three sensors. In all of these models, the change in conductance density must occur slowly relative to the firing properties of the neuron. In other words, the change in channel density should be occuring on a time scale of minutes or hours rather than the milliseconds or seconds involved in neuronal signalling.

Fig. 3 shows an example of a self-tuning model as it adjusts its conductances to produce its equilibrium activity level. This model has two Ca^{2+} currents, a Na^{+} current, three different K^{+} currents, and three activity sensors. The maximal conductance of each of the currents is plotted over time, and the voltage traces that the model produces at points during the tuning process are indicated. At the beginning of this simulation, the neuron was firing single large action potentials, and it had a large Na^{+} conductance. As the neuron moved to its final equilibrium state, it downregulated its Na^{+} conductance and also altered all of its other conductances (Fig. 3B). Note that quite similar activity patterns are produced at several points (3, 5, 6, 7, 8) during this adjustment process, and that there is a fairly significant change in conductance density that produces relatively little change in firing properties as the neuron converges towards its equilibrium point (Fig. 3A). The implications of this are profound: biological neurons that are constantly "self-tuning" may have quite similar activity patterns but significantly different conductance densities at different times. Moreover, different individual neurons with similar activities, again may be expressing significantly different conductance densities.

Biological neurons change their properties in response to altered activity levels

There is a growing biological literature consistent with the notion that biological neurons may be constantly tuning their conductance densities in response to their own activity levels. Firstly, numerous ion channels have been "knocked-out" or deleted with relatively little obvious phenotype. In many cases, the phenotype of the knock-outs is less than would have been expected from pharmacological blockades of the

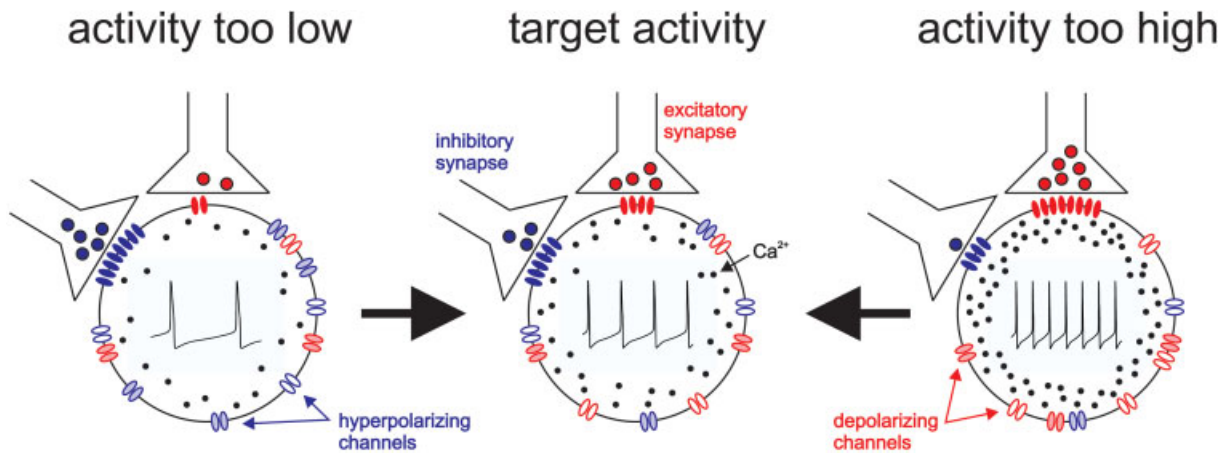


Figure 2. Cartoon illustrating basic mechanisms of activity-dependent homeostatic regulation in model neurons and circuits. The intracellular calcium concentration in biological and model neurons is a good measure for the cell's electrical activity. If the activity level is too low (left), the calcium concentration falls below its target value. Upregulation of depolarizing membrane currents and downregulation of hyperpolarizing membrane currents in response to the lowered calcium concentration can return the neuron's activity to its target level. Similarly, increasing excitatory and decreasing inhibitory synaptic inputs can act as a negative feedback to stabilize the level of activity. If the firing rate and thus the calcium concentration is too high (right), regulating membrane and synaptic currents in the opposite direction will also re-establish the target activity level.

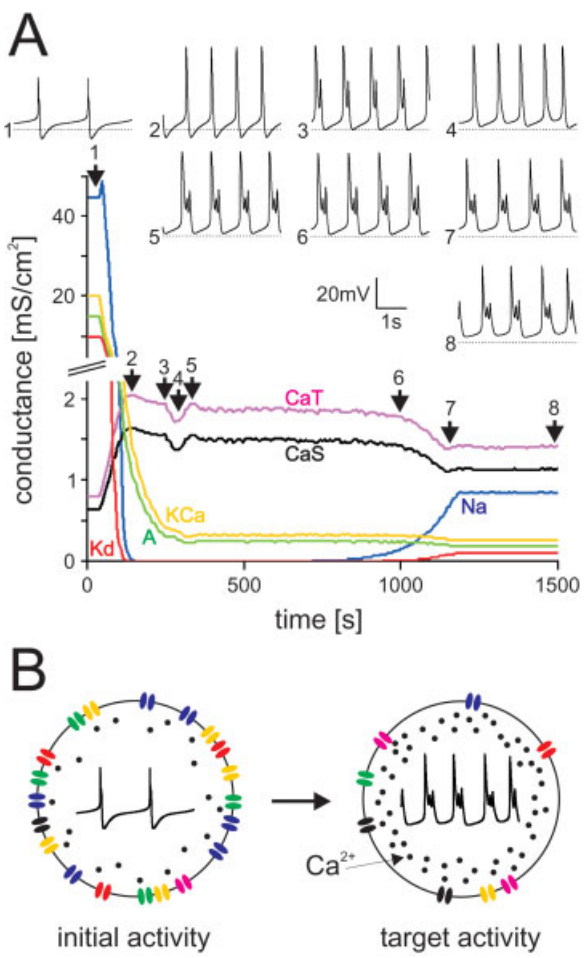


Figure 3. Activity-dependent conductance regulation in a model neuron with three calcium sensors. **A:** Maximal conductances (colored traces) and voltage traces at different times (insets) as a regulating model neuron approaches its target activity. Note that similar firing patterns (3, 5–8) result from different combinations of conductances during the regulation process. **B:** Cartoon illustrating the downregulation of the sodium (blue), calcium-dependent and transient potassium (yellow and green), and delayed rectifier (red) conductances and upregulation of the transient and slow calcium conductances (purple and black) between the initial state of the model and its target activity and the accompanying increase in intracellular calcium to the target level.

same ion channel. This is consistent with the interpretation that the absence of a gene for an ion channel can often be compensated for, as neurons self-tune to similar activity patterns with a different mix of ion channels. Secondly, during development there is a sequential acquisition of the expression of different channel types.[30] It is now clear that this normal sequential progression of ion channel expression depends on activity early in development[31,32] and can be altered by precocious expression of channels.[33] This spontaneous activity and early excitability is associated with changes in intracellular Ca^{2+} that appear to play a critical role in the development of excitability.[34,35] Moreover, the increase in activity and associated intracellular Ca^{2+} seems to be required for the appropriate development of the outward K^+ currents.[34] This is consistent with intracellular Ca^{2+} concentrations being an internal sensor of a neuron's activity.

The most direct evidence in favor of the idea that neurons monitor their own activity and then regulate their conductance densities to maintain a homeostatic level of activity comes from experiments with cultured neurons. In the experiments shown in Fig. 4, cultured cortical neurons were incubated for several days with tetrodotoxin (TTX) to silence them. Subsequently, when the TTX is washed out, the neurons are more excitable than before the TTX treatment (Fig. 4A). This increased excitability is caused by an increased Na^+ current density and a decrease in K^+ current densities (Fig. 4B,C).[36,37]

