Journal of Mathematical Psychology, in press

A Tutorial on Computational Cognitive Neuroscience: Modeling the Neurodynamics of Cognition

F. Gregory Ashby & Sebastien Helie
University of California, Santa Barbara

Computational Cognitive Neuroscience (CCN) is a new field that lies at the intersection of computational neuroscience, machine learning, and neural network theory (i.e., connectionism). The ideal CCN model should not make any assumptions that are known to contradict the current neuroscience literature and at the same time provide good accounts of behavior and at least some neuroscience data (e.g., single-neuron activity, fMRI data). Furthermore, once set, the architecture of the CCN network and the models of each individual unit should remain fixed throughout all applications. Because of the greater weight they place on biological accuracy, CCN models differ substantially from traditional neural network models in how each individual unit is modeled, how learning is modeled, and how behavior is generated from the network. A variety of CCN solutions to these three problems are described. A real example of this approach is described, and some advantages and limitations of the CCN approach are discussed.

Keywords: computational cognitive neuroscience, neural network modeling, neuroscience

1. Introduction

The emerging new field of Computational Cognitive Neuroscience (CCN) lies at the intersection of computational neuroscience and the similar fields of machine learning, neural network theory, connectionism, and artificial intelligence. Like computational neuroscience, CCN strives for neurobiological accuracy and like connectionism, a major goal is to account for behavior. In other words, using Marr's (1982) nomenclature, CCN strives to develop models that can simultaneously satisfy the algorithmic and implementation levels. One main advantage of CCN is that it offers many more constraints on the resulting models than more traditional approaches. As a result, two researchers independently modeling the same behavior are more likely to converge on highly similar models with this new approach, and for this reason the resulting models should have a permanence that is unusual with older approaches. A growing number of researchers build and test CCN models (e.g., Anderson, Fincham, Qin, & Stocco, 2008; Ashby, Ell, Valentin, & Casale, 2005; Frank, 2005; Hartley, Taylor, & Taylor, 2006; Leveille, Versace, & Grossberg, 2010), and an annual CCN conference is now included as a satellite to the *Annual Meeting of the Psychonomic Society*.

2. A brief history

The field of computational neuroscience became popular with Hodgkin and Huxley's (1952) Nobel Prize winning efforts to model the generation of action potentials in the giant squid axon. Most models in this field include, at most, only a single neuron. For example, a common computational neuroscience approach, called compartment modeling, models a neuron's axons and dendrites as cylinders and the soma as a sphere. Next, partial differential equations that describe the propagation of action potentials are written for each of these compartments. A standard application will try to account for patch-clamp data collected from a variety of locations on the cell. Some compartment models are extremely accurate and complex. For example, some single-cell models have hundreds or even thousands of compartments (e.g., Bhalla & Bower, 1993; Segev & Burke, 1998). Historically, computational neuroscience models have almost never tried to account for behavior.

This research was supported in part by Award Number P01NS044393 from the National Institute of Neurological Disorders and Stroke and by support from the U.S. Army Research Office through the Institute for Collaborative Biotechnologies under grant W911NF-07-1-0072. We thank Todd Maddox, Dennis Rünger, Darrell Worthy, and Martijn Meeter for their helpful comments. Correspondence concerning this article should be addressed to F. Gregory Ashby, Department of Psychological & Brain Sciences, University of California, Santa Barbara, CA 93106. (e-mail: ashby@psych.ucsb.edu).

In most cases, such a goal is precluded by the complexity of the single-cell models that are used.

Neural network theory began with similar origins in the work of McCulloch and Pitts (1943). However, because the goal quickly became to model behavior, neural network theory diverged from computational neuroscience with the work of Newell, Shaw, and Simon (1958) and Rosenblatt (1958). At that time, there simply was not enough known about the neural basis of behavior to support a research program that tried to model behavior in a biologically accurate way. Thus the fields of artificial intelligence and the more modern related field of machine learning place almost all emphasis on behavior and almost none on neuroscience.

Modern neural network theory (e.g., Haykin, 2008) and connectionism (Rumelhart & McClelland, 1986) take an intermediate approach in the sense that biologically plausible properties are often seen as advantages, although they rarely are requirements. Neural network models have some features in common with the brain. Included in this list are distributed representation, continuous flow, and the modeling of memory as changes in synaptic strengths. Even so, almost all neural network models include many features that are now known to be incompatible with brain function. For example, there is generally no attempt to identify units in neural network models with specific brain regions, and even when there is, there is little attempt to model inputs and outputs to these regions in a biologically accurate way. Similarly, units in neural network models typically do not behave like real neurons, and the learning algorithms that are used often have little biological plausibility (e.g., backpropagation).

These observations are not criticisms. The vast majority of computational neuroscientists are not psychologists and many have no fundamental interest in behavior. Similarly, artificial intelligence and machine learning researchers are generally interested in optimizing the performance of their models, not in modeling human behavior. Neural network theory (i.e., connectionism) often does have the goal of modeling behavior and generally does view the neural-like properties of neural network models as an advantage of this approach. Even so, many applications of neural network models are to behaviors that are so complex or so poorly understood that it would be premature to attempt to build more biologically detailed models (these fields focus on Marr's 'algorithmic' level). The focus of these earlier approaches is well motivated because "the explication of each level involves issues that are rather independent of the other two" (Marr, 1982, p. 25). However, Marr also acknowledged that "these three levels are coupled" (p. 25). So, the new field of CCN is not meant to supplant these older approaches, but rather to fill a new niche by trying to focus on the "coupling" of the levels by using recent discoveries in psychology and neuroscience.

The field of CCN began shortly after the cognitive neuroscience revolution of the 1990's. The first break with existing approaches came with attempts to associate nodes in fairly traditional connectionist or neural network models with specific brain regions. This trend toward increased biological detail continued with more biologically plausible learning algorithms, and more realistic models of the individual units (e.g., Ashby, Alfonso-Reese, Turken, & Waldron, 1998; Cohen, Braver, & O'Reilly, 1996; Cohen & Servan-Schreiber, 1992; McClelland, McNaughton, & O'Reilly, 1995). During this time there were also attempts to formulate general modeling principles of this new approach (O'Reilly, 1998; O'Reilly & Munakata, 2000). The present article represents a natural extension and summary of this earlier work.

This article is organized as follows. Section 3 gives some motivation for adopting a CCN approach. Section 4 describes the CCN principles that guide model development and model testing. Section 5 describes some common approaches used in CCN to model individual units or neurons. Section 6 briefly reviews the biochemistry that underlies some common forms of long-term synaptic plasticity, and describes simple computational models of these learning-related changes in synaptic strength. Section 7 reviews some solutions to the problem of generating behavior from single-unit activity. Section 8 describes an example of the CCN approach, and Section 9 closes with some general comments and conclusions.

3. Why use CCN models?

Before getting into the details of how to develop CCN models, it is natural to ask what advantages CCN has over other approaches. First, CCN modeling increases the number of constraints on behavioral models. Newell (1992) argued that "cognitive theory is radically underdetermined by data" (p. 426). Although Newell was arguing for the use of 'unified' theories of cognition (e.g., cognitive architectures), another possible solution to this problem is to add neuroscience constraints to the modeling process (i.e., going deep instead of going wide). Rather than just selecting among models based on goodness-of-fit to behavioral data, CCN adds the extra constraint that the winning model should also function in a manner that is consistent with existing neuroscience data. Adding neuroscience constraints should reduce the class of candidate models, and equally important it should reduce the heterogeneity of this class. For example, if neuroscience data implicate

the hippocampus in some behavior, then models of this behavior must all share some hippocampal-like properties. This reduction in model heterogeneity should cause different labs to converge on similar models and thereby facilitate rapid scientific progress.

Second, attending to the neuroscience data can expose relationships between seemingly unrelated behaviors. For example, cognitive neuroscience models of (information-integration) category learning and (implicit) sequence learning had independently identified similar cortical-striatal circuits (e.g., Ashby et al., 1998; Grafton, Hazeltine, & Ivry, 1995). This raised the possibility that these two seemingly disparate behaviors shared some previously unknown deep functional similarity. Several studies have explored this possibility. First, Willingham, Wells, Farrell, and Stemwedel (2000) had showed that implicit motor sequence production is disrupted when the response key locations are switched, but not when the hands used to depress the keys are switched. Ashby, Ell, and Waldron (2003) showed that this same pattern of results holds for information-integration categorization. Without linking categorization and sequence learning through their hypothesized underlying neural circuits, this dependence of information-integration categorization on response location learning would have been much more difficult to discover. More recently, an inactivation study showed that the basal ganglia are not required for the production of overlearned motor sequences (Desmurget & Turner, 2010), thereby suggesting that the same may be true of information-integration categorization (as was predicted by the CCN model of Ashby et al., 2007). This prediction was recently confirmed with an fMRI experiment (Waldschmidt & Ashby, 2011).

Third, in many cases, studying the underlying neuroscience leads to surprising and dramatic behavioral predictions that would be difficult or impossible to derive from a purely cognitive approach. For example, information-integration category learning was hypothesized to depend on dopamine-mediated reinforcement learning at cortical-striatal synapses (Ashby et al., 1998). Because the reward follows the behavior, the dopamine must operate on a memory trace that identifies recently active synapses. The most likely candidate for this trace is partially phosphorylated CaMKII, which loses its sensitivity to dopamine after just a few seconds (e.g., Lisman Schulman, & Cline, 2002; see section 6.1 for details). Thus, attention to the underlying neuroscience generates a novel and surprising prediction: delaying feedback by just a few seconds should impair information-integration category learning, but not other forms of category learning (e.g., rule-based) thought to rely on executive attention and working memory. Several studies have confirmed these predictions (Maddox, Ashby, & Bohil, 2003; Maddox & Ing, 2005).

Fourth, CCN models are especially amenable to a converging operations approach to model testing because they make predictions about both behavioral and neuroscience data. Thus, rather than simply testing them against behavioral data, it should also be possible to test CCN models against a variety of neuroscience data, including single-unit recording data, lesion data, psychopharmacological data, fMRI data, and possibly even EEG data. The ability to test CCN models against such a broad spectrum of data should facilitate the process of testing, rejecting, and refining new models.

4. CCN Ideals

One thing that sets CCN apart from previous modeling traditions is that its principles of model building and testing are unique. In traditional cognitive-based mathematical modeling of behavior, the overriding criterion for establishing the validity of a model is goodness-of-fit to the behavioral data (usually penalized for model complexity; see, e.g., Helie, 2006; Pitt, Kim, Navarro, & Myung, 2006). In general, there is a secondary goal of encapsulating existing cognitive theory, but most cognitive theories are extremely difficult to falsify, and as a result, if a cognitive model fits data well then it is almost never rejected because of the cognitive assumptions it makes. There are many examples where models making very different cognitive assumptions provide approximately equal levels of goodness-of-fit, so in many cognitive domains there are many competing mathematical models that make very different cognitive assumptions. For example, the results from many memory experiments can be well fit by a variety of models that make radically different cognitive assumptions (e.g., Raaijmakers & Shiffrin, 2004), and unfortunately, appeals to cognitive theory have not done much to winnow down this crowded field. Many other examples exist in the cognitive literature, including the well known difficulty in discriminating between serial and parallel models of visual or memory search (e.g., Townsend & Ashby, 1983), the ability of exemplar, prototype, and decision bound models of categorization to mimic each other (Ashby & Maddox, 1993), and the difficulty in discriminating between single- and dual-process models of recognition memory (e.g., Diana, Reder, Arndt, & Park, 2006; Jang, Wixted, & Huber, 2009).

These problems are greatly reduced in CCN because goodness-of-fit to behavioral data is only one of a number of criteria that are used to assess model validity. This section describes four ideal principles used during model building and testing in CCN. It should be stressed

that these are ideals. Arguably, no existing models meet all these criteria. Nevertheless, these principles are useful for helping researchers build and evaluate CCN models.

4.1. The Neuroscience Ideal. *A CCN model should not make any assumptions that are known to contradict the current neuroscience literature.*

In general, the Neuroscience Ideal means that when building or evaluating a CCN model, the validity of four types of assumptions should be considered. First, the model should only postulate connections among brain regions that have been verified in neuroanatomical tracing studies. Second, the model should correctly specify whether each projection is excitatory or inhibitory. Third, the qualitative behavior of units in each brain region should agree with studies of single neurons in these regions. Finally, any learning assumptions that are made should agree with existing data on neural plasticity [e.g., long-term potentiation (LTP) and long-term depression (LTD)]. If a model makes an assumption that is known to be incompatible with the neuroscience literature then the model should be rejected, regardless of how well it accounts for behavioral data.

Note that the Neuroscience Ideal does not say that a CCN model must be compatible with *all* existing neuroscience data. In other words, not all errors are equal and the Neuroscience Ideal weighs errors of commission much more heavily than errors of omission (Meeter, Jehee, & Murre, 2007). Every model is an abstraction and thus omits some of the complexity found in the natural world. One key to building a successful CCN model is to identify the critical features of the existing neuroscience literature that are most functionally relevant to the behavior being modeled. For example, neuroanatomical tracing studies will identify more interconnections among brain regions than typically should be included in a CCN model because for the behavior under study some of these interconnections are likely to be more functionally important than others.

