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Homeostasis and Synaptic Scaling: A Theoretical Perspective

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Homeostasis and Synaptic Scaling: A Theoretical Perspective

by

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Homeostasis and Synaptic Scaling: A Theoretical Perspective

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The synaptic input received by neurons in cortical circuits is in constant flux. From both environmental sensory changes and learning mechanisms that modify synaptic strengths, the excitatory and inhibitory signals received by a post-synaptic cell vary on a continuum of time scales. These variable inputs inherent in different sensory environments, as well as inputs changed by Hebbian learning mechanisms (which have been shown to destabilize the activity of neural circuits) serve to limit the input ranges over which a neural network can effectively operate. To avoid circuit behavior which is either quiescent or epileptic, there are a variety of homeostatic mechanisms in place to maintain proper levels of circuit activity. This article provides a basic overview of the biological mechanisms, and consider the advantages and disadvantages of homeostasis on a theoretical level.

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Chapter 1: INTRODUCTION

The mammalian brain is exposed to dynamic environments and transient sensory stimuli, and must use this sensory information to navigate in the environment. Synaptic learning mechanisms such as Hebbian-like plasticity exist to store information and correlations in sensory input - however, these learning mechanisms are known to destabilize network activity [47]. The brain is even less stable when considering the extensive positive feedback loops inherent in brain regions such as the cerebral cortex [7]. To accommodate stable function in light of these changes in network input and network configuration, the system must adapt to stay within a functional regime. There are a plethora of adaptational mechanisms working in concert within neural circuits to aid learning and simultaneously promote functional stability [47]. If a neural circuit becomes either too active or too silent, then the network output can lose all informative significance. The three main types of homeostatic mechanisms can be divided categorically as: synaptic scaling, intrinsic excitability, and network homeostasis. Each mechanism has a diversity of functional significance., and in many cases these cannot be considered biologically separate entities given the complex nature of signaling pathways and receptors. Additionally, it should be noted that the homeostatic mechanisms are the culmination of an array of complex and opposing forces. There are multiple mechanisms by which a neuron can change firing rates, including: receptor composition, changes in release of neurotransmitter and secreted factors, receptor-protein affinity and more. These neurobiological forces drive neurons and their connections to respond in certain ways under different conditions for a consistent baseline behavior.

Chapter 2: LEARNING MECHANISMS AND HOMEOSTASIS

The most widely recognized neural correlate of learning and memory lies in the synaptic strength between two neurons. Modification of synaptic strengths is accomplished by long-term potentiation (and long-term depression), and is the result of two neurons firing in close (distant) temporal proximity. These mechanisms can be modeled by Hebbian learning rules, and are a powerful tool for learning and memory in neural circuitry. Though despite the apparent utility, one consequence of Hebbian learning is that it maximally increases the variance of the neuronal output, which leads to unstable and dysfunctional network dynamics [43]. This is consistent with intuition: If two neurons fire in close proximity to one another, then the synaptic connection between them is strengthened - which leads to the neurons firing together more often. This positive feedback results in network instability, and a compromise must be reached between the ideal information storage and more pragmatic information transfer, i.e. network stability.

If a neuron is to contribute to the computational function of a neural circuit, then the activity of the neuron must on average fall within some information-maximizing firing rate. Experiments show that neurons are able to maintain an approximate rate of firing [29, 45, 49]. Clearly a perpetually silent or perpetually active neuron carries no information. The concept is illustrated by the binary entropy plot shown below. When considering a single binary value (neuron) with multiple occurrences (spikes or no spikes), the most information is conveyed when the neuron fires approximately half of the time.

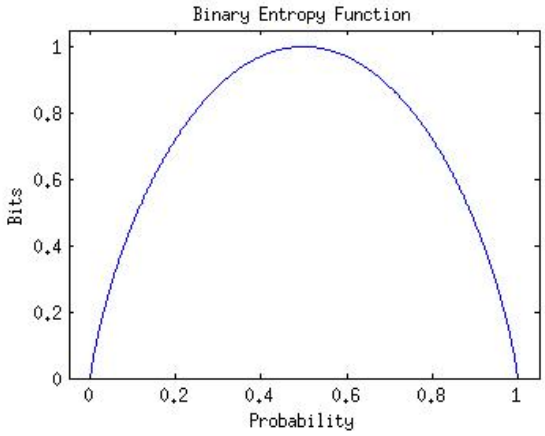

Figure 2.1: Binary Entropy Plot

There are many theories and experimental results which give insight into the phenomenon of neural coding, though the exact language is still unknown [5]. One of the most classic theories of neural coding is that of the rate code; the main postulate is that neurons in a network communicate to each other primarily through firing rates. It is well known that neurons of different types, and even neurons within the same type, have a wide range of firing rates and characteristic properties of firing patterns (such as bursting). What are the rules then that govern the modification of firing rates? and what is the relationship between learning and systematic changes in firing rates?

Chapter 3: SYNAPTIC SCALING

Synaptic scaling is a homeostatic mechanism by which neurons regulate their firing rates towards a theoretical equilibrium point. Occurring on a time-scale longer than LTP or LTD, synaptic scaling is a neuron-wide phenomenon where by the connection strength of each synapse is scaled up or down multiplicatively [47]. The transmission strength of a synapse is altered by a proportional increase or decrease in the density of the relevant receptors on a synapse. This scheme allows the neuron to maintain the relative strengths of the synapses while changing firing rates [25,51]. Blocking post-synaptic firing leads to enhanced accumulation of certain receptors on the post-synaptic membrane at excitatory synapses and so scales up transmission [19]. Part of the mechanism functions through a change in the internal calcium influx and subsequent change in activation of calcium/calmodulin dependent (CaM) kinase kinase (CaMKK), and CaMK-IV pathways, which lead to a modification in the post-synaptic density of glutamatergic AMPA and NMDA receptors [19]. Thus, synaptic scaling in part occurs in the post-synaptic terminal as changes in receptor composition [1]. Despite the large role of the post-synaptic terminal in synaptic scaling, receptor activity indicates a pre-synaptic role as well [53]. The post-synaptic scaling pathway has specific and crucial molecular differences when compared to the pathways involved in LTP, and can be considered a separate process despite similar functional similarities [28, 38]. One difference between the processes of LTP and synaptic scaling can be found at the AMPA receptor: synaptic scaling adds a C-terminus to the GluR2 AMPA receptor, while LTP modifies sequences on the GluR1 receptor subunit [15]. Another difference between the two mechanisms is the scale at which they operate, LTP and LTD are largely synapse-specific, where as synaptic scaling affects all synapses. Conclusively, synaptic scaling appears to exist solely as a homeostatic mechanism, and is generally not believed to participate in learning per se.

3.1 Synaptic Scaling - Pre or Post?

Synaptic scaling is thought to occur in the post-synaptic neuron through changes in receptor composition. Although, some recent evidence for pre-synaptic participation in synaptic scaling was discovered, seen by changes of neurotransmitter transporter composition, as well as auto receptors (auto-receptors on the pre-synaptic terminal are receptors that regulate the amount of neurotransmitter released from the pre-synaptic neuron.) The mechanisms of synaptic scaling in the pre-synaptic and post-synaptic neuron seem to be dependent on different molecular pathways. The role of pre-synaptic scaling involvement can be considered limited, because blockade of the post-synaptic scaling pathways - for example by knockdown of the GluA2 subunit, blocks the majority of synaptic scaling [15]. The post-synaptic role in scaling is interesting when considering that STP is largely pre-synaptic. The distinction between the two types of synaptic strength modification may give insights into the different computational roles and objectives. Perhaps the relationship between synaptic scaling and LTP on the post-synaptic neuron is parallel to an as yet unknown connection between pre-synaptic scaling and STP, which would indicate a short time scale vs. long time scale difference between pre-synaptic and post-synaptic roles, respectively. Intuitively from a neuron-focused point of view, the minor modifications of input through hundreds of synapses from as many neurons may change slowly and have little effect on the activity of a neuron. Conversely, all post-synaptic targets of a neuron receive the input from one neuron. This is a comparison between one synapse and many. Thus, it may come down to a measure of network destabilization effect and the necessity for homeostasis: slow vs. quick. The precise advantages of this time-scale configuration are not clear, though are certainly amenable to analysis or simulation.

Along the same lines, two interesting computational modeling studies have observed advantages of homeostatic mechanisms consistent with what is known about homeostasis in mammalian neural circuits. One study saw that Hebbian learning, in tandem with synaptic scaling is able to detect features of complex input, while Hebbian learning by itself failed in this regard. Another study looked at the stability of network activity under different types of synaptic scaling, and found

an increased stability when the synaptic scaling depends on both the pre and post-synaptic neuron. Thus, the translation from biological information systems to mathematical algorithms is able to provide rich insight into the qualitative reasoning behind the structure of neural circuits.