A cell-autonomous tuning rule can produce network stability

To what extent can neuron-autonomous rules govern the stability of network dynamics? Data suggest that cell-autonomous activity sensors might be sufficient to stabilize network function. If the STG is removed from descending modulatory inputs, it slows down or becomes silent, as the effects of the modulatory substances that maintain the bursting properties of the neurons wear off. These preparations remain silent or relatively inactive for a period from 1 to 5 days, after which they resume cycling.[5,38–40] The recovery of function is accompanied by altered patterns of channel expression,[41] consistent with enhanced cellular excitability triggered by the loss of the modulatory drive that was previously maintaining pyloric rhythm activity. At this point, it is not clear whether the primary signal for the changed excitability is the loss of the neuromodulators themselves, or of the activity that they evoke. Nonetheless, a modeling study using neurons that were able to self-tune their conductance densities, demonstrated that a network can self-organize with only the tuning signals in the individual neurons of the network.[5]

Tuning the voltage dependence of currents

In most of the self-tuning models described above the voltage dependence of the currents was not tuned and only the maximal conductance, or number of channels, was regulated. However, neuromodulators can dramatically alter the voltage dependence of currents, and phosphorylation of channels or changes in subunit composition can also affect the shape of the activation and inactivation curves used to describe voltage-dependent currents.[12] Small shifts in the voltage dependence of currents that activate close to the threshold for action potential or burst production can markedly influence the properties of neurons.[42] Therefore, it is also important for

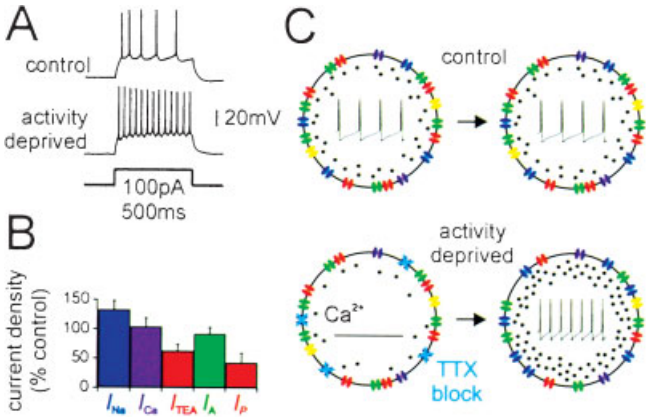


Figure 4. Homeostatic membrane conductance regulation in activity-deprived biological neurons. **A:** Spike trains in response to somatic current injection in cortical pyramidal neurons after 7–9 days in control and in activity-deprived cultures in which firing was prevented with TTX. The activity-deprived neurons have upregulated their excitability. **B:** Average current densities of activity-deprived neurons in % of control values. The neurons responded to activity-deprivation by increasing their sodium currents and decreasing their outward currents I_{TEA}, I_A, and I_P while the calcium currents remained unchanged. Modified from Desai NS, Rutherford LC, Turrigiano GG. Nature Neurosci 1999;2:515–520 with permission of Nature Publishing Group. **C:** Cartoon of the assumed conductance changes in control (top) and activity-deprived neurons (bottom). While the conductances and activity pattern of the control neurons remain the same, the lower calcium concentration in the activity-deprived neurons causes them to upregulate currents that increase their excitability. When the TTX-block is removed, they respond to the same injection current with a higher firing rate than the control neurons.

neurons to appropriately regulate the voltage dependence of their currents. Recent modeling studies[7,8] use an optimization procedure that results from tuning of all the properties of a current, both the maximal conductance and its voltage dependence.

Homeostatic regulation of synaptic inputs

A great deal of both experimental and theoretical work addresses the mechanisms of modifications of synaptic strength in learning and development, and the consequences of these changes for network structure. It has only been recently that attention has been paid to the mechanisms by which neurons regulate the strength of all of their synaptic inputs, so that they control their total synaptic drive. This has been termed "synaptic scaling" and has been elegantly studied in cultured cortical neurons.[43–48] In these experiments, the authors have carried out long-term manipulations of activity by placing the cultures in TTX or other pharmacological treatments, and have demonstrated that the excitatory synaptic inputs increase and inhibitory inputs decrease when the neuron is deprived of activity (Fig. 5).