A related problem is that when building most CCN models it will be necessary to make some choices for which the neuroscience literature is little help – either because there are no neuroscience data or because the existing data are equivocal. Thus, the Neuroscience Ideal should not be interpreted as suggesting that all known neuroscience must be incorporated into a CCN model or that every feature of a CCN model must be grounded in neuroscience, but rather only that the neuroscience that is incorporated should not contradict the existing neuroscience literature. Finally, it is important to keep in mind that the Neuroscience Ideal is just that: an ideal. No model is ever correct and, even if one were eventually able to design a model fully compatible with the Neuroscience Ideal, this would make the model so complex that it likely would be impossible to test.[1] For these reasons, the Neuroscience Ideal should be balanced with the following heuristic.

4.2. The Simplicity Heuristic. *No extra neuroscientific detail should be added to the model unless there are data to test this component of the model or the model cannot function without this detail.*

This is just a version of Occam's razor. It is especially important with CCN models however, because unlike cognitive models, there will almost always be many extra neuroscientific details that one could add to a CCN model. For example, one could use multi-compartment models of each neuron or even model specific ion channels. Adding untested complexity, even if it is neuroscientifically valid, increases the number of free parameters in the model and the computing time required for fitting. In addition, when untested details are added, it becomes difficult to determine whether the success of the model is due to these details or to the more macroscopic properties that inspired the model in the first place.

The phrase "to test this component of the model" in the Simplicity Heuristic should be interpreted loosely. For example, if previous research shows that a behavior is dependent on the cerebellum then the cerebellum could be included in the model, even if no cerebellar data will be fit by the model (e.g., single unit recordings or lesion data).

4.3. The Set-in-Stone Ideal. *Once set, the architecture of the network and the models of each individual unit should remain fixed throughout all applications.*

Connections between brain regions do not change from task to task, nor does the qualitative nature via which a neuron responds to input. Thus, the model's analogues of these features should also not change when the empirical application changes. This ideal greatly reduces the mathematical flexibility of CCN models. Ideally, the overall architecture is constrained by known neuroanatomy and the model of each individual unit is constrained by existing single-unit recording data from the analogous brain region. Thus, although a CCN model

[1] The reader is referred to Meeter et al. (2007) for further discussion of other common untested assumptions in CCN models.

will initially have many unknown constants, most of these will be set by single-unit recording data and then, by the Set-in-Stone Ideal, they will remain invariant across all applications of the model. If some of the details turn out to be incorrect after they have been 'set-in-stone', then the incorrect details should be changed and a new model should be constructed. However, note that such revisions do not add flexibility to the existing model; rather they lead to the creation of a new model. Thus, after a constant is set in stone, it should not be considered a free parameter in any future application of the model.

The Set-in-Stone Ideal applies to the brain areas that constitute the focus of explanation of the model, and should not be expected to apply to brain regions that are either upstream or downstream from this hypothesized network. For example, many models of learning, memory, or cognition will require visual input. In tasks where variation in behavior depends primarily on processing within the hypothesized network rather than on details of the visual processing, it is common to grossly oversimplify the model of this visual input. For example, a simple square wave might be used, rather than a spiking model. Applying such a model to a different task, which depends on different visual inputs, might require changing the abstract model of visual input. Similarly, a model of working memory might include a greatly oversimplified model of motor responding that could change when the model is applied to a new task with different motor requirements. So in summary, the Set-in-Stone Ideal is meant to apply to the brain regions that are the focus of the model and not to the inputs or outputs of that model.

4.4. The Goodness-of-Fit Ideal. *A CCN model should provide good accounts of behavioral data and at least some neuroscience data.*

A model must make predictions at both the behavioral and neuroscience levels to classify as a CCN model. If it only makes behavioral predictions then it should be classified as a cognitive model, whereas if it only makes neuroscience predictions then it should be classified as a computational neuroscience model. Thus, in general, CCN models are more ambitious than traditional cognitive models because CCN models are expected to account simultaneously for a wider range of data than cognitive models. Note that the only term that makes this statement an ideal rather than a requirement is the word "good". Every CCN model should make both behavioral and neuroscience predictions, but the ideal CCN model provides good accounts of both data types.

There are many different types of neuroscience data, so there is wide latitude in how this ideal can be approached. For example, a CCN model might be tested against single-unit recording data, BOLD responses from fMRI experiments, or even behavioral data collected from animal or human participants with some specific brain lesion, or under the influence of some particular psychoactive drug.

Because a CCN model can be tested against data from multiple sources, it can gain or lose support more easily than a cognitive model. For instance, following the Neuroscience Ideal (Section 4.1), the collection of new neuroscience data could invalidate a model by turning an error of omission into an error of commission. For example, a model might posit a direct projection from the pre-supplementary motor area (preSMA) to SMA. After all, given their names, this seems a sensible assumption. Recent neuroanatomy studies however, suggest that preSMA does not project to SMA (Dum & Strick, 2005), and therefore this discovery invalidates any CCN model that posits such a projection, regardless of how well it fits behavioral data. Another possibility however, is that new neuroscience data could verify a previously unsupported assumption, thereby lending new support to the CCN model. Of course, similar outcomes could follow the collection of behavioral data; a model prediction could be verified or invalidated after new behavioral data are collected. What is crucial here is that both types of data can be used to argue for or against the CCN model. This is different from cognitive or computational neuroscience models that restrict their application to only one data type.

4.5. Relation to previous lists of CCN characteristics

The list of ideals proposed in Sections 4.1-4.4 is not the first attempt to specify the essential characteristics of CCN models explicitly. For instance, O'Reilly (1998) proposed six principles for computational models of the cortex: (1) biological realism, (2) distributed representations, (3) inhibitory competition, (4) bidirectional activation propagation, (5) error-driven learning of specific tasks and, (6) Hebbian learning of task-free statistical properties of the environment. Most of these principles are related to the Neuroscience Ideal above in that they specify biological constraints that should be included in any CCN model of the cortex. Hence, they can be seen as an unpacking of the Neuroscience Ideal.

A decade later, Meeter et al. (2007) proposed a list of more general criteria. Specifically, they suggested that a good CCN model (1) has few assumptions, (2) is inflexible and, (3) exhibits ontological clarity. The first of these is similar to our Simplicity Heuristic, while the second is similar to the Set-in-Stone Ideal. Both sets of

criteria emphasize that a model should be simple and inflexible (two ideas that are mathematically related). The last criterion, ontological clarity, is similar to our Goodness-of-Fit Ideal, in that the scope of the model must be clearly established in order to determine what kind of data needs to be fit and what kind of experiments should be run. In other words, the rules need to be set early on to specify what counts as evidence for or against the CCN model.

4.6. Discussion

The Neuroscience Ideal makes the relationship between computational neuroscience and CCN explicit by ensuring that no biological detail in the CCN model is inconsistent with existing neuroscientific data (as in computational neuroscience). However, following the Simplicity Heuristic, CCN models typically make simplifying assumptions about the biological details included in the model. This is because the lowest level of data usually accounted for by CCN models is single-cell recordings. Hence, although an increasing amount of data is now available about the molecular neurobiology of neurons, these data are usually not accounted for by CCN models. This makes CCN models biologically simpler (and thus more scalable) than most computational neuroscience models.

The Set-in-Stone Ideal is used to control the growth of complexity in the model. Theoretically, the Set-in-Stone Ideal is an implementational constraint: the same brain is used in every task. Computationally, the Set-in-Stone Ideal is used to fix the value of most constants in the model, thus drastically reducing the CCN model complexity. Once set-in-stone, the Goodness-of-Fit Ideal states that many different types of data should be used to test the adequacy of CCN models, at least some of which are behavioral and some neuroscientific. In addition, the Goodness-of-Fit Ideal makes the relationship between connectionism and CCN models explicit: The biological details in the CCN model should not make the model unscalable and prevent it from explaining behavioral data (i.e., it should scale up like a regular connectionist model). However, before doing any data fit, one needs to clearly define the scope of the model.

These principles are used to guide model development and evaluation. Because of the Neuroscience Ideal there are three areas where the mathematical details of CCN models differ substantially from traditional connectionist models. The first fundamental difference is in how each individual unit is modeled and the second is in how learning is modeled. The third difference concerns the generation of behavior from neurally realistic individual units. Sections 5 - 7 discuss some example CCN solutions to these problems.

5. Modeling Individual Units

There are many choices for modeling individual units. The classic solution is still the Hodgkin-Huxley model (1952). This is a set of four coupled differential equations. One describes fast changes in intracellular voltage and three describe slow changes in various ion concentrations (i.e., for Na^+, K^+, and Cl^-). The model correctly accounts for action potentials (both the upstroke and downstroke), the refractory period, and subthreshold depolarizations that fail to produce a spike. From a computational perspective, perhaps the greatest drawback is that four differential equations must be solved for every unit in the model. Also, for most CCN applications the Hodgkin-Huxley model violates the Simplicity Heuristic because rarely do such applications attempt to account for data that depend on intracellular concentrations of sodium, potassium, or chloride.

For these reasons, there have been a number of attempts to produce models with fewer equations that display as many of the desirable properties of the Hodgkin-Huxley model as possible. Some of these attempts are described in the following subsections.

5.1 The leaky integrate-and-fire model

The simplest cell model, and also the oldest (Lapicque, 1907), is the leaky integrate-and-fire model (e.g., Koch, 1999). Suppose neuron B receives an excitatory projection from neuron A. Let $V_A(t)$ and $V_B(t)$ denote the intracellular voltages at time t in neurons A and B, respectively. Then the leaky integrate-and-fire model assumes that the rate of change of $V_B(t)$ is given by

$$\frac{dV_B(t)}{dt} = \alpha\, f\left[V_A(t)\right] + \beta - \gamma V_B(t), \qquad (1)$$

where α, β, and γ are constants and the function $f[V_A(t)]$ models temporal delays in the propagation of an action potential from the pre- to the postsynaptic neuron. This function is described in detail in Section 5.4. The parameter α is a measure of synaptic strength because the larger this value the greater the effect of an action potential in the presynaptic cell. In many applications, learning is modeled by assuming that α changes as a function of experience. The parameter β determines the spontaneous firing rate of cell B, and γ determines the rate at which charged ions leak out of the cell.

Equation 1 does not produce spikes. Rather it predicts continuous and smooth changes in activation. To generate spikes from this model a threshold V_{peak} is set on $V_B(t)$. When $V_B(t)$ exceeds V_{peak} it is reset to V_{reset} and a spike is drawn by hand. An example of activation

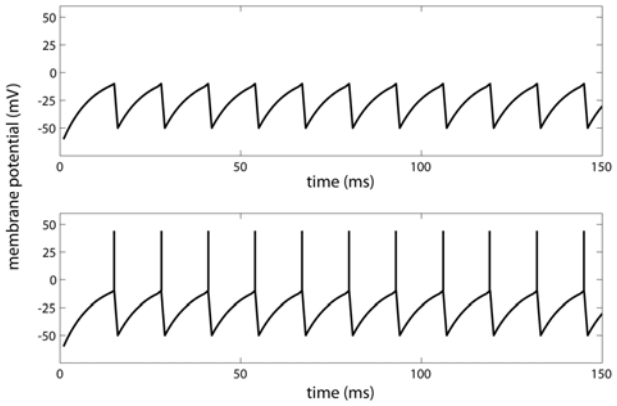

Figure 1. The leaky integrate-and-fire model (with $\beta = 1/60$, $\gamma = 7/60$, $V_{peak} = -10$, and $V_{reset} = -50$). The top panel shows the membrane potential predicted by Eq. 1. In the bottom panel vertical lines have been drawn by hand to simulate spiking.

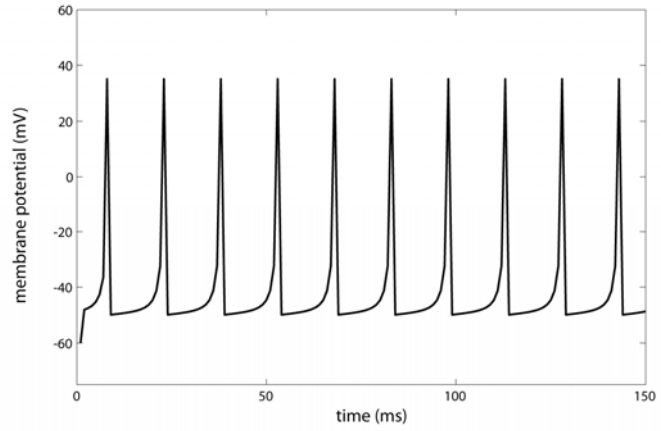

Figure 2. Spike train produced by the quadratic integrate-and-fire model of Eq. 2 (with $\beta = 11.83$, $\gamma = .117$, $V_r = -60$, $V_t = -40$, $V_{peak} = 35$, and $V_{reset} = -50$).

produced by this model is shown in Figure 1. The top panel shows the membrane potential predicted by the model when $V_{peak} = -10$ and $V_{reset} = -50$. The bottom panel adds hand-drawn spikes.

The fact that the leaky integrate-and-fire model does not naturally predict spiking is widely considered a weakness of the model (e.g., Izhikevich, 2007). Also, it does a relatively poor job of describing msec by msec changes in the membrane potential of real neurons and it is not flexible enough to model qualitative differences in the dynamics of different types of neurons. For these reasons, other single-equation models have been developed.

5.2 The quadratic integrate-and-fire model

Perhaps the most popular single-equation alternative replaces the linear decay term in the leaky integrate-and-fire model with a quadratic polynomial. The resulting model is known as the quadratic integrate-and-fire model (Ermentrout, 1996; Latham, Richmond, Nelson, & Nirenberg, 2000). For the scenario modeled in Eq. 1, the quadratic integrate-and-fire model assumes that the rate of change of $V_B(t)$ is given by

$$\frac{dV_B(t)}{dt} = \alpha\, f[V_A(t)] + \beta + \gamma[V_B(t) - V_r][V_B(t) - V_t] \quad (2)$$

where α, β, and γ are constant, V_r is the resting membrane potential, V_t is the instantaneous threshold potential and, as before, the function $f[V_A(t)]$ models temporal delays in the propagation of an action potential from one neuron to another. Unlike the leaky integrate-and-fire model, Eq. 2 produces the upstroke of action potentials by itself, although it does not produce the downstroke. To create spikes, when $V_B(t)$ reaches V_{peak} it is reset to V_{reset}. Figure 2 shows an example of the spiking behavior produced by Eq. 2.

When comparing the leaky and quadratic integrate-and-fire models, the appropriate comparison is between Figure 2 and the top panel of Figure 1 since these show the membrane potential predictions of the two models. The quadratic integrate-and-fire model requires an extra voltage resetting step to generate the downstroke of the action potential. Even so, the upstroke is produced via the model's natural dynamics and therefore the model naturally produces spikes – unlike the leaky integrate-and-fire model. Thus, the quadratic integrate-and-fire model is generally viewed as a superior alternative to the leaky integrate-and-fire model (Izhikevich, 2007).

5.3 The Izhikevich model

Even more realistic behavior is possible if a second differential equation is added that models slow changes in ion concentration. One of the first of these two-equation models was the FitzHugh-Nagumo model (FitzHugh, 1961; Nagumo, Arimoto, & Yoshizawa, 1962). In this model, the rate of change in voltage (i.e., the derivative) is modeled as a cubic polynomial and slow changes in ion concentrations are modeled with a linear differential equation. Izhikevich (2003) proposed a similar model that replaces the cubic polynomial with the quadratic integrate-and-fire model. The Izhikevich (2003) model requires less computing time to evaluate than the FitzHugh-Nagumo model, has simpler dynamics, and can account for some qualitative firing phenomena that are outside the scope of the FitzHugh-

Nagumo model (e.g., tonic and rebound bursting; Izhikevich, 2004). The Izhikevich (2003) model assumes

$$\frac{dV_{\mathrm{B}}(t)}{dt} = \alpha\, f\left[V_{\mathrm{A}}(t)\right] + \beta + \gamma\left[V_{\mathrm{B}}(t) - \mathrm{V_r}\right]\left[V_{\mathrm{B}}(t) - \mathrm{V_t}\right] - U_{\mathrm{B}}(t) \qquad (3)$$

$$\frac{dU_{\mathrm{B}}(t)}{dt} = \lambda\left[V_{\mathrm{B}}(t) - \mathrm{V_r}\right] - \omega U_{\mathrm{B}}(t),$$

where the quadratic integrate-and-fire model is as before and λ and ω are constants. In these equations $V_{\mathrm{A}}(t)$ and $V_{\mathrm{B}}(t)$ again denote intracellular voltages at time t and $U_{\mathrm{B}}(t)$ is an abstract regulatory term that is meant to describe slow recovery in unit B after an action potential is initiated. $U_{\mathrm{B}}(t)$ could represent activation in the K^+ current or inactivation in the Na^+ current, or some combination of both. As before, when $V_{\mathrm{B}}(t)$ reaches $\mathrm{V_{peak}}$ it is reset to $\mathrm{V_{reset}}$. At the same time however, $U(t)$ is also reset to $U(t) + \mathrm{U_0}$.

The Eq. 3 model is highly flexible and produces some extremely realistic spiking behavior. Figure 3 shows examples of 20 qualitatively different kinds of dynamical behavior that can be produced from this model (from Izhikevich, 2003) when different numerical values are chosen for its parameters. Especially when noise is added, many of these are almost indistinguishable from single unit recordings collected from real neurons (for many examples, see Chapter 8, Izhikevich, 2007). One reasonable strategy, which follows from the Simplicity Heuristic, is to use the Eq. 3 model for any units in the network for which single-unit recording data are available. If no such data are available then the simpler quadratic integrate-and-fire model could be used instead. Numerical solutions of Eqs. 1 – 3 are readily obtained using Euler's method. For example, Izhikevich (2007) provides Matlab code that solves Eqs. 3 using this approach.

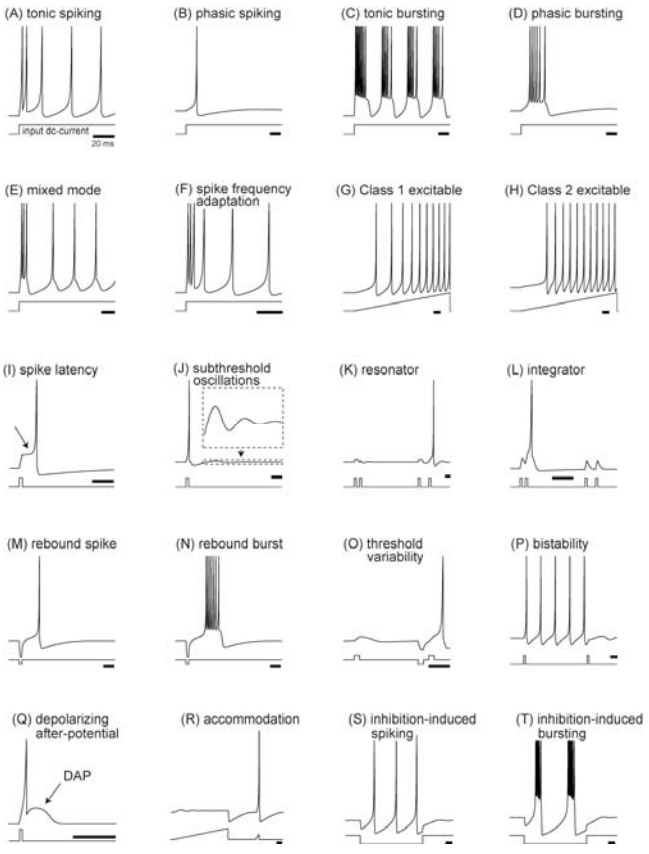

Figure 3. Examples of some of the different dynamics that can be modeled with Eq. 3. An electronic version of this figure and reproduction permissions are freely available at www.izhikevich.com.

5.4 Axons and synaptic delays

Regardless of which model is used, the free parameters that determine the dynamics of each unit should be set so that the behavior of the unit is as consistent as possible with what is known about the behavior of the real neurons the unit is meant to model. Then by the Set-in-Stone Ideal these parameter values should remain invariant across all applications of the model.

Equations 1 – 3 describe changes in membrane potential at one particular spatial location within a neuron. They do not describe the propagation of action potentials throughout the cell. Modeling the propagation of action potentials is considerably more complex. The standard approach (e.g., Koch, 1999) is to write partial differential equations that describe how the action potential would propagate down a perfect cylinder in the case of an axon or dendrite and throughout a sphere in the case of the soma. The standard partial differential equation that results is called the cable equation (e.g., Koch, 1999). As mentioned earlier, in this approach a neuron is modeled as a collection of cylinders and spheres, each of which is called a compartment. Separate partial differential equations are written for each compartment and all these equations are used to predict how an action potential propagates from a dendrite down to the end of an axon.

Compartment models of this type are highly complex, at least compared to the ordinary differential equations in the Izhikevich (2003) model of Eq. 3, for example. They also make predictions that are far more detailed than could be tested with standard single-unit recording data. Instead they typically require extensive patch-clamp data to test. For most CCN applications, compartment models would be used only to predict the time it takes an action potential to travel from a dendrite to the end of an axon. If this is the goal then simpler alternatives should be used.

In addition to the time it takes a spike to propagate down the length of a neuron there are also significant temporal delays at each synapse. When an action potential reaches the end of an axon, it opens synaptic vesicles, neurotransmitter is released, it diffuses across the synapse, binds to receptors on the postsynaptic membrane, and either opens ion channels in the case of ionotropic receptors or else activates a G-protein in the case of metabotropic receptors. In either case, there is a further delay (longer in the latter case) until the postsynaptic cell is depolarized. In addition to the extra temporal delays they induce, these synaptic processes also temporally smear the effects of the action potential. The action potential is a spike but its postsynaptic effects are not.

The problem is to model the temporal delays of spike propagation and the temporal smearing that occurs at the synapse in a simple way that can be combined with any of the single- or double-equation models of spiking considered above. A standard solution is to use the so-called alpha function (e.g., Rall, 1967). This is the function $f\,[V_A(t)]$ in Eqs. 1 – 3. The idea is that every time the presynaptic cell spikes, the following input is delivered to the postsynaptic cell (with spiking time t = 0):

$$f(t) = \frac{t}{\lambda}\exp\left(\frac{\lambda - t}{\lambda}\right). \quad (4)$$

This function has a maximum value of 1.0 and it decays to .01 at $t = 7.64\lambda$. Thus, λ can be chosen to model any desired temporal delay. If a second spike occurs before $f(t)$ decays to zero then a second alpha function is added to the residual $f(t)$ (again, with time of the second spike t = 0).

6. Learning

There are many forms of neural plasticity that operate over a wide range of different time scales. A complete review of this literature is well beyond the scope of this article (for reviews, see e.g., Malenka & Siegelbaum, 2001; Stanton, Bramham, & Scharfman, 2005). The plasticity-related phenomena that are widely thought to form the neural basis of learning and memory are long-term potentiation (LTP) and long-term depression (LTD) (e.g., Grimwood, Martin, & Morris, 2001). LTP and LTD refer to a long-lasting increase and decrease, respectively, in the efficacy of a synapse, which results from simultaneously stimulating the pre- and postsynaptic neurons. LTP and LTD have been closely studied in many different brain regions and in many different cell types. For computational modeling, it is especially important to understand LTP and LTD at glutamatergic synapses, since glutamate is the most common excitatory neurotransmitter in the brain and virtually all long-range cortical projections are glutamatergic. Sections 6.1 and 6.2 review some biological details of how LTP and LTD are thought to be mediated in the brain, while Sections 6.3 and 6.4 present computational models of these processes. Readers already familiar with (or not interested in) the biological details of LTP and LTD can skip to Section 6.3 without losing the thread of discussion.

6.1 LTP

The most widely studied form of LTP at glutamatergic synapses requires activation of postsynaptic NMDA receptors. Glutamate binds to a number of different types of receptors, but for our purposes these can be divided into two classes – NMDA and non-NMDA (e.g., Nestler, Hyman, & Malenka, 2001). A common member of the non-NMDA class is the AMPA receptor (see Figure 4). The AMPA receptor is mainly a Na^+ channel—that is, when glutamate binds to the AMPA receptor, it opens a channel that allows Na^+ to enter the cell, thereby causing depolarization (top of Figure 4). The NMDA receptor is a channel for Na^+ and Ca^{2+}. However, at resting membrane potentials, an

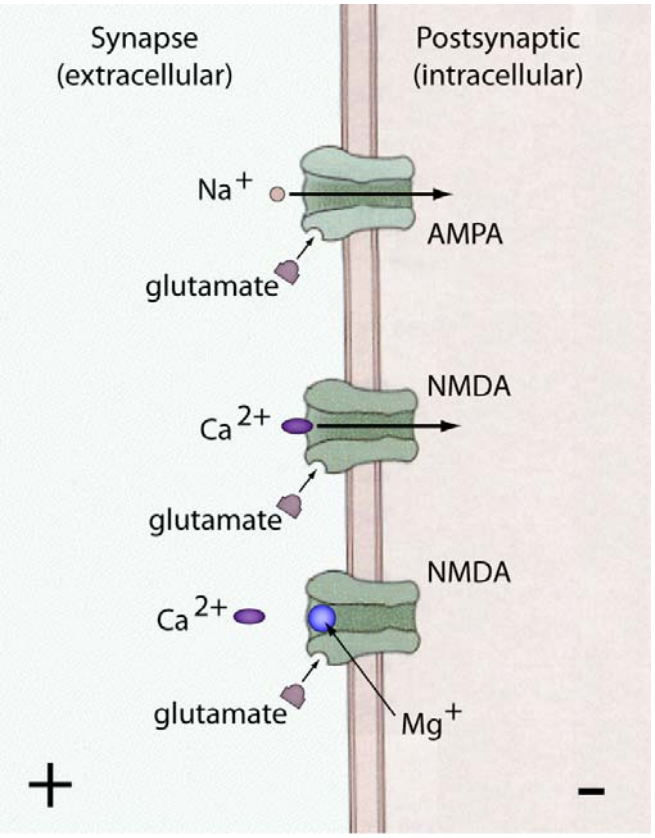

Figure 4. AMPA and NMDA glutamate receptors (Na^+ = sodium, Ca^{2+} = calcium, Mg^+ = magnesium).

extracellular Mg^{2+} plug prevents Na^{+} and Ca^{2+} from entering the cell through the NMDA receptor, even after glutamate binding (bottom of Figure 4). The plug is removed only if the cell is partially depolarized, which might occur, for example, after Na^{+} ions enter through the AMPA receptor. Once a critical level of depolarization is reached, and assuming glutamate is bound to the NMDA receptor, then the Mg^{2+} plug dissociates and Na^{+} and Ca^{2+} ions rush into the cell through the open NMDA channel (middle of Figure 4). From a modeling perspective the practical effect of the Mg^{2+} plug is that the NMDA receptor has a higher threshold for activation than the AMPA receptor.

There is now good evidence that one important synaptic trigger for NMDA-mediated LTP is calcium/calmodulin-dependent protein kinase II (CaMKII). When activated, CaMKII can remain in the active state for an hour or longer and during this time it initiates a variety of processes that eventually increase the efficacy of the synapse (e.g., by increasing the number of AMPA receptors on the same spine; Lisman Schulman, & Cline, 2002).

It takes several seconds before CaMKII becomes fully activated (i.e., phosphorylated) and during this time it is vulnerable to deactivation by certain proteins, such as protein phosphatase 1 (PP-1). The neuromodulator dopamine however, can counteract the inhibiting effects of PP-1. When dopamine is released presynaptically, it binds to postsynaptic D1 receptors and this event triggers a postsynaptic chemical reaction that eventually neutralizes PP-1. As a result, the increased binding of dopamine to D1 receptors potentiates NMDA-mediated LTP. However, these facilitating effects of dopamine are time sensitive because the dopamine must arrive during the critical few seconds when CaMKII is vulnerable to PP-1.

A large literature shows that dopamine neurons in the ventral tegmental area (VTA) and substantia nigra pars compacta (SN_{pc}) increase their firing above baseline following unexpected rewards (e.g., Hollerman & Schultz, 1998; Mirenowicz & Schultz, 1994; Schultz, 1998). Thus, this form of dopamine-enhanced LTP should be in effect following an unexpected reward in any brain region that is a target of VTA or SN_{pc} dopamine neurons and that expresses dopamine D1 receptors. This includes all of frontal cortex but not for example, visual or auditory cortex. In these regions however, there is evidence that acetylcholine may play a modulatory role similar to DA in LTP and LTD (e.g., Gu, 2003; McCoy, Huang, & Philpot, 2009).

6.2 LTD

LTD has not received as much attention as LTP in the literature, and fewer details are known. LTD is produced by a variety of mechanisms, one of which also requires NMDA receptor activation (e.g., Bear & Linden, 2001; Kemp & Bashir, 2001).[2] When the NMDA receptor is weakly activated, intracellular Ca^{2+} levels rise only modestly, and this modest increase potentiates the dephosphorylating effects of PP-1 (O'Dell & Kandel, 1994). In addition to dephosphorylating CaMKII, PP-1 also dephosphorylates AMPA receptors (Lee, Barbarosie, Kameyama, Bear, & Huganir, 2000). In their dephosphorylated state, AMPA receptors are less effective at depolarizing the cell (Derkach, Barria, & Soderling, 1999), and therefore dephosphorylating AMPA receptors weakens the synapse. Thus, when the presynaptic cell fires only weakly, the synapse is weakened.

6.3 Reinforcement Learning

As described above, dopamine modulates synaptic plasticity in any brain region receiving a prominent dopamine projection. From a computational perspective however, the effects of this modulation on learning are likely to differ drastically across brain regions. In the striatum[3], dopamine in the synapse is quickly cleared by dopamine active transporter (DAT). Thus, if some behavior is unexpectedly rewarded, striatal dopamine levels should quickly rise and cortical-striatal synapses that were recently active are likely to be strengthened. Striatal dopamine levels will then quickly fall back to baseline, so synapses that are active prior to a future non-rewarded behavior will likely not be strengthened. These conditions closely match the conditions identified in the machine learning literature as reinforcement learning (Dayan & Abbott, 2001; Sutton & Barto, 1998). Reinforcement learning is critical for skill acquisition because it increases the probability that successful actions are repeated and decreases the probability of unsuccessful actions (Thorndike, 1911). Not surprisingly, many researchers have proposed that dopamine serves as the training signal in striatal-based

[2] Note that more than one form of LTD has been discussed in the literature (e.g., homosynaptic, heterosynaptic). However, homosynaptic LTD is more prominent and the presence of heterosynaptic LTD without support from homosynaptic LTD is still under debate (e.g., Abraham, Logan, Wolff, Benuskova, 2007). Hence, this presentation focuses on homosynaptic LTD.

[3] The striatum is a major input structure within the basal ganglia.

reinforcement learning (e.g., Houk, Adams, & Barto, 1995).

In contrast to the striatum, cortex has almost no DAT. Instead, cortical dopamine is slowly degraded by the enzyme catechol-o-methyl transferase (COMT). COMT works on a much slower time scale than DAT. For example, the delivery of a single food pellet to a hungry rat elevates dopamine levels in prefrontal cortex for approximately 30 minutes (Feenstra & Botterblom, 1996). Thus, whereas striatal dopamine is quickly cleared from the synapse (e.g., Cragg, Rice, & Greenfield, 1997), in frontal cortex and in the hippocampus this process takes much longer (for reviews, see e.g., Seamans & Robbins, 2010; Seamans & Yang, 2004; Tzschentke, 2001). As a consequence, if the first response in a training session receives an unexpected reward, cortical dopamine levels will quickly rise and they are likely to remain elevated throughout the entire session. If the second response in the session is an error, then the residual dopamine from the first (rewarded) response will strengthen inappropriate synapses – namely, those responsible for producing the incorrect response. This would undo the beneficial learning that occurred following a correct response. For this reason, it has been proposed that this poor temporal resolution effectively rules out dopamine as a trial-by-trial reinforcement training signal in cortex (Ashby, Ennis, & Spiering, 2007). Instead, although dopamine might facilitate cortical LTP, there is much evidence that synaptic plasticity at cortical-cortical synapses follows classical Hebbian learning rules (as described in Section 6.4.1.1; for a review, see Feldman, 2009).

6.4 Models of LTP and LTD

The structural changes that accompany LTP and LTD can be modeled in a variety of ways. One critical decision is whether to build a discrete-time or a continuous-time model. This choice largely depends on the nature of the data that the model will be tested against. If the data have a discrete trial-by-trial structure (i.e., the time is reset at the beginning of each trial), as is common in many cognitive-behavioral experiments, then by the Simplicity Heuristic a discrete-time model should be used because no data would exist to test the extra assumptions required of a continuous-time model. On the other hand, when modeling a continuous-time task (i.e., when the time is reset only once, typically at the beginning of the experiment), a continuous-time learning model is required. A cognitive example might be a sequence learning task in which feedback is provided following each response and there is no pause between responses.[4] The next subsection presents examples of learning models that have proven useful in previous modeling efforts. Note that alternative learning rules can be designed as long as they respect the neurobiological constraints listed above.

6.4.1 Discrete-Time Models of Learning

6.4.1.1 Learning at Synapses that Lack Fast Dopamine Reuptake

Discrete-time learning models are considerably simpler than continuous-time models. For example, Ashby et al. (2007) used the following model of LTP and LTD at synapses that lack fast dopamine reuptake (e.g., cortical-cortical synapses). Let $w_{A,B}(n)$ denote the strength of the synapse on trial n between presynaptic unit A and postsynaptic unit B. The following difference equation is used to adjust the strength of this synapse between trials n and n+1:

$$w_{A,B}(n+1) = w_{A,B}(n) + \alpha_w \int f\left[V_A(t)\right] dt \left[\int \left[V_B(t)\right]^+ dt - \theta_{NMDA}\right]^+ \left[w_{\max} - w_{A,B}(n)\right] - \beta_w \int f\left[V_A(t)\right] dt \left\{\left[\theta_{NMDA} - \int \left[V_B(t)\right]^+ dt\right]^+ - \theta_{AMPA}\right\}^+ w_{A,B}(n) \quad (5)$$

where $V_A(t)$ and $V_B(t)$ are the intracellular voltages in the pre- and postsynaptic units at time t, respectively. Note that $\int f\left[V_A(t)\right] dt$ is the integrated alpha function output of the presynaptic unit, where the integral is taken over the time course of the trial. The function $[g(t)]^+$ equals $g(t)$ when $g(t) > 0$, and 0 when $g(t) \leq 0$. Thus, $\int \left[V_B(t)\right]^+ dt$ measures the total instantaneous positive voltage in the postsynaptic unit, since the delays and temporal smearing of the alpha function are omitted. The terms α_w, β_w, θ_{NMDA}, θ_{AMPA}, and w_{max} are all constants. Of these, θ_{NMDA} denotes the threshold for strong activation of the NMDA receptor, and θ_{AMPA} denotes the activation threshold of the AMPA receptor (with $\theta_{NMDA} > \theta_{AMPA}$). The second (positive) term describes the conditions under which LTP occurs (postsynaptic activation great enough to strongly activate the NMDA receptor) and the third (negative) term describes conditions that produce LTD (postsynaptic activation above the AMPA threshold but below the threshold for strong NMDA activation). Note that this model assumes that the change in synaptic strength is proportional to the product of the pre- and postsynaptic activations (and the final rate limiting term that prevents the strength of the

[4] For a more thorough discussion of time, and its consequences on CCN modeling, see Meeter et al. (2007).

synapse from exceeding w_{max}). The constants α_w and β_w are learning rates. In brain regions that are targets of dopamine but that lack fast dopamine reuptake, such as frontal cortex, these parameters might be assumed to fluctuate with dopamine levels.

This model is closely related to the machine learning construct of Hebbian learning. In modern forms of Hebbian learning, the LTD term in Eq. 5 is known as the anti-Hebbian term (Földiák, 1990). The Eq. 5 model is also closely related to the BCM model proposed by Bienenstock, Cooper, and Munro (1982). The primary difference is that the BCM model also allows the threshold for LTP (i.e., θ_{NMDA}) to vary as a function of prior activation history. For example, there is evidence that this threshold can decrease following prolonged periods of low activity and increase following prolonged periods of high activity (Kirkwood, Rioult, & Bear, 1996). Such flexibility could be added to the current model by allowing θ_{NMDA} to vary across conditions.

6.4.1.2 Learning at Synapses with Fast Dopamine Reuptake

In the striatum, dopamine reuptake is fast, so at cortical-striatal synapses LTP and LTD follow a form of reinforcement learning. Ashby and Crossley (2011) proposed the following discrete-time model of synaptic plasticity at cortical-striatal synapses.

$$\begin{aligned} w_{A,B}(n+1) = w_{A,B}(n) &+ \alpha_w \int f\left[V_A(t)\right]dt\left[\int\left[V_B(t)\right]^+ dt - \theta_{NMDA}\right]^+ \left[D(n) - D_{base}\right]^+ \left[w_{\max} - w_{A,B}(n)\right] \\ &- \beta_w \int f\left[V_A(t)\right]dt\left[\int\left[V_B(t)\right]^+ dt - \theta_{NMDA}\right]^+ \left[D_{base} - D(n)\right]^+ w_{A,B}(n) \\ &- \gamma_w \int f\left[V_A(t)\right]dt\left\{\left[\theta_{NMDA} - \int\left[V_B(t)\right]^+ dt\right]^+ - \theta_{AMPA}\right\}^+ w_{A,B}(n) \end{aligned} \quad (6)$$

where $w_{A,B}(n)$ denotes the strength of the synapse on trial n between cortical unit A and striatal unit B. D_{base} is the baseline dopamine level, $D(n)$ is the amount of dopamine released following feedback on trial n, and α_w, β_w, γ_w, θ_{NMDA}, θ_{AMPA}, and w_{max} are all constants. The first line describes the conditions under which LTP occurs (striatal activation above the threshold for strong NMDA receptor activation and dopamine above baseline) and lines two and three describe conditions that produce LTD. The first possibility (line 2) is that postsynaptic activation is strong but dopamine is below baseline, as for example, one would expect on trials when an error occurred. The last line (line 3) implements LTD on trials when postsynaptic activation is weak – that is, above the AMPA threshold but below the NMDA threshold. Note that this term is independent of dopamine levels. Thus, weak postsynaptic activation causes LTD regardless of whether the response was correct or incorrect. Finally, note that synaptic strength does not change if postsynaptic activation is below the AMPA threshold.

The conditions assumed in Eq. 6 for LTP to occur (i.e., first line) are well accepted and essentially model the processes described in Section 6.1. The second form of LTD described in Eq. 6 (line 3) also has empirical support (Ronesi & Lovinger, 2005). Line 2 however, is more speculative. There is solid evidence for LTD at cortical-striatal synapses (Shen, Flajolet, Greengard, & Surmeier, 2008), possibly mediated by dopamine D2 receptors, but these effects are complex. For example, other neurotransmitter systems are likely involved (e.g., acetylcholine and nitrous oxide; Calabresi, Picconi, Tozzi, & Di Filippo, 2007; Kreitzer & Malenka, 2008; Wang et al., 2006). Currently, the Eq. 6 model does not violate the Neuroscience Ideal, but as more is learned about the conditions that produce LTP and LTD at cortical-striatal synapses, this is likely to change. When a clearer picture emerges, Eq. 6 should be revised accordingly.

6.4.1.3 Modeling dopamine release

The Eq. 6 model of reinforcement learning requires that we specify the amount of dopamine released on every trial in response to the feedback signal [the $D(n)$ term]. The more the dopamine level increases above baseline (D_{base}), the greater the increase in synaptic strength, and the more it falls below baseline, the greater the decrease.

