Journal Club

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# Emergent Basal Ganglia Pathology within Computational Models

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Review of Leblois et al. (http://www.jneurosci.org/cgi/content/full/26/13/3567)

Advances in neurobiology and increased computational capabilities have paved the way for more realistic neuronal network models. For a model to be complete, it must account for known neuroanatomy, network electrophysiology, pharmacology, pathophysiology, and behavioral findings. Although the vast interconnectedness of the brain makes the formulation of a complete model computationally restrictive, scaled models of anatomical subsystems have offered new insights into brain function.

One particularly attractive system to model is the basal ganglia. The anatomy and electrophysiology of this system of subcortical, prosencephalic nuclei has been well described and is thus ideal for modeling. The basal ganglia consist of four main subnuclei: striatum, globus pallidus [internal segment (GPi) and external segment (GPe)], subthalamic nucleus (STN), and substantia nigra [compact (SNc) and reticular (SNr)]. Movement disorders such as Parkinson's disease (PD) have been traced to basal ganglia dysfunction. Consequently, the basal ganglia are traditionally classified as part of the extrapyramidal motor system.

Parkinson's disease is characