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a0005

Homeostasis at Multiple Spatial and Temporal Scales

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s0005

Introduction

p0005 For neural circuits to function normally, many properties of the nervous system require precise regulation. Temperature, pH, and ionic gradients, for instance, need to be maintained at relative constant levels, despite fluctuations in the cellular environment. Complex homeostatic mechanisms are at work to keep them at their desired values. In general, a property is said to be under homeostatic control if a desired output is restored after a perturbation. Typically, homeostatic control is characterized by a desired output level (the set point), sensors that report a mismatch between the actual output and the set point, and mechanisms that restore the output to the set point level.

p0010 Like temperature and pH, neural activity appears to be under homeostatic control to prevent activity in neural circuits from becoming too high or too low. Throughout life, neural circuits are constantly perturbed by changes in synaptic strength, connectivity, morphology, sensory input, and protein turnover. When left unchecked, these disturbances may alter neural activity levels beyond the range in which neural circuits can operate properly. For example, for controlled activity propagation in feedforward networks as well as stable ongoing activity in recurrent networks, synaptic strengths should be just so that each action potential triggers on average one action potential in another neuron; otherwise, activity will explode or die out. Without normalizing mechanisms, changes in synaptic strengths – brought about by Hebbian synaptic plasticity, for example – will thus destabilize network activity.

s0010

Changes in Neural Circuits during Development and Adulthood

p0015 During development, the number and strength of synapses alter dramatically. Once initial synaptic connections are established during the early stages of development, refinement of connections takes place by elimination of axons that project to the wrong targets and further elaboration of axons that project to the correct targets. This process of fine-tuning connectivity thus involves both synapse elimination and continued synapse formation. In many cases, the net effect is that the total number of synapses onto a postsynaptic cell increases during the period in which elimination occurs. For example, during the elimination of polyneuronal innervation in the neuromuscular junction, the total synaptic area on the muscle endplate becomes larger. Similarly, during the refinement of connections onto the lateral geniculate nucleus and cortex that creates ocular dominance columns, the number of synapses onto postsynaptic cells increases considerably. Despite these changes in synapse numbers during development, neural circuits have to remain functional.

p0020 In adulthood, synaptic strengths are also not constant but increase or decrease as a result of activity-dependent synaptic plasticity. In neural network models, correlation-based synaptic plasticity rules have been shown to lead to a hyperexcitable network without a stabilizing mechanism such as, for example, conservation of the average level of neural activity.

p0025 Likewise, the number of neurons is not constant but changes as new cells are generated (neurogenesis) and existing cells die (apoptosis). Neurogenesis occurs not only during development but, in brain areas such as the dental gyrus of the hippocampus, also in adulthood. Homeostatic mechanisms will therefore be necessary to regulate the changes in neural activity resulting from the insertion or deletion of neurons.

p0030 During development, neurons can experience a great amount of structural growth, which will affect their electrophysiological properties. The neural circuits in which they operate nevertheless have to remain functional. This requires that activity-dependent regulatory processes, targeting, for example, synaptic or intrinsic properties, must tune circuits to maintain their appropriate patterns of network activity during periods of neuronal growth.

p0035 Other changes during development that can affect electrical activity include switches in the subunit composition of neurotransmitter receptors. For example, the γ-aminobutyric acid $(GABA)_A$ receptor, the main inhibitory receptor in the mammalian brain, shows a subunit switch in the neonatal visual cortex around the time of eye opening. As a result of this switch, the duration of the inhibitory postsynaptic current decreases, effectively reducing the level of inhibition.

s0015

Experimental Evidence for Homeostasis of Neural Activity

p0040 Several experimental observations support the idea of homeostatic regulation of neural activity. First, in neuronal cultures, firing rates are restored after manipulation of the global level of activity or the

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activity level in single cells. In cultured cortical networks composed of excitatory and inhibitory neurons, application of bicuculline (which reduces inhibition) initially raises the activity. After 2 days in bicuculline, however, activity returns to control levels. Conversely, blockade for 2 days of spiking activity with tetrodotoxin generates a hyperactive network when tetrodotoxin is removed. In this network, the firing rates of both excitatory and inhibitory neurons are increased. Suppressing activity in a single hippocampal neuron by overexpressing an inward rectifier K^+ channel initially reduces firing rates. After a few days, however, the activity of the neuron is restored to control levels. Second, at the neuromuscular junction, changes in presynaptic efficacy induce compensatory changes in postsynaptic efficacy and vice-versa, effectively keeping neuromuscular transmission at a relatively constant level. For example, reducing the number of synapses causes a compensatory increase in the postsynaptic response to a single vesicle of neurotransmitter. Conversely, hyperpolarization of muscle fibers induces an increase in presynaptic release. Third, the removal of neuromodulatory synaptic inputs to stomatogastric ganglion (STG) neurons initially slows or abolishes the typical STG pyloric rhythm of alternating bursts of activity. However, after a period of days, normal rhythmic burst firing resumes. The presence of a wide variety of activity-dependent mechanisms that counteract changes in activity forms further evidence for the homeostatic control of neural activity.

The Set Point

In the context of homeostatic control of neural activity, the set point represents the desired level of neural activity to which neurons or neural networks strive to return after experiencing a perturbation. There are, however, many open questions regarding the nature of such a set point:

1. What is the spatial scale of the set point? Do neurons or perhaps subneuronal structures (such as neurites) have their own individual set points, or is the set point specified at the level of neuronal populations? Under some conditions, homeostasis of neural activity can be a cell-autonomous process. Hyperpolarizing single hippocampal pyramidal cells in neuronal cultures by overexpressing an inward rectifier K^+ channel initially decreases firing rates, but after a few days, firing rates are restored to normal levels. The scaling of excitatory synapses on inhibitory neurons is dependent on the activity-dependent release of brain-derived neurotrophic factor from nearby pyramidal neurons, which perhaps suggests that homeostasis of neural activity in interneurons is not cell-autonomous. An important question is whether cell-autonomous homeostatic processes are capable of achieving homeostasis of activity at the network level. Some studies suggest that this may indeed be the case, but there are also examples showing that synaptic and cellular homeostatic rules do not achieve homeostasis of neural activity at the network level, at least under some conditions (see below).

2. Does the set point involve activity as it occurs over the entire day or only during certain periods of the day? The temporal range of the set point may span long periods of ongoing activity or perhaps only periods during which a neuron or a neural circuit actively processes particular synaptic inputs. Another possibility is that the set point involves only neural activity during sleep. In neuronal cultures, homeostasis appears to involve ongoing activity. At the neuromuscular junction, peak depolarization is precisely restored after postsynaptic activity manipulations, suggesting that the set point involves an adequate response to synaptic input.

3. What aspects of neural activity are under homeostatic control? At the level of individual neurons, the possibilities that have been suggested include a temporal average of firing rate, membrane potential, intracellular Ca^{2+} concentration, amount of excitatory synaptic receptor activation, or a particular pattern of spiking activity. At the level of neuronal populations, a spatial average of firing rate or a particular spatial pattern of activity could be under homeostatic control. In STG neurons the set point may involve a precise pattern of burst firing. In neuronal cultures the set point may involve the average firing rate of neurons. Furthermore, perhaps there is not a single set point but a range of activities that is allowed.

4. How is the set point encoded? The set point may be encoded as an explicit cellular property, or alternatively it could come about as an emergent property of a large number of interacting processes. Although it may not be explicitly encoded as such, the attractor state of a complex system may function as a set point. For example, spike timing-dependent plasticity (STDP) contributes to stabilizing neural activity levels, but it does not contain an explicit set point. In this form of long-term synaptic plasticity, presynaptic action potentials that precede postsynaptic spikes strengthen a synapse, whereas presynaptic action potentials that follow postsynaptic spikes weaken it. STDP has the effect of keeping the total synaptic input to the neuron roughly constant, independent of the presynaptic firing rates. In the Bienenstock, Cooper, and Munro model, the set point of postsynaptic activity is not explicitly specified but arises as a

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result of the local synaptic learning rule. If the threshold value of postsynaptic activity above which long-term potentiation of synapses occurs increases faster than linearly with the average postsynaptic activity, the synaptic strengths will adjust to keep the postsynaptic activity near a particular value.