Although there are a number of powerful models of dopamine release, Eq. 6 requires only that we specify the amount of dopamine released to the feedback signal on each trial. The key empirical results are (e.g., Schultz, Dayan, & Montague, 1997; Tobler, Dickinson, & Schultz, 2003): 1) midbrain dopamine cells fire tonically, 2) dopamine release increases above baseline following unexpected reward, and the more unexpected the reward the greater the release, and 3) dopamine release decreases below baseline following unexpected absence of reward, and the more unexpected the absence, the greater the decrease. One common interpretation of these results is that over a wide range, dopamine firing is proportional to the reward prediction error (RPE):

$$\text{RPE} = \text{Obtained Reward} - \text{Predicted Reward}. \quad (7)$$

A simple model of dopamine release can be built by specifying how to compute Obtained Reward, Predicted Reward, and exactly how the amount of dopamine release is related to the RPE. The Ashby and Crossley (2011) solution to these three problems is as follows. If reward valence is not varied, then a simple model can be

used to compute obtained reward. Specifically, define the obtained reward R_n on trial n as +1 if correct or reward feedback is received, 0 in the absence of feedback, and -1 if error feedback is received.

Predicted reward can be computed from a simplified version of the well-known Rescola-Wagner (1972) model. Let P_n denote the Predicted Reward on trial n. Then according to this account

$$P_{n+1} = P_n + \eta(R_n - P_n). \quad (8)$$

where η is a constant (in Ashby & Crossley, 2011, η = 0.075). It is well known that when computed in this fashion, P_n converges exponentially to the expected reward value and then fluctuates around this value until reward contingencies change.

Ashby and Crossley (2011) assumed that the amount of dopamine release is related to the RPE in the manner reported by Bayer and Glimcher (2005). Specifically, they assumed that

$$D(n) = \begin{cases} 1 & \text{if RPE} > 1 \\ .8\,\text{RPE} + .2 & \text{if } -.25 \le \text{RPE} \le 1 \\ 0 & \text{if RPE} < -.25 \end{cases} \quad (9)$$

Note that the baseline dopamine level is .2 (i.e., when the RPE = 0) and that dopamine levels increase linearly with the RPE. However, note also the asymmetry between dopamine increases and decreases. As is evident in the Bayer and Glimcher (2005) data, a negative RPE quickly causes dopamine levels to fall to zero, whereas there is a considerable range for dopamine levels to increase in response to positive RPEs.

6.4.2 Continuous-Time Models of Learning

If a continuous-time model is needed, then more detail must be added to these models. For example, the evidence is good that the magnitude and even the direction of plasticity at a synapse depends not only on the magnitude of the pre- and postsynaptic activations, but also on the timing. This phenomenon is known as spike-timing dependent plasticity. Considerable data show that if the presynaptic neuron fires just before the postsynaptic neuron then LTP occurs, whereas if the postsynaptic cell fires first then LTD occurs (e.g. Bi & Poo, 2001; Sjöström, Rancz, Roth, & Häusser, 2008). Furthermore, the magnitude of both effects seems to fall off exponentially as the delay between the spikes in the pre- and postsynaptic neurons increases. Let T_{pre} and T_{post} denote the time at which the pre- and postsynaptic cells fire. Then a popular model of spike-timing dependent plasticity (e.g., Zhang, Tao, Holt, Harris, & Poo, 1998) assumes that the scaling factor on the magnitude of LTP/LTD equals

$$\Delta = \begin{cases} e^{-(T_{post} - T_{pre})/TM_+} & \text{if } T_{post} - T_{pre} > 0 \\ -e^{(T_{post} - T_{pre})/TM_-} & \text{if } T_{post} - T_{pre} < 0 \end{cases}. \quad (10)$$

where TM_+ and TM_- are constant. The idea is that the magnitude of LTP is computed based on the strength of the pre- and postsynaptic activations, for example by using Eq. 5 or 6, and then this value is multiplied by Δ.

For continuous-time models of reinforcement learning, a more detailed model of dopamine release is required. The model described in Section 6.4.1.3 only specifies how much dopamine is released on each trial. It does not specify when this dopamine is released. A number of much more detailed models have been proposed that mimic the dynamics of dopamine release (Best, Nijhout, & Reed, 2009; Brown, Bullock, & Grossberg, 1999; Houk et al., 1995; Tan & Bullock, 2008). One of these could be incorporated to model the dynamics of dopamine release more accurately (if such data are to be accounted for by the CCN model, as per the Simplicity Heuristic).

6.4.3 Local versus global learning rules

Learning rules in neural network models can be classified as local or global. Local rules, like backpropagation, modify every synapse using a different error signal. In contrast, global learning rules use the same error signal at every synapse. The learning models described in this section are all global rules. For example, each dopamine neuron (in the SN_{pc}) projects to many medium spiny neurons[5] in the striatum. Thus, following feedback, roughly equal amounts of dopamine will be released at all of these synapses, regardless of whether they were recently active or inactive. The evidence is good that most of the brain uses global learning rules. The one notable exception seems to be at synapses between parallel fibers and Purkinje cells in the cerebellum, which are thought to be modified in a form of supervised learning where the unique training signal is supplied by cerebellar climbing fibers (Houk, 2010; Jörntell & Hansel, 2006).

One dangerous property of global learning is that it can lead to an attractor state in which response accuracy is constrained to remain at chance. Consider a simple two-stimulus, two-response task in which the network must learn to emit one response if stimulus A is presented and another response if stimulus B is

[5] Medium spiny neurons are GABAergic and represent ~ 96% of the neurons in the striatum.

presented. Suppose this learning is mediated via a process in which, after training, stimulus A activates one striatal medium spiny neuron more strongly than the others. On each trial, the cell with the highest activation makes the response (when there is a tie, the response is chosen randomly). In CCN models this requires that the strength of the cortical-striatal synapse at the correct medium spiny neuron increase more during training than the strength at any competing synapses. Initially we expect the unit or units in sensory cortex that encode the perceptual representation of stimulus A to project to multiple medium spiny neurons with approximately equal synaptic strength. If two synaptic strengths are equal, then the pre- and postsynaptic activations will be identical at these two synapses (since the presynaptic activation is from the same cortical unit), and therefore any global learning algorithm will specify an equal amount of strengthening or weakening of these synapses on every trial, regardless of whether the response was correct or incorrect. Thus, if there is no noise then once the weights become equal they must remain equal for all time, thereby preventing the network from learning the desired associations. Adding noise to the postsynaptic activation breaks the model free from this attractor state. When noise is added, the postsynaptic activations at the two synapses will not be the same, even if the presynaptic activations and synaptic strengths are identical. As long as the postsynaptic activations are different, the change in synaptic strength will be different at the two synapses.

A second but equally important consideration when using global learning rules is lateral inhibition. Because all synapses are modified using the same error signal, global learning rules work best when only a few units are activated. This way, only those synapses that are most directly responsible for the behavior are significantly modified. One biologically plausible method of reducing the number of active units is via lateral inhibition (Bogacz, Usher, Zhang, & McClelland, 2007). In the brain, lateral inhibition among competing excitatory neurons is most commonly mediated via projections of these excitatory neurons onto inhibitory (e.g., GABAergic) interneurons.

Lateral inhibition is often more efficacious in the presence of noise (which increases activation differences), and when activation in a unit has an immediate effect on other competing units. Recall that the alpha function from Eq. 4 delays downstream activation effects. Therefore, to reduce this delay in inhibitory interneurons, a smaller value of λ should be used in the interneuron alpha function than when modeling projection neurons that connect separate brain regions. This is biologically justified because (1) projection neurons tend to have much longer axons than interneurons (e.g., stellate cells) and, (2) GABA receptors, which are frequent targets of interneurons, generally have faster effects than glutamate receptors, which are common targets of projection neurons. Some of the delay modeled by the alpha function is the time it takes action potentials to propagate down the axon and synaptic delays.

7. Generating behavior

The models described so far predict how neural activation changes in specific brain regions under different experimental conditions. Of course, neural activations are not behaviors, so to account for behavioral data with these models, some assumptions must be added that describe how neural activation is related to behavior. In most cases, this process involves three steps. The first is to identify which brain region in the hypothesized network controls the behavioral response – that is, one must decide where to place the decision units. The second step is to decide, in each unit, what function of neural activity should drive the decision. For example, should the decision be based on the number of spikes, or the spiking rate, or perhaps on the integrated membrane potential? Finally, in tasks with multiple response alternatives, the third step is to decide how to resolve the competition among the various competing units in the critical brain region.

7.1 Step 1. What brain region controls behavior?

The decision about where to place the decision units depends on one's knowledge of the task and the relevant neuroscience literature, and on one's modeling goals. In tasks that require finger or arm movements, typical choices would be the supplementary motor area, dorsal or ventral premotor cortex, or primary motor cortex. In contrast, if the task requires an eye movement response then the critical area may be in the lateral intraparietal area, the supplementary eye fields, the frontal eye fields, or the superior colliculus. On the other hand, in many cases the goal may be to model cognition rather than the specific motor response that implements the outcome of the relevant cognitive processes. Ignoring motor processing simplifies the modeling because all areas downstream of the critical cognitive region can be omitted. Note that this strategy will underestimate response time since some key synapses will be omitted, but it might not affect accuracy predictions at all, especially in tasks where errors are due to cognitive failures, rather than to simple motor errors. For example, models of working memory typically assume that the key decision units are in prefrontal cortex (e.g., Ashby et al., 2005; Frank, Loughry, & O'Reilly, 2001), since an

extensive literature implicates the prefrontal cortex as the most critical site for working memory. As a result, models of working memory often grossly oversimplify or omit altogether projections from prefrontal cortex to premotor and motor cortices.

7.2 Step 2. What function of neural activity drives the decision?

After the anatomical location of the decision units has been selected, the next step is to decide what function of activity in these units will initiate the behavior. In general there are three popular choices, the feasibility of which may depend on which model of individual neural activity is used. The intracellular choice is integrated neural activation. This is a common choice if the integrate-and-fire model is used for each unit in the network. Recall that in the integrate-and-fire model (see Section 5.1), a threshold is set on the solution of Eq. 1 and a spike is generated when this threshold is exceeded. To select a response, this same algorithm could be used, although typically a different threshold would be set for initiating a spike as opposed to a motor response. This method is problematic with the Izhikevich (2003) model because in that model activation [i.e., V_B (t) in Eq. 3] is meant to model intracellular voltage, and thus is negative when the unit is at rest. Another problem with this method is conceptual. At best, we expect the motor response to be driven by the output of the units in the decision region. Intracellular activation is not output. Thus, using the integrated intracellular activation to initiate a behavior removes the decision from the actual neural events that trigger that behavior by at least one unnecessary step.

A second choice is to use spiking behavior in the decision units to initiate model behaviors. For example, a threshold could be set on the number of spikes emitted by the decision unit, with a behavioral response occurring when this threshold is first exceeded. Spikes are closer to the output of the unit than intracellular activation, which is an advantage. However, spike number is a discrete variable, which introduces a discontinuity that can complicate the parameter estimation process. Also, as discussed in Section 5.4, the postsynaptic effect of neural activity in the decision unit is not a series of spikes. The neurochemical and physical nature of the synapse causes a temporal smearing of the spike trains.

A third choice that avoids these weaknesses is to use the integrated output alpha function:

$$\int_0^t f\left[V_B(t)\right]dt\,. \qquad (11)$$

where f [ ] is defined in Eq. 4. For example, a threshold could be set on this integral and a behavior initiated when this threshold is first exceeded. This decision variable is continuous and as close to the behavior as possible without adding another downstream unit to the model. Note that the integral in Eq. 11 is taken over a single neuron, but in the real brain there is redundancy and it is likely that more than one neuron computes this integral simultaneously. In this case, the integral should be over multiple neurons. However, in practice, one neuron is often simulated for each response and Eq. 11 is used.

7.3 Step 3. How is a response selected when there are multiple alternatives?

There has been considerable work on this problem in the field of neuroscience over the past decade or so. Especially illuminating have been studies in which single-unit recordings were made from putative decision neurons during a task in which an animal had to select among competing motor responses on each trial (for reviews, see e.g., Bogacz, Wagenmakers, Forstmann, & Nieuwenhuis, 2009; Rangel & Hare, 2010; Wang, 2008). For example, in an early and influential study, Shadlen and Newsome (2001) reported that neurons in the lateral intraparietal area reliably predicted the eye-movement response of monkeys in a task that required the animals to determine the direction of motion of random dot patterns. Furthermore, these neurons displayed the push-pull profile that one might expect from a classic diffusion process – that is, neurons that predicted a movement of the eyes to the right increased their firing rate when the correct response to the stimulus was a rightward movement and decreased their firing rate when the stimulus signaled a leftward movement. The formal correspondence between these properties and the diffusion process was quickly noted (e.g., Smith & Ratcliff, 2004).

Of course, generalizing the diffusion model to more than two alternatives is not straightforward, but it is well known that an accumulator or race model with lateral inhibition among the channels mimics a diffusion process (Bogacz et al., 2007; Usher & McClelland, 2001). Thus, in tasks with more than two response alternatives, a sound yet reasonably simple solution is to set a criterion on each decision unit and allow the first unit that crosses this threshold to control the response, but also to build in lateral inhibition among all decision units (McMillen & Holmes, 2006; Usher, Olami, & McClelland, 2002).