3.2 Synaptic Scaling in Development

A major need for homeostasis is evident when considering developmental processes. Massive organization and restructuring of neural circuits takes place in young mammals. Neural growth and the associated changes affect circuitry dynamics in neural networks, and therefor affect inputs to specific neurons. This phenomenon is particularly overt in ocular dominance and the critical period in rodents. During development, monocular deprivation changes the ability of the two eyes to drive neurons within the binocular portion of the visual cortex, such that neurons connected to the deprived eye will shift their responsiveness from the deprived eye to the non deprived eye [14, 34]. Homeostatic mechanisms are clearly in play here, as LTP is not be possible without activity. More striking evidence though is that under binocular deprivation the visual cortex maintains global levels of activity [34].

The mechanisms of homeostasis are important for development, though interestingly are turned on or off differentially depending on the layer, cell type, and the age of the animal in relation to the critical period. In layer 4 (which is considered the 'input' layer) homeostatic mechanisms are active up until the critical period. This is different from upper cortical layers, where homeostasis is turned on during the critical period [12, 25].

Chapter 4: INTRINSIC EXCITABILITY

Synaptic scaling is one way by which a neuron can achieve homeostasis. Another and less understood mechanism to achieve firing rate homeostasis is by modulation of intrinsic excitability. Intrinsic excitability is defined as the neural excitatory response to current (this is illustrated physiologically as a change in spiking threshold). Changes in intrinsic excitability are seen in response to long term changes in firing rates, and behave qualitatively similar to synaptic scaling. Though as can be seen in the figure below, synaptic scaling and changes in intrinsic excitability are quantitatively different. The cellular basis of intrinsic excitability lies in the density of voltage-gated sodium channels as well as persistent potassium currents, and is at least in part mediated by metabotropic glutamate receptor dependent changes in IH currents. The differences between synaptic scaling and increases in intrinsic excitability pose several interesting questions. Do these mechanisms exist for fundamentally different reasons? or are they merely redundant functions with the same objective?

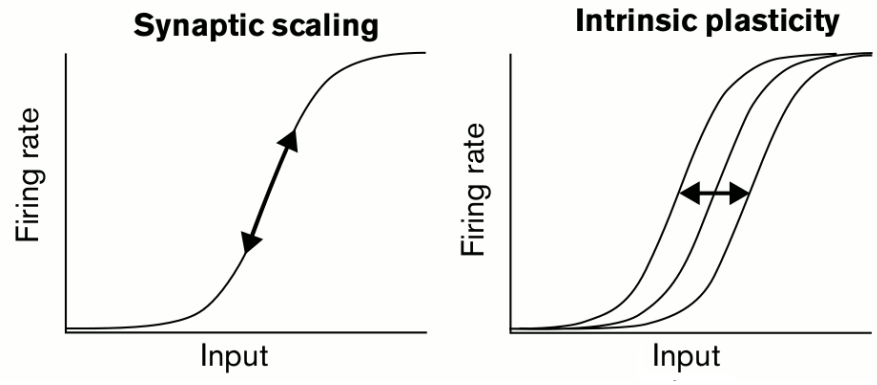

Figure 4.1: Synaptic Scaling versus Intrinsic Plasticity
Borrowed from Turrigiano and Nelson 2000.

Intrinsic excitability is seen here to promote the homeostasis of network activity, although it can also behave heterostatically in a different context. When attempting to explain the rationale of intrinsic excitability in homeostasis, it may help to consider the other side of the coin. In an experiment performed by Xu et al., intrinsic excitability increased as a function of similar pathways

in the late phase of LTP, and in this context requires NMDA glutamate receptor subtypes, calcium influx, and CaMKII [54]. This increase in intrinsic excitability argues against a purely homeostatic function of firing rate, and indicates that intrinsic plasticity may additionally be involved in learning and memory [55]. Perhaps intrinsic excitability homeostasis is to intrinsic plasticity as synaptic scaling is to LTP.