5. How are differences between the actual activity and the set point activity level sensed? Many experimental studies indicate that intracellular Ca^{2+} concentration is a good indicator of neural activity, and cells appear to be capable of sensing the difference between actual and desired Ca^{2+} levels. The intracellular Ca^{2+} concentration increases in response to activity (e.g., through enhanced influx through *N*-methyl-D-aspartate channels and voltage-sensitive Ca^{2+} channels) and decreases during inactive periods. Intracellular Ca^{2+} is an important messenger signal for a wide variety of cellular processes and can modulate, for example, levels of gene expression. Different firing patterns, such as bursting or regular spiking, result in different temporal profiles of Ca^{2+}. These profiles can be captured by integrating Ca^{2+} on different timescales.

s0025

Mechanisms Contributing to the Homeostasis of Neural Activity

p0050 A variety of mechanisms operating at different spatial and temporal scales have been suggested to contribute to the homeostasis of neural activity.

s0030

Synaptic Scaling

p0055 In cortical cultures, changing the level of network activity causes dynamic adjustments in the relative strengths of excitatory and inhibitory connections. Raising activity results in reduced feedback excitation and increased feedback inhibition onto pyramidal neurons. Lowering activity produces the opposite set of changes. A few days of pharmacological activity blockade in cortical cell cultures increases the amplitude of miniature excitatory postsynaptic currents (mEPSCs) and evoked EPSCs in pyramidal cells. Conversely, prolonged enhanced activity reduces the amplitude of mEPSCs. Similar bidirectional activity-dependent changes in mEPSC size have been observed in spinal cell cultures. It is interesting that activity blockade scales down the amplitude of miniature inhibitory postsynaptic currents (mIPSCs), in the opposite direction of excitatory currents. The expression site of homeostatic excitatory synaptic plasticity in cortical cultures is a controversial issue. Synaptic scaling of mEPSCs occurs in part postsynaptically by changes in the number of glutamate receptors, but also presynaptically by changes in release probability. The pre- or postsynaptic expression site has recently been shown to depend on the time neurons have spent *in vitro*. Synaptic scaling of mIPSCs is accompanied by a change in the number of $GABA_A$ receptors clustered at synaptic sites. Chronic suppression of activity in a single hippocampal neuron increases excitatory synaptic strengths on the neuron, but not sufficiently to alter inhibitory synaptic strengths.

p0060 It remains to be explored whether homeostatic synaptic plasticity operates *in vivo* and in cell cultures similarly. Recent evidence suggests that excitatory synapses in intact rodent visual cortex are upregulated after sensory deprivation. Two days of monocular deprivation scales up mEPSC amplitudes by 15–30% in a layer- and age-dependent manner. However, these changes are smaller than those seen in culture. One possible explanation is that sensory deprivation only partially reduces activity compared with the complete activity block in cultures.

p0065 An important issue is the conditions under which homeostatic synaptic plasticity can cause the network to settle into a desired activity level. It seems rather obvious that an individual neuron in isolation may be able to keep its activity close to a set point value by increasing synaptic excitation and decreasing synaptic inhibition. Neurons in the brain, however, are not isolated but embedded in circuits with recurrent synaptic connectivity. Such neural networks are known to be very sensitive to the balance of synaptic excitation and inhibition. An altered balance of excitation and inhibition may affect synchrony in the network and in extreme conditions result in hyperactivity or other nonphysiological oscillatory states. Thus, scaling excitatory and inhibitory synaptic strengths in opposite directions may have undesirable effects for the stability of network activity. This is an important issue that can be explored in neural network models.

Intrinsic Excitability

s0035

p0070 Intrinsic excitability is also regulated by activity. Chronic activity blockade in cortical cell cultures enhances Na^+ currents and reduces K^+ currents in pyramidal cells, resulting in an enhanced responsiveness to current injections. Fast Na^+ conductances in pyramidal cells are upregulated by approximately 30% and K^+ conductances (of the delayed rectifier and a persistent outward current) are downregulated by about 30–60% after 2 days of activity blockade. Inhibitory neurons also display an increased excitability after chronic activity blockade, but through a different mechanism. In somatostatin-positive inhibitory

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neurons, the densities of a passive leak current and the hyperpolarization-activated (H^-) current are down-regulated, which increases excitability mostly through a decrease in membrane input conductance. Intrinsic excitability may also be modified in an adaptive manner at the very short timescale of minutes. In hippocampal CA1 pyramidal neurons, an increase in H-current can be observed within tens of minutes of enhanced activity, which reduces firing rates in response to current injections. Reducing background activity results in an increased excitability within tens of minutes through a decrease in a sustained K^+ conductance.