8. A Complete Example

There are many recent examples of the CCN approach (e.g., Ashby et al., 2005; Chadderdon & Sporns, 2006; Frank, 2006; Frank & Claus, 2006; Hartley, Burgess, Lever, Cacucci, & O'Keefe, 2000; Monchi, Taylor, & Dagher, 2000; O'Reilly & Frank, 2006; Reynolds & O'Reilly, 2009). For illustrative purposes consider the model proposed by Ashby and Crossley (2011) to account for context effects in striatal-mediated learning. A simplified version of the architecture of the model is shown in Figure 5. Briefly, the idea is that a key component of striatal-mediated learning is provided by cholinergic interneurons in the striatum known as TANs (i.e., Tonically Active Neurons). The TANs are assumed to exert a tonic inhibitory influence over cortical inputs to the striatum that prevents the execution of any striatal-dependent actions. The model assumes that the TANs learn to pause in rewarding environments, and this pause releases the striatal output neurons from this inhibitory effect, thereby facilitating the learning and expression of striatal-dependent behaviors. When rewards are no longer available, the TANs cease to pause, which protects striatal learning from decay. The model accounts for a variety of single-cell recording data, and some classic behavioral phenomena, including fast reacquisition following extinction.

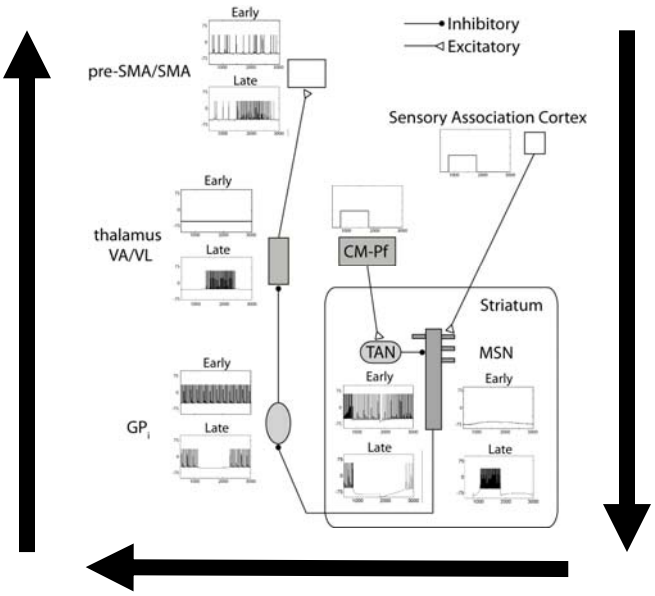

Figure 5. The neural architecture of the Ashby and Crossley (2010) model in a task with one response alternative. The thick black arrows represent the information flow. Also shown are activations from trials early and late in training, i.e., before and after the TAN has learned that the environment is rewarding. Initially the stimulus does not cause the TAN to pause, and therefore the MSN does not fire to stimulus presentation. As a result, the firing rate of the premotor unit (pre-SMA/SMA) does not change after stimulus onset. After training, the TAN pauses to the stimulus, which releases the MSN from its tonic inhibition. This allows the MSN to fire to the stimulus, which causes the firing rate in pre-SMA/SMA to increase above baseline (SMA = supplementary motor area, VA = ventral anterior nucleus of the thalamus, VL = ventral lateral nucleus of the thalamus, CM-Pf = centremedian and parafascicular nuclei of the thalamus, GP_i = internal segment of the globus pallidus, MSN = medium spiny neuron, TAN = tonically active neuron).

All projections shown in Figure 5 are known to exist. All projections labeled as excitatory are known to be glutamatergic, and so are unambiguously excitatory. Except for the projections from the TAN to the medium spiny neurons, all projections labeled as inhibitory are known to be GABAergic, and so are unambiguously inhibitory. There are three aspects of Figure 5 that could be considered speculative. First, many projections and brain areas are omitted from the model. Second, the TAN projections to the medium spiny neurons are known to be cholinergic and acetylcholine can have either excitatory or inhibitory effects depending on the postsynaptic receptor it activates. The inhibitory label on this projection in Figure 5 is based on data showing that TAN activation reduces the effects of cortical activation on medium spiny neuron firing (e.g., Pakhotin & Bracci, 2007). Even so, there is evidence that TAN activation also has postsynaptic excitatory effects (Gabel & Nisenbaum, 1999) that are omitted from the model.

Third, and most important, the functions ascribed to the network shown in Figure 5 are speculative. This last point is especially important because it is a characteristic of all CCN models. Neuroanatomical studies do not ascribe function to the networks they identify. To understand the function of a network, one must relate its activity to the behavior that it controls. This is the goal of CCN modeling, so it will almost always be the case that CCN models assign a speculative function to a (hopefully) known neural network.

After settling on the architecture shown in Figure 5, the next challenge was to build a model of TAN firing. The TANs are challenging to model, because they have unusual dynamics. For example, when excitatory input is delivered to the TANs, they fire an initial burst and then pause (Kimura, Rajkowski, & Evarts, 1984; Reynolds, Hyland, & Wickens, 2004). This is clearly seen in the top panel of Figure 6, which shows an *in vivo* intracellular recording from a single TAN of an anesthetized rat (from Reynolds et al., 2004). In this

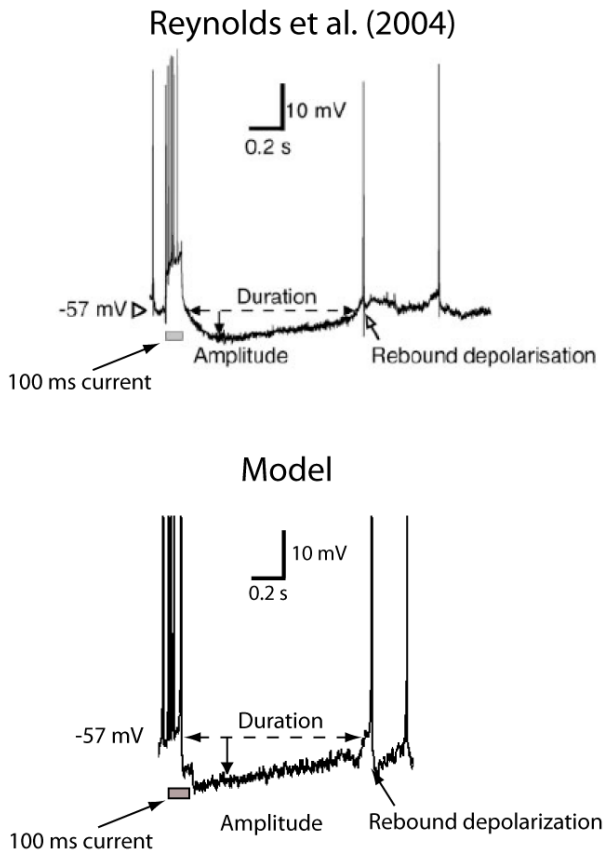

Figure 6. Patch-clamp recording from the TAN of a rat (top panel; from Reynolds et al., 2004) and simulated responses of the Ashby and Crossley (2010) TAN model (bottom panel) during a patch clamp experiment when positive current is injected into the cell for 100 ms (denoted by the solid gray rectangle).

experiment, a suprathreshold positive current of 100 ms duration was injected into the cell (denoted by the small gray bar in the figure). Figure 6 shows that the TAN responded with an initial burst followed by a prolonged after-hyperpolarization that caused a pause in firing that persisted for approximately 900 ms.

Ashby and Crossley (2011) developed a model of TAN firing that displays these same qualitative properties by modifying the Izhikevich (2003) model of intrinsically bursting cortical neurons (Eq. 3). The bottom panel of Figure 6 shows the response of this model under the same experimental conditions that were used to collect the recordings in the top panel. Note that the model also fires a burst to the injected current and then pauses for roughly 900 ms. Thus, the model displays the same temporal dynamics as real TANs. The medium spiny neurons in the network were also modeled via the Izhikevich (2003) two-equation model (Eq. 3). This is because the model was tested against single-unit recording data from real medium spiny neurons. The model was only tested against single-unit recordings from TANs and medium spiny neurons, so all other units in the network were modeled with the single-equation quadratic integrate-and-fire model (Eq. 2). The only synapses in the model displaying synaptic plasticity were at cortical – medium spiny neuron synapses and at the CM-Pf – TAN synapse. Evidence suggests that at both types of synapses, LTP and LTD follows dopamine-mediated reinforcement learning rules (Aosaki, Graybiel, & Kimura, 1994a; Arbuthnott, Ingham, & Wickens, 2000; Calabresi, Pisani, Mercuri, & Bernardi, 1996; Reynolds & Wickens, 2002; Suzuki, Miura, Nishimura, & Aosaki, 2001). Thus, learning at these synapses was modeled via Eqs. 6 – 9.

Figure 5 also illustrates an application of the entire model to a simple conditioning task in which the participant must execute some specific response (e.g., button press) when a certain sensory cue is presented (e.g., a tone) in order to receive a reward. Figure 5 shows activation in each brain region in the model during two trials of the experiment – one early in training and one late in training – before and after the model has learned to respond reliably to the sensory cue. Note that the CM-Pf and sensory cortex activations are both modeled as simple square waves that are assumed to coincide with the stimulus presentation. Initially the TAN has not yet learned that the cue is associated with reward, so it fails to pause when the stimulus is presented. As a result of the tonic inhibition from the TAN, the medium spiny neuron does not fire to the stimulus, although stimulus presentation does move it from the down state to the up state.[6] In the absence of any inhibitory input from the striatum, the globus pallidus[7] does not slow its high spontaneous firing rate, and therefore the thalamus is prevented from firing to other excitatory inputs. The network is assumed to make a behavioral response when the firing rate in any premotor unit first exceeds a threshold (as described in Section 7). In this example, the premotor unit fires at a slow tonic rate, but note that this rate does not increase during stimulus presentation. As a result, the model does not respond on this trial. Later in training, however, the TAN pauses when the stimulus is presented. This pause allows the medium spiny neuron to fire a vigorous burst, which inhibits the globus pallidus. The pause in pallidal firing allows the thalamus to respond to its other excitatory inputs, and the resulting burst from the thalamus drives the firing rate in the premotor unit above the response threshold. The model now responds to the sensory cue.

[6] The up and down states refer to intracellular voltage that are below the spiking threshold. In the up state, the spiking threshold is reduced, and a smaller input is required to produce a spike.

[7] The globus pallidus is a major basal ganglia output structure.

The spiking data shown in Figure 5 could also be used to test the model against fMRI BOLD responses. Logothetis and colleagues reported evidence that the BOLD response is more closely related to local field potentials than to the spiking output of individual neurons (Logothetis, 2003; Logothetis, Pauls, Augath, Trinath, Oeltermann, 2001). Local field potentials integrate the field potentials produced by small populations of cells over a sub-millimeter range, and they vary continuously over time. So to test the model against fMRI data, the first step is to convert from the spiking data shown in Figure 5 to local field potentials. This can be done by low-pass filtering the Figure 5 spike trains. Next, the methods of Ashby and Waldschmidt (2008) can be used to test the model against BOLD responses collected in an experiment (see also Anderson et al., 2008). First, the local field potentials predicted by the model are transformed to predicted BOLD responses by numerically convolving the local field potentials with a hemodynamic response function (or by using a nonlinear method, such as Volterra kernels; e.g., see Ashby, 2011). The second step is to identify exactly which voxels should be used to provide the data that the model will be tested against. The third and final step is to compare the observed and predicted BOLD responses in each of these voxels.

The model can also now be tested against single-unit recording data from any brain region included in the model or against behavioral data. For example, Ashby and Crossley (2011) showed that the model provides good accounts of single-unit recording data collected from TANs of monkeys before and after conditioning (Aosaki et al., 1994b), from medium spiny neurons of a rat during the conditioning, extinction, and reacquisition of an instrumental response (Barnes, Kubota, Hu, Jin, & Graybiel, 2005), and from medium spiny neurons of a monkey during category learning. In addition, they showed that, at the behavioral level, the model correctly predicts that reacquisition following extinction occurs much faster than original acquisition, which is among the best known phenomena in the conditioning literature.

The model highlighted here has considerable biological detail but it lacks some types of complexity that are common in many other models. For example, even when applied to more complex tasks, each brain region in the Figure 5 model includes only a few units and the model is essentially feedforward – that is, it includes no recurrent projections that could cause reverberation or synchronous firing. It is important to note however, that these limitations hold for this example, but not for the CCN approach in general. CCN models like the one shown in Figure 5 could be constructed with many units in each region and with recurrent projections. For example, using the Eq. 3 model for each individual unit, Izhikevich (2005) constructed a model that included as many units as there are neurons in the human brain (i.e., 10^{11}) and approximately 10^{15} synapses. Simulations of this model were excessively time consuming (i.e., 50 days on a beowulf cluster of 27 processors were required to simulate 1 second of activity), so such large-scale simulations are currently of limited value in psychology. Nevertheless, this huge model illustrates that there really are no upper limits on the complexity of CCN models.

9. Conclusions

Compared to purely cognitive models, CCN models have several important advantages. First, whereas cognitive models are limited to making predictions about purely behavioral dependent measures (i.e., accuracy and response time), CCN models should also be able to make predictions about other types of data. Included in this list are data collected using fMRI, EEG, TMS, and single-unit recordings. In addition, neuroscience models can often make predictions about how drugs, genes, and focal lesions affect behavior.