The *Drosophila* neuromuscular junction has been extensively used as a preparation with which to study homeostatic regulation of the synaptic drive to a muscle fiber.[10,49] In these experiments, the postsynaptic muscle fibers were hyperpolarized by overexpressing K^+ channels. In response to this perturbation the presynaptic neuron increased its release of neurotransmitter so that the postsynaptic action of the neurotransmitter remained the same.[49] A similar result was found with cultured *Xenopus* neuromuscular junctions,[50] where the excitability of the presynaptic neuron was enhanced by treatments that blocked the postsynaptic actions of the motor neuron.

Using activity to tune inhibitory synapses

Although there are many studies on the implications of activity-dependent regulation of the efficacy of excitatory synapses, much less work has been done to ask what rules might result in the long-term control of inhibitory synapses. As many motor networks function almost exclusively with inhibitory neurons, it is equally important to develop possible learning rules for tuning of inhibition. As a starting point, a three-cell network of the crustacean pyloric rhythm was constructed. In this model, the strengths of the synapses into a particular cell were tuned using two rules, one a global measure of the neuron's total excitability similar in concept to synaptic scaling, and the second a synapse specific rule that asked how effective each presynaptic neuron was in influencing the postsynaptic cell's activity. These rules, which are highly consistent with the biological data previously described,[51] allows the network to self-assemble into a functional rhythmic circuit from randomly assigned initial synaptic strengths (Fig. 6). Interestingly, in these simulations, during the tuning process the networks found many parameter regions (3,4,5) over which almost indistinguishable network dynamics were seen. This makes the point that similar network dynamics can result from

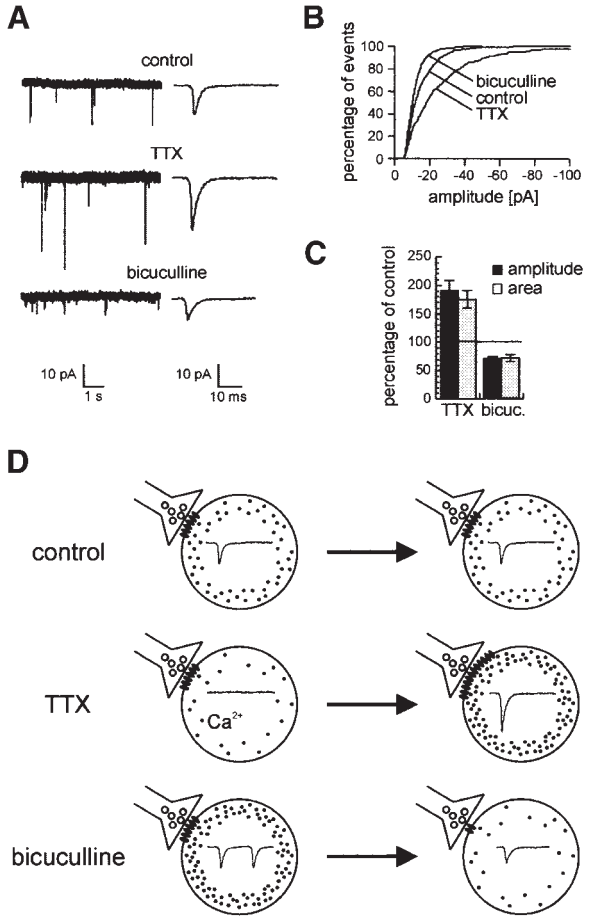


Figure 5. Activity-dependent regulation of synaptic strength in biological neurons. **A:** Miniature excitatory post-synaptic currents (mEPSCs) recorded from neocortical neurons after 48 hours in control cultures (top) or in cultures in which TTX abolished firing (middle) or bicuculline blocked inhibitory synaptic inputs (bottom). The average mEPSC waveforms on the right were obtained from raw data as shown on the left. **B:** Cumulative amplitude histograms for mEPSCs recorded under each condition. Activity-deprivation shifts the distribution to larger, reduced inhibition to smaller amplitudes. **C:** Average mEPSC amplitudes and areas of neurons cultured in TTX or bicuculline in % of control values. **D:** A possible mechanism underlying the changes illustrated in A–C. The lower calcium concentration caused by activity-deprivation (middle) leads to an increase in synaptic strength by upregulating synaptic receptor density. When the TTX is removed, the recorded mEPSC is larger than in neurons grown under control conditions (top). Conversely, the elevated calcium concentration caused by the higher firing rate in bicuculline leads to a down-regulation of synaptic receptor density (bottom). After 48 hours in culture, the mEPSC is smaller than in control. Modified from Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB. Nature 1998;391:892–896 with permission of Nature Publishing Group.