p0075 In model neurons (and networks) with activity-dependent regulation of maximal conductances of ionic currents, conductances may adjust to restore a given pattern of electrical activity following a perturbation. For example, in a multicompartmental model neuron, regulation of some of the maximal conductances (of the fast Na^+ current, the delayed rectifier K^+ current, and the transient K^+ current) by the local intracellular Ca^{2+} concentration acts as a gain control mechanism to restore the neuron to its optimal firing range after potentiating a set of synapses. Another example concerns a model of a bursting STG neuron, in which the maximal conductances of seven voltage-dependent membrane currents are regulated by Ca^{2+} sensors acting on different timescales. When the electrical activity of this model neuron is perturbed, such as by changing the reversal potential for the K^+ currents or by applying hyperpolarizing current, the maximal conductances adjust to restore the original bursting pattern. Under some conditions, activity-dependent regulation of intrinsic excitability, operating at the level of individual neurons, may stabilize network activity in models of synaptically connected neurons. In a model of the neocortex, neurons fire initially asynchronously and at low firing rates. Removing the external synaptic inputs strongly reduces the firing rates of all neurons. Activity-dependent regulation of some of the maximal conductances in pyramidal cells (of the fast and persistent Na^+ currents and two types of K^+ current) restores an irregular state with low firing rates comparable to that in the intact model. Another example concerns a three-neuron network model of the pyloric circuit of the STG. The small network model recovers rhythmicity after blockade of neuromodulatory synaptic inputs using activity-dependent regulation of some of the maximal conductances (of a K^+ current and a Ca^{2+} current).

s0040 Structural Plasticity

p0080 Neurite elongation and branching are under the control of the growth cone (a specialized structure at the tip of a growing neurite) and are sensitive to the Ca^{2+} concentration inside the growth cone. Electrical activity in general increases the Ca^{2+} influx through voltage-gated Ca^{2+} channels. In neuronal cultures, raising the level of neural activity has been found to cause retraction of neurites, whereas lower levels allow further outgrowth. Model studies have shown that this activity-dependent neurite outgrowth will contribute to the homeostasis of neural activity, both in purely excitatory and in mixed networks of excitatory and inhibitory cells. In purely excitatory networks, for example, when the level of activity is too high, the neuron will withdraw neurites and, consequently, lose connections with other neurons, resulting in a decrease in neural activity. Conversely, when the activity is too low, neurites will grow out and new connections will be formed, resulting in an increase in neural activity. Experimental work on the Xenopus retinotectal system suggests that neuronal activity, via activation of Ca^{2+}/calmodulin-dependent protein kinase, slows the outgrowth of axonal and dendritic arbors and controls synapse formation. In the developing spinal cord, the intracellular Ca^{2+} in growth cones has been found to regulate axon elongation, with the rate of axon elongation being inversely proportional to the frequency of Ca^{2+} transients. Many experimental studies have demonstrated considerable structural plasticity in the adult brain, including synapse formation and elimination and remodeling of axons and dendrites, which might be influenced by activity. Large-scale changes in dendrites can occur in response to environmental enrichment and with pharmacological manipulations. In the superior cervical ganglion of the spinal cord, highly dynamic dendritic branches have been found. Recent long-term imaging studies in the *in vivo* adult neocortex have found high levels of structural plasiticity of axonal branches and boutons. In addition, *in vivo* and *in vitro* studies have revealed rich dynamics of postsynaptic dendritic spines, including spine formation, retraction, and shape changes. Changes in spine number are likely to indicate synapse formation and elimination.

p0085 If the size of the dendritic tree increases or decreases, then the activity of the neuron can change not only as a result of loss or formation of synaptic connections, but in principle also directly as a consequence of altered morphology. In many cell types – including pyramidal cells in visual cortex, somatosensory cortex, prefrontal cortex, and hippocampus – firing patterns (both spike frequency and spike pattern) are correlated with dendritic morphology. Results from modeling studies suggest a causal relationship between dendritic morphology and firing patterns. For example, models of neocortical neurons that have the same channel densities and kinetics but differ in their dendritic shape and size can generate

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firing patterns ranging from regular spiking to bursting when stimulated at the soma with a fixed current injection. Both dendritic size and dendritic branching structure may influence firing patterns, especially the cell's propensity for generating bursts (the occurrence of clusters of spikes with short interspike intervals).

s0045 **Number of Inhibitory and Excitatory Cells**

p0090 Insertion of new excitatory neurons into adult neuronal networks, as takes place in the dentate gyrus of the hippocampus, requires the existence of homeostatic mechanisms to regulate the resulting changes in neural activity. One of the possibilities, for which there is some experimental evidence, is that not all the newly generated neurons become excitatory granule cells but that some take on features typical of inhibitory GABAergic basket cells. A related mechanism is the conversion of preexisting granule cells to the GABAergic phenotype. Into maturity, granule cells express low levels of the inhibitory transmitter GABA.