Second, grounding a model in neuroscience adds a huge number of constraints that can be used to rapidly confirm or falsify the model, and therefore quickly improve our understanding of the scientific domain under study (as described in Section 4). With only behavioral results to supply constraints, cognitive models are difficult to differentiate. For example, many studies have shown that people are exquisitely sensitive to across-trial correlations between features during category learning. This result is so well accepted that it must be predicted by any complete theory of human categorization. The problem is that many alternative computational models can account for this result (e.g., exemplar models, Medin, Altom, Edelson, & Freko, 1982; decision bound models, Maddox & Ashby, 1993). The same is true for many other purely behavioural results. For this reason, when the major theories in a field attend only to behavioral phenomena, it seems likely that there will be many alternative models that seem almost equally viable. In such an unsettled world, it can be difficult to see progress.

In contrast, by building models that are based in neuroscience, cumulative progress may become easier. For example, many studies have shown that the striatum is critical to category learning. This result is now so well established that any theory of category learning that attends to neuroscience must assign some key role to the striatum. Since the neuroanatomy of the striatum is well understood, along with its major inputs and outputs, this means that any neuroscience-sensitive theory of category learning must converge on a similar architecture. More

details will be added, and a somewhat different computational role might be assigned to certain components, but it is unlikely that this basic architecture will disappear from any future theory. Continuity of this type can facilitate progress.

CCN is not meant to replace the cognitive modeling that has dominated mathematical psychology since its inception. There are still many behavioral phenomena where a CCN approach is premature. In most cases, a more detailed understanding of the behavior is required to build a CCN model as compared to a more traditional cognitive model. CCN modeling requires a good understanding of the cognitive processes that mediate the behavior, but also an understanding of how these processes are mediated in the brain. Thus, rather than serve as competitors, CCN and cognitive modeling are complementary. Cognitive modeling results will often be critical to the process of building up the knowledge base needed to develop a CCN model. Likewise, cognitive modelers can use CCN to more rigorously test and refine their models.

References

Abraham, W. C., Logan, B., Wolff, A., & Benuskova, L. (2007). "Heterosynaptic" LTD in the dentate gyrus of anesthetized rat requires homosynaptic activity. *Journal of Neurophysiology*, *98*, 1048-1053.

Anderson, J. R., Fincham, J. M., Qin, Y., & Stocco, A. (2008). A central circuit of the mind. *Trends in Cognitive Sciences*, *12*, 136-143.

Aosaki, T., Graybiel, A. M., & Kimura, M. (1994a). Effect of the nigrostriatal dopamine system on acquired responses in the striatum of behaving monkeys. *Science, 265,* 412-415.

Aosaki,T., Tsubokawa, H., Ishida, A., Watanabe, K., Graybiel, A.M. & Kimura, M. (1994b). Responses of tonically active neurons in the primate's striatum undergo systematic changes during behavioral sensorimotor conditioning. *Journal of Neuroscience, 14,* 3969-3984.

Arbuthnott, G. W., Ingham, C. A., & Wickens, J. R. (2000). Dopamine and synaptic plasticity in the neostriatum. *Journal of Anatomy*, *196*, 587–596.

Ashby, F. G. (1982). Deriving exact predictions from the cascade model. *Psychological Review*, *89*, 599–607.

Ashby, F. G. (2011). *Statistical analysis of fMRI data*. Cambridge, MA: MIT Press.

Ashby, F. G., Alfonso-Reese, L. A., Turken, A. U., & Waldron, E. M. (1998). A neuropsychological theory of multiple systems in category learning. *Psychological Review*, *105*, 442-481.

Ashby, F. G., & Crossley, M. J. (2011). A computational model of how cholinergic interneurons protect striatal-dependent learning. *Journal of Cognitive Neuroscience*, *23*, 1549-1566.

Ashby, F. G., Ell, S. W., Valentin, V., & Casale, M.B. (2005). FROST: A distributed neurocomputational model of working memory maintenance. *Journal of Cognitive Neuroscience, 17*, 1728-1743.

Ashby, F. G., Ell, S. W., & Waldron, E. M. (2003). Procedural learning in perceptual categorization. Memory & Cognition, 31, 1114-1125.

Ashby, F. G., Ennis, J. M., & Spiering, B. J. (2007). A neurobiological theory of automaticity in perceptual categorization. *Psychological Review*, *114*, 632-656.

Ashby, F. G., & Maddox, W. T. (1993). Relations between prototype, exemplar, and decision bound models of categorization. *Journal of Mathematical Psychology*, *37*, 372-400.

Ashby, F. G., & Maddox, W. T. (2005). Human category learning. *Annual Review of Psychology, 56,* 149-178.

Ashby, F. G., Waldschmidt, J. G. (2008). Fitting computational models to fMRI data. *Behavior Research Methods, 40, 713-721.*

Barnes, T. D., Kubota, Y., Hu, D., Jin, D. Z., & Graybiel, A. M. (2005). Activity of striatal neurons reflects dynamic encoding and recoding of procedural memories. *Nature, 437*, 1158-1161.

Bayer, H. M. & Glimcher, P. W. (2005). Midbrain dopamine neurons encode a quantitative reward prediction error signal. *Neuron, 47,* 129-141.

Bear, M. F., & Linden, D. J. (2001). The mechanisms and meaning of long-term synaptic depression in the mammalian brain. In In W. M. Cowan, T. C. Südhof, & C. F. Stevens (Eds.), *Synapses* (pp. 455-517). Baltimore, MD: Johns Hopkins University Press.

Best, J. A., Nijhout, H. F., & Reed, M. C. (2009). Homeostatic mechanisms in dopamine synthesis and release: A mathematical model. *Theoretical Biology and Medical Modelling, 6*, 21-41.

Bhalla, U. S., & Bower, J. M. (1993). Exploring parameter space in detailed single cell models: Simulations of the mitral and granule cells of the olfactory bulb. *Journal of Neurophysiology*, *69*, 1948 –1965.

Bi, G., & Poo, M. (2001). Synaptic modification of correlated activity: Hebb's postulate revisited. *Annual Review of Neuroscience*, *24*, 139-166.

Bienenstock, E. L., Cooper, L. N., & Munro, P. W. (1982). Theory for the development of neuron selectivity: Orientation specificity and binocular interaction in visual cortex. *Journal of Neuroscience*, *2*, 32–48.

Bogacz, R., Usher, M., Zhang, J., & McClelland, J. L. (2007). Extending a biologically inspired model of choice: multi-alternatives, nonlinearity and value-based multidimensional choice. *Philosophical*

Transactions of the Royal Society of London. Series B, Biological Sciences, *362*, 1655-1670.

Bogacz, R., Wagenmakers, E.-J., Forstmann, B. U., & Nieuwenhuis, S. (2009). The neural basis of the speed–accuracy tradeoff. *Trends in Neurosciences*, *33*, 10-16.

Brown, J., Bullock, D., & Grossberg, S. (1999). How the basal ganglia use parallel excitatory and inhibitory learning pathways to selectively respond to unexpected rewarding cues. *Journal of Neuroscience, 19,* 10502-10511.

Calabresi, P., Picconi, B., Tozzi, A., & Di Filippo, M. (2007). Dopamine-mediated regulation of corticostriatal synaptic plasticity. *Trends in Neurosciences*, *30*, 211-219.

Calabresi, P., Pisani, A., Mercuri, N. B., & Bernardi, G. (1996). The corticostriatal projection: from synaptic plasticity to dysfunctions of the basal ganglia. *Trends in Neurosciences*, *19*, 19-24.

Chadderdon, G., & Sporns, O. (2006). A large-scale neurocomputational model of task-oriented behavior selection and working memory in prefrontal cortex. *Journal of Cognitive Neuroscience*, *18*, 242-257.

Cohen, J. D., Braver, T. S., & O'Reilly, R. C. (1996). A computational approach to prefrontal cortex, cognitive control, and schizophrenia: Recent developments and current challenges. *Philosophical Transactions of the Royal Society, Series B, 351,* 1515-1527.

Cohen, J. D., & Servan-Schreiber, D. (1992). Context, cortex and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychological Review*, *99*, 45-77.

Cragg, S.J., Rice, M. E., & Greenfield, S. A. (1997). Heterogeneity of electrically evoked dopamine release and reuptake in substantia nigra, ventral tegmental area, and striatum. *Journal of Neurophysiology*, *77*, 863–873.

Dayan, P. & Abbott, L. F. (2001). *Theoretical neuroscience: Computational and mathematical modeling of neural systems*. Cambridge, MA: MIT Press.

Derkach, V., Barria, A. & Soderling, T. R. (1999). Ca2+/calmodulin-kinase II enhances channel conductance of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate type glutamate receptors. *Proceedings of the National Academy of Science, USA*, *96*, 3269-3274.

Desmurget, M., & Turner, R. S. (2010). Motor sequences and the Basal Ganglia: kinematics, not habits. *The Journal of Neuroscience*, *30*, 7685-7690.

Diana, R. A., Reder, L. M., Arndt, J. & Park, H. (2006). Models of recognition: A review of arguments in favor of a dual-process account. *Psychonomic Bulletin & Review, 13, 1-21*.

Dum, R. P., & Strick, P. L. (2005). Frontal lobe inputs to the digit representations of the motor areas on the lateral surface of the hemisphere. *Journal of Neuroscience, 25,* 1375-1386.

Ermentrout, G. B. (1996). Type I membranes, phase resetting curves, and synchrony. *Neural Computation, 8*, 979-1001.

Feenstra, M. G., & Botterblom, M. H. (1996). Rapid sampling of extracellular dopamine in the rat prefrontal cortex during food consumption, handling and exposure to novelty. *Brain Research*, *742*, 17–24.

Feldman, D. E. (2009). Synaptic mechanisms for plasticity in neocortex. *Annual Review of Neuroscience*, *32*, 33–55.

FitzHugh, R. A. (1961). Impulses and physiological states in theoretical models of nerve membrane. *Biophysical Journal*, *1*, 445-466.

Földiák, P. (1990). Forming sparse representations by local anti-Hebbian learning. *Biological cybernetics, 64, 165*-170.

Frank, M. J. (2005). Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. *Journal of Cognitive Neuroscience*, *17*, 51-72.

Frank, M. J. (2006). Hold your horses: A dynamic computational role for the subthalamic nucleus in decision making. *Neural Networks, 19,* 1120-1136.

Frank, M. J. & Claus, E. D. (2006). Anatomy of a decision: Striato-orbitofrontal interactions in reinforcement learning, decision making and reversal. *Psychological Review, 113,* 300-326.

Frank, M. J., Loughry, B., & O'Reilly, R. C. (2001). Interactions between frontal cortex and basal ganglia in working memory: A computational model. *Cognitive, Affective, and Behavioral Neuroscience, 1*, 137–160.

Gabel, L. A., & Nisenbaum, E. S. (1999). Muscarinic receptors differentially modulate the persistent potassium current in striatal spiny projection neurons. *Journal of Neurophysiology*, *81*, 1418-1423.

Grafton, S. T., Hazeltine, E., & Ivry, R. (1995). Functional mapping of sequence learning in normal humans. *Journal of Cognitive Neuroscience*, *7*, 497-510.

Greengard, P., Allen, P. B., & Nairn, A. C. (1999). Beyond the dopamine receptor: The DARPP-32/protein phosphatase-1 cascade. *Neuron*, *23*, 435-447.

Grimwood, P. D., Martin, S. J., & Morris, R. G. M. (2001). Synaptic plasticity and memory. In W. M. Cowan, T. C. Südhof, & C. F. Stevens (Eds.), *Synapses* (pp. 519-570). Baltimore, MD: Johns Hopkins University Press.

Gu, Q. (2003). Contribution of acetylcholine to visual cortex plasticity. *Neurobiology of Learning and Memory*, *80*, 291–301.

Hartley, M., Taylor, N, Taylor, J. (2006). Understanding spike-time-dependent plasticity: A biologically motivated computational model. *Neurocomputing*, *69,* 2005-2016.

Hartley, T., Burgess, N., Lever, C., Cacucci, F., & O'Keefe, J. (2000). Modeling place fields in terms of the cortical inputs to the hippocampus. *Hippocampus*, *10*, 369–379.

Haykin, S. (2008). *Neural networks and learning machines* (3rd Ed.). Upper Saddle River, NJ: Prentice Hall.

Hélie, S. (2006). An introduction to model selection: Tools and algorithms. *Tutorials in Quantitative Methods for Psychology*, *2*, 1-10.

Hodgkin, A. L., Huxley, A. F. (1952). A quantitative description of membrane and its application to conduction and excitation in nerve. *Journal of Physiology*, *117*, 500–544.

Hollerman, J. R., & Schultz, W. (1998). Dopamine neurons report an error in the temporal prediction of reward during learning. *Nature Neuroscience, 1,* 304–309.

Houk J. C. (2010). Voluntary movement: Control, learning and memory. In G. F. Koob, M. Le Moal, & R. F. Thompson (Eds.). *Encyclopedia of Behavioral Neuroscience* (pp. 455-458). Oxford, Academic Press.

Houk, J., Adams, J., & Barto, A. (1995). A model of how basal ganglia generate and use neural signals that predict reinforcement. In J. Houk, J. Davis, & D. Beiser (Eds.), *Models of information processing in the basal ganglia* (pp. 249–270). Cambridge, MA: MIT Press.

Izhikevich, E. M. (2003). Simple model of spiking neurons. *IEEE Transactions on Neural Networks, 14*, 1569-1572.