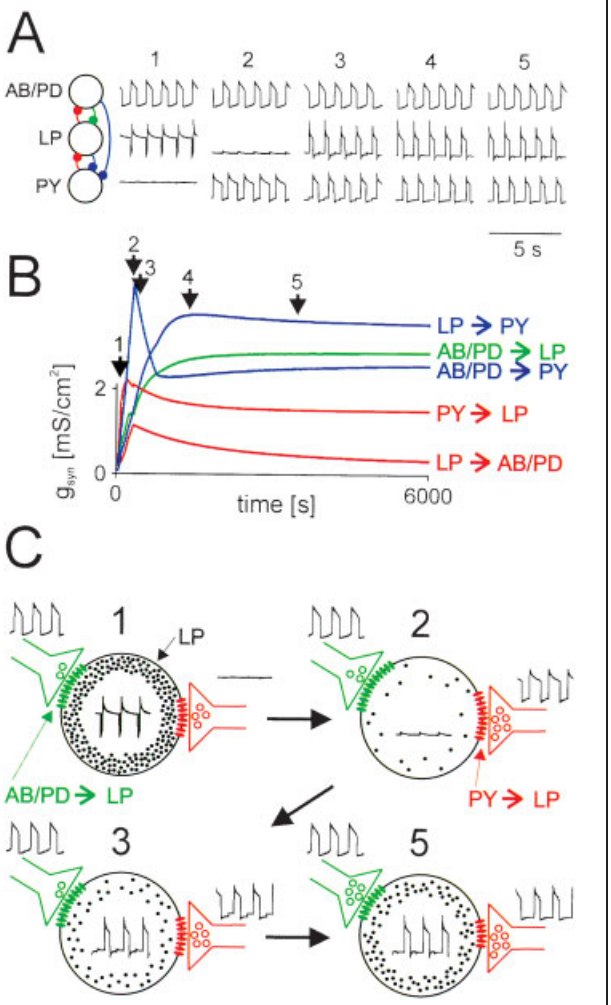


Figure 6. Self-assembly of a model neural network by activity-dependent synapse modification. **A:** Voltage traces of the AB/PD (top), LP (middle) and PY neurons (bottom) in a model pyloric network (left) at different times during activity-dependent tuning of the five inhibitory synapses that leads to the establishment of a tri-phasic pyloric rhythm. **B:** Synaptic conductances of all five synapses during the self-tuning. Note that similar tri-phasic rhythms are produced at times 3, 4 and 5 in spite of different underlying synapse conductances. Modified from Soto-Trevino C, Thoroughman KA, Marder E, Abbott LF. Nat Neurosci 2001;4:297–303 with permission of Nature Publishing Group. **C:** Cartoon snapshots of the LP neuron's activity and calcium concentration and the synapses it receives from the AB/PD neuron and the PY neuron at different times during the tuning process. Because the model illustrated here uses both a global synapse modification rule that changes all synapses onto a given cell jointly and a synapse-specific rule that depends on the presynaptic and postsynaptic activity level, the two synapses can vary independently, allowing the network to explore many combinations of synapse strengths.

a range of synaptic strengths, and that each synapse may not need to be "perfectly" tuned for acceptable physiological outputs.

Conclusions

The adult nervous system must continuously compensate for ongoing processes of synthesis and turnover of the ion channels that govern neuronal excitability and the receptors that bind neurotransmitter. New biological data are consistent with the interpretation that neurons use internal activity sensors to tune the complement of membrane proteins that govern signalling and excitability. Because neuronal and network activity depend on a large number of interacting nonlinear processes, there are multiple sets of membrane conductances and synaptic strengths that can produce neurons with similar firing properties and networks with similar dynamics. This argues that individual neurons of the same class may each have found an acceptable solution to a genetically determined pattern of activity, but there may be considerable variance in the underlying mechanisms governing those activity states.

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