s0050 Discussion

p0095 Besides keeping neural activity in the range where neural circuits can operate properly, homeostasis of neural activity has been postulated to lead to some additional beneficial properties. For example, homeostatic synaptic plasticity may prevent the runaway of synaptic strengths during Hebbian modifications or facilitate the competition between synapses during development.

p0100 Modeling studies have shown that homeostatic activity-dependent neurite outgrowth leads to a number of interesting emergent phenomena, including a transient phase of high network connectivity during development, size differences between the spatial extent of neurites of excitatory and inhibitory neurons, and compensatory sprouting of remaining cells following cell death. Furthermore, activity-dependent neurite outgrowth has been found to construct networks with a critical connectivity level in which the frequency of spontaneous network bursts of activity shows a power law relationship with burst duration and size. This critical connectivity has been shown to optimize information transmission while preventing runaway network excitation.

p0105 It is generally believed that homeostatic synaptic plasticity acts to restore a target pattern of activity in networks after a perturbation. However, under some conditions, rather than restoring a desired activity state, homeostatic plasticity rules may instead lead to pathological forms of neural activity. In a computer model of the neocortex with a biologically based homeostatic plasticity rule that operates to maintain firing rates, pathological neural activity has been found to develop after complete cortical deafferentation (such as may occur after severe head trauma). Homeostatic synaptic plasticity increases the network excitability to a level at which only synchronized bursting activity becomes possible.

p0110 Under some conditions, model networks consisting of excitatory and inhibitory cells in which individual neurons adapt their intrinsic excitability may become unstable. The stability of the adaptation at the network level critically depends on the relation between the cellular adaptation rates of both neuron populations, combined with their respective gains. If input–output relations of both excitatory and inhibitory cells have equal gain, the inhibitory cells need to adapt more slowly than the excitatory cells for a network to remain stable and attain its target state. If this condition is not met, the activity level in the network keeps increasing until the network abruptly falls silent, after which activity gradually builds up again.

p0115 Models exploring the consequences of homeostatic, activity-dependent neurite outgrowth have shown that networks with both excitatory and inhibitory cells can under some conditions develop into a pathological network state. This state, in which the average activity is still at set point level, is characterized by a high level of network connectivity and fast, epileptiform oscillations in electrical activity. Blocking electrical activity in the network for a certain period of time during development can induce the network to evolve into this state. It is interesting and perhaps counterintuitive that the higher the level of inhibition (e.g., the number of inhibitory cells) during the early stages of development, the more likely the network is to end up in the pathological state. As a consequence of the interactions between excitation, inhibition, and outgrowth, too much inhibition prevents the normal pruning of exuberant connections, resulting in a network with epileptiform activity. This model result may shed light on experimental observations that in rat pups with hypoxic-ischemic encephalopathy, epileptiform activity later on in life appears to be due to the preferential survival, not loss, of inhibitory elements.

See also: Neurogenesis in the intact adult brain (00013); Neuronal plasticity after cortical damage (00014); Synaptic plasticity: neuronal sprouting (00130); Dendrite Development, Synapse Formation and Elimination (00347); Plasticity of intrinsic excitability (00811); Spike-timing-dependent plasticity models (01398); Neural oscillators and dymanmical systems models (01404); Spiking neuron models (01405); Stomatogastric ganglion models (01432);

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Potassium Homeostasis in Glia (01721); Calcium Homeostasis in Glia (01722); Activity-dependent remodelling of presynaptic boutons (01801).

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Abstract:

Neural circuits are constantly perturbed throughout life by changes in synaptic strength, connectivity, morphology, sensory input, and protein turnover. When left unchecked, these disturbances will alter neural activity levels beyond the range in which neural circuits can operate properly. A variety of mechanisms operating at different spatial and temporal scales have been suggested to contribute to the homeostasis of neural activity. Important questions that remain to be answered involve the nature of the set point of such homeostasis and whether synaptic and cellular mechanisms are capable of achieving homeostasis of activity at the network level.

Keywords: Development; Homeostasis; Homeostatic plasticity; Iintrinsic excitability; Models; Structural plasticity; Synaptic scaling

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