Chapter 5: NETWORK HOMEOSTASIS

There are many stages at which homeostatic mechanisms can operate and exist. One of the most difficult scales to understand technically is that of network-level homeostasis. The difficulty here lies in the complexity of extensive feedback connections, combined with the sophisticated dynamics of smaller-scale homeostatic mechanisms working in tandem. The first step towards understanding network dynamics is understanding the homeostatic differences between cell types - mainly the differences between inhibitory and excitatory cells. This difference is consistent with the roles of these cells, and the idea that network activity is the culmination of the 'push-pull' between activation and inhibition. Consistently, there are inverse homeostatic modulations at excitatory to inhibitory synapses junctions (E-I), excitatory to excitatory (E-E), and inhibitory to excitatory (I-E). An increase in network activity results in weakened E-E connections, and strengthened E-I and I-E connections. A decrease or blockade of activity results in the opposite modifications of connection strength: an increase in E-E, and a decrease in E-I and I-E. The complete pathways for inhibitory scaling mechanisms have yet to be elucidated [22, 25], though the general picture is consistent with the role of inhibitory neurons working to regulate network activity [36].

An example of network homeostasis can be seen in invertebrate central pattern generators (CPG): changing one aspect of the CPG temporarily disrupts periodicity, though this is restored over a time period of hours to days. Disruptions of these homeostatic mechanisms in Humans can lead to disease states such as Epilepsy. Epilepsy is characterized by an over-activation and ubiquitous synchrony of certain brain regions. Epilepsy can also be the result of traumatic changes in anatomic circuitry (injury). These two causes of Epilepsy allow for two possibilities: either circuitry configurations in the brain are responsible for maintaining some wide-level homeostasis (perhaps through negative feedback), or there is an inconsistency in the distribution of cell types responsible for restricting hyper-activation of the network. These possibilities are not mutually exclusive, and network homeostasis is surely the result of both factors. Regardless of the specific network-wide mechanisms contributing to activity homeostasis, it is evident that many scales of

homeostasis are necessary to maintain proper levels of activity.

Chapter 6: DISCUSSION

There are many instances in which firing rate has shown to correlate highly with some behavior, this has been highly evident in brain regions responsible for motor response. Thus, downstream brain regions must at least in part be responsive to firing rate coding. How then does firing rate coding serve as a useful method of information transfer if there are homeostatic mechanisms in place? One possible explanation is that the time course over which homeostasis acts is much longer than the time course of firing-rate specific signals in neural circuits. It is clear that homeostatic mechanisms act over a wide range of scales: from network level homeostasis of activity, down to individual synapses. Imagine then the two possible extremes of homeostatic activity: on one end of the spectrum is a network in which there is no homeostasis. This hypothetical network would only be subject to LTP, and have symptomatic activity destabilization leading to dysfunctional behavior. On the other end of the spectrum it is possible to imagine a network for which each synapse, neuron, and neural circuit have fast homeostasis such that synapse, neuron, and network activity is approximately constant throughout time, and exhibits only minor fluctuations in activity as a result of insignificant LTP and LTD. Clearly both of these networks are flawed, and the optimal homeostasis lies somewhere between these two extremes.

What then would the optimal homeostasis be a function of? Considering the question qualitatively, it must be a function of at least: average firing rate, rate of LTP and LTD, network circuitry, and distribution of neuron type. Average firing rate of neurons in a network is a factor on the basis that: higher firing rates lead to quicker destabilization. Rate of LTP and LTD is important because this dynamic force dictates the speed of destabilization, and if homeostasis is to stabilize then it must function accordingly. Network circuitry may be a factor when considering possible negative or positive feedback loops. A negative feedback loop would require less homeostasis than a destabilizing positive feedback loop. Lastly, inhibitory neurons serve to limit the requirement for homeostasis. It is generally accepted that inhibition acts to oppose and regulate activation of specific neural circuits. In a network consisting only of excitatory neurons, homeostasis would

have to act on a timescale comparable to fluctuations in network activity - which would lead to a reduced role of Hebbian mechanisms, since homeostasis would essentially 'over-write' LTP and LTD driven changes in synaptic strength. It is likely that the presence of inhibitory neurons allows for reduced homeostasis (synaptic scaling and homeostatic intrinsic plasticity), and consequently increases network information storage.

The homeostasis of neural activity is becoming recognized for its relevance to disease states as well as in normal circuit behavior. A complete understanding of homeostasis and learning mechanisms at a circuit level can guide research in probing the underlying cellular mechanisms responsible for the behavioral disfunction symptomatic of disease. Modeling studies may provide specific insight into the computational strategies employed by the brain, and a quantitative understanding of how changes in these strategies can lead to deficits in learning or behavior. Does intrinsic excitability play an active role in learning? In what ways do synaptic scaling and intrinsic plasticity overlap in terms of redundancy, or how do their activities play distinct functional roles? The full picture has yet to be elucidated, both in terms of molecular pathways and functional significance for information storage.

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