Izhikevich, E. M. (2004). Which model to use for cortical spiking neurons? *IEEE Transactions on Neural Networks, 15*, 1063-1070.

Izhikevich, E. M. (2005). Large-scale simulation of the human brain. http://vesicle.nsi.edu/users/izhikevich/human_brain_simulation/Blue_Brain.htm

Izhikevich, E. M. (2007). *Dynamical systems in neuroscience: The geometry of excitability and bursting*. Cambridge, MA: MIT Press.

Jang, Y., Wixted, J. T., & Huber, D. E. (2009). Testing signal-detection models of yes/no and two-alternative forced-choice recognition memory. *Journal of Experimental Psychology: General*, *138*, 291-306.

Jörntell, H., & Hansel, C. (2006). Synaptic memories upside down: Bidirectional plasticity at cerebellar parallel fiber-Purkinje cell synapses. *Neuron*, *52*, 227–238.

Kemp, N., & Bashir, Z. I. (2001). Long-term depression: A cascade of induction and expression mechanisms. *Progress in Neurobiology*, *65*, 339-365.

Kimura, M., Rajkowski, J., & Evarts, E. (1984). Tonically discharging putamen neurons exhibit set-dependent responses. *Proceedings of the National Academy of Sciences, USA*, *81*, 4998-5001.

Kirkwood, A., Rioult, M. G., & Bear, M. F. (1996). Experience-dependent modification of synaptic plasticity in visual cortex. *Nature*, *381*, 526–528.

Koch, C. (1999). *Biophysics of computation*. New York: Oxford.

Kreitzer, A. C., & Malenka, R. C. (2008). Striatal plasticity and basal ganglia circuit function. *Neuron*, *60*, 543-554.

Lapicque, L. (1907). Recherches quantitatives sur l'excitation électrique des nerfs traitée comme une polarization. *Journal de Physiologie et de Pathologie Générale*, *9*, 620-635.

Latham, P. E., Richmond, B. J., Nelson, P. G., & Nirenberg, S. (2000). Intrinsic dynamics in neuronal networks. I. Theory. *Journal of Neurophysiology*, *83*, 808-827.

Lee, H. -K., Barbarosie, M., Kameyama, K., Bear, M. F., & Huganir, R. L. (2000). Regulation of distinct AMPA receptor phosphorylation sites during bidirectional synaptic plasticity. *Nature*, *405*, 955–959.

Lerner, T. N., & Kreitzer, A. C. (2011). Neuromodulatory control of striatal plasticity and behavior. *Current Opinion in Neurobiology*, *21*, 1-6.

Leveille, J., Versace, M., and Grossberg, S. (2010). Running as fast as it can: How spiking dynamics form object groupings in the laminar circuits of visual cortex. *Journal of Computational Neuroscience*, *28*, 323-346.

Lisman, J., Schulman, H., & Cline, H. (2002). The molecular basis of CaMKII function in synaptic and behavioural memory. *Nature Reviews Neuroscience*, *3*, 175-190.

Logothetis, N. K. (2003). The underpinnings of the BOLD functional magnetic resonance imaging signal. *The Journal of Neuroscience, 23*, 3963-3971.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412*, 150-157.

Maddox, W. T., & Ashby, F. G. (1993). Comparing decision bound and exemplar models of categorization. *Perception & Psychophysics*, *53*, 49-70.

Maddox, W. T., & Ashby, F. G. (2004). Dissociating explicit and procedural-learning based systems of

perceptual category learning. *Behavioural Processes*, *66*, 309-332.

Maddox, W.T., Ashby, F.G., & Bohil, C. J. (2003). Delayed feedback effects on rule-based and information-integration category learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *29*, 650-662.

Maddox, W. T., & Ing, A. D. (2005). Delayed feedback disrupts the procedural-learning system but not the hypothesis-testing system in perceptual category learning. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 31*, 100–107.

Malenka, R. C., & Siegelbaum, S. A. (2001). Synaptic plasticity. In W. M. Cowan, T. C. Südhof, & C. F. Stevens (Eds.), *Synapses* (pp. 393-453). Baltimore, MD: Johns Hopkins University Press.

Marr, D. (1982). *Vision: A Computational Investigation into the Human Representation and Processing of Visual Information*. New York: Freeman.

McCoy, P. A., Huang, H.-S., & Philpot, B. D. (2009). Advances in understanding visual cortex plasticity. *Current Opinion in Neurobiology*, *19*, 298–304.

McCulloch, W. S., & Pitts, W. (1943). A logical calculus of the ideas immanent in nervous activity. *Bulletin of Mathematical Biology*, *5*, 115-133.

McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. *Psychological Review, 102,* 419-457.

McMillen, T., & Holmes, P. (2006). The dynamics of choice among multiple alternatives. *Journal of Mathematical Psychology*, *50*, 30–57.

Medin, D. L., Altom, M. W., Edelson, S. M., & Freko, D. (1982). Correlated symptoms and simulated medical classification. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *8*, 37-50.

Meeter, M., Jehee, J., & Murre, J. (2007). Neural models that convince: Model hierarchies and other strategies to bridge the gap between behavior and the brain. *Philosophical Psychology*, *20*, 749-772.

Merchant, H., Zainos, A. Hernandez, A., Salinas, E., & Romo, R. (1997). Functional properties of primate putamen neurons during the categorization of tactile stimuli. *Journal of Neurophysiology, 77,* 1132-1154.

Mirenowicz, J., & Schultz, W. (1994). Importance of unpredictability for reward responses in primate dopamine neurons. *Journal of Neurophysiology, 72,* 1024–1027.

Monchi, O., Taylor, J. G., & Dagher, A. (2000). A neural model of working memory processes in normal subjects, Parkinson's disease, and schizophrenia for fMRI design and predictions. *Neural Networks*, *13*, 953–973.

Nagumo, J., Arimoto, S., & Yoshizawa, S. (1962). An active pulse transmission line simulating nerve axon. *Proceedings of the Institute of Radio Engineers*, *50*, 2061-2070.

Nestler, E. J., Hyman, S. E., & Malenka, R. C. (2001). *Molecular neuropharmacology* (Second Edition). New York: McGraw-Hill.

Newell, A. (1992). Précis of Unified theories of cognition. *Behavioral and Brain Sciences*, *15*, 425-492.

Newell, A., Shaw, J. C., & Simon, H. A. (1958). Elements of a theory of human problem solving. *Psychological Review*, *65*, 151-166.

O'Dell, T. J., & Kandel, E. R. (1994). Low-frequency stimulation erases LTP through an NMDA receptor-mediated activation of protein phosphatases. *Learning & Memory*, *1*, 129-139.

O'Reilly, R. C. (1998). Six principles for biologically based computational models of cortical cognition. *Trends in Cognitive Sciences*, *2*, 455-462.

O'Reilly, R. C., & Frank, M. J. (2006). Making working memory work: A computational model of learning in the frontal cortex and basal ganglia. *Neural Computation, 18,* 283-328.

O'Reilly, R. C., & Munakata, Y. (2000). *Computational explorations in cognitive neuroscience***.** Cambridge, MA: MIT Press.

Pakhotin, P. & Bracci, E. (2007). Cholinergic interneurons control the excitatory input to the striatum. *Journal of Neuroscience, 27,* 391-400.

Pitt, M. A., Kim, W., Navarro, D. J. & Myung, J. I. (2006). Global model analysis by parameter space partitioning**.** *Psychological Review, 113,* 57-83.

Raaijmakers, J. G. W., & Shiffrin, R. M. (2004). Models of memory. In H. Pashler & D. Medin (Eds.), *Stevens' Handbook of Experimental Psychology, Third Edition, Volume 2: Memory and Cognitive Processes* (pp. 43-76). New York: Wiley.

Rall, W. (1967). Distinguishing theoretical synaptic potentials computed for different soma-dendritic distributions of synaptic input. *Journal of Neurophysiology, 30*, 1138-1168.

Rangel, A., & Hare, T. (2010). Neural computations associated with goal-directed choice. *Current Opinion in Neurobiology*, *20*, 262–270.

Rescorla, R. A. & Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In A. H. Black & W. F. Prokasy, *Classical conditioning II: Current research and theory*. New York: Appleton-Century-Crofts.

Reynolds, J. N. J., Hyland, B. I., & Wickens, J. R. (2004). Modulation of an afterhyperpolarization by the substantia nigra induces pauses in the tonic firing of striatal cholinergic interneurons. *Journal of Neuroscience, 24*, 9870-9877.

Reynolds, J. N. J., & Wickens, J. R. (2002). Dopamine-dependent plasticity of corticostriatal synapses. *Neural Networks, 15*, 507-521.

Reynolds, J. R., & O'Reilly, R. C. (2009). Developing PFC representations using reinforcement learning. *Cognition, 113,* 281-292.

Ronesi, J., & Lovinger, D. M. (2005). Induction of striatal long-term synaptic depression by moderate frequency activation of cortical afferents in rat. *Journal of Physiology, 562*, 245–256.

Rosenblatt, F. (1958). The perceptron: A probabilistic model for information storage and organization in the brain. *Psychological Review*, *65*, 386-406.

Rumelhart, D. E., McClelland, J. L., & the PDP research group. (1986). *Parallel distributed processing: Explorations in the microstructure of cognition. Volume I.* Cambridge, MA: MIT Press.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science*, *275*, 1593-1599.

Seamans, J. K., & Robbins, T. W. (2010). Dopamine modulation of prefrontal cortex and cognitive function. In K. A. Neve (Ed.), *The dopamine receptors* (2nd Ed., pp. 373-398). New York: Humana Press.

Seamans, J. K., & Yang, C. R. (2004). The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Progress in Neurobiology*, *74*, 1–57.

Schultz, W. (1998). Predictive reward signal of dopamine neurons. *Journal of Neurophysiology, 80,* 1–27.

Segev, I., & Burke, R. (1998). Compartmental models of complex neurons. In C. Koch & I. Segev (Eds.), *Methods in neuronal modeling* (pp. 93-128). Cambridge, MA: MIT Press.

Shadlen, M. N., & Newsome, W. T. (2001). Neural basis of a perceptual decision in the parietal cortex (Area LIP) of the rhesus monkey. *Journal of Neurophysiology*, *86*, 1916-1936.

Shen, W., Flajolet, M., Greengard, P., & Surmeier, D. J. (2008). Dichotomous dopaminergic control of striatal synaptic plasticity. *Science*, *321*, 848-851.

Sjöström, P. J., Rancz, E. A., Roth, A., & Häusser, M. (2008). Dendritic excitability and synaptic plasticity. *Physiological Reviews*, *88*, 769-840.

Smith, P. L., & Ratcliff, R. (2004). Psychology and neurobiology of simple decisions. *Trends in Neurosciences, 27*, 161-168.

Stanton, P. K., Bramham, C., & Scharfman, H. E. (Eds.) (2005). *Synaptic plasticity and transsynaptic signaling*. New York: Springer.

Sun, R. (Ed.) (2006). *Cognition and multi-agent interaction: From cognitive modeling to social simulation*. New York: Cambridge University Press.

Sutton, R. S. & Barto, A. G. (1998). *Reinforcement learning*. Cambridge, MA: MIT Press.

Suzuki, T., Miura, M., Nishimura, K., & Aosaki, T. (2001). Dopamine-dependent synaptic plasticity in the striatal cholinergic interneurons. *Journal of Neuroscience, 21,* 6492-6501.

Tan, C. O., & Bullock, D. (2008). A local circuit model of learned striatal and dopamine cell responses under probabilistic schedules of reward. *Journal of Neuroscience*, *28*, 10062–10074.

Thorndike, E. L. (1911). *Animal Intelligence*. Macmillan.

Tobler, P. N., Dickinson, A., & Schultz, W. (2003). Coding of predicted reward omission by dopamine neurons in a conditioned inhibition paradigm. *Journal of Neuroscience*, 23, 10402-10.

Townsend, J. T., & Ashby, F. G. (1983). *Stochastic modeling of elementary psychological processes*. New York: Cambridge University Press.

Tzschentke, T. M. (2001). Pharmacology and behavioral pharmacology of the mesocortical dopamine system. *Progress in Neurobiology*, *63*, 241–320.

Usher, M., Olami, Z., & McClelland, J. L. (2002). Hick's law in a stochastic race model with speed-accuracy tradeoff. *Journal of Mathematical Psychology*, *46*, 704-715.

Waldschmidt, J. G., & Ashby, F. G. (2011). Cortical and striatal contributions to automaticity in information-integration categorization. *Neuroimage*.

Wang, X.-J. (2008). Decision making in recurrent neuronal circuits. *Neuron, 60*, 215-234.

Wang, Z., Kai, L., Day, M., Ronesi, J., Yin, H. H., Ding, J., Tkatch, T., Lovinger, D. M., & Surmeier, D. J. (2006). Dopaminergic control of corticostriatal long-term synaptic depression in medium spiny neurons is mediated by cholinergic interneurons. *Neuron*, *50*, 443–452.

Willingham, D. B., Wells, L. A., Farrell, J. M., & Stemwedel, M. E. (2000). Implicit motor sequence learning is represented in response locations. *Memory & Cognition*, *28*, 366-375.

Zhang, L. I., Tao, H. W., Holt, C. E., Harris, W. A., & Poo, M.-M. (1998). A critical window for cooperation and competition among developing retinotectal synapses. *Nature*, *395*, 37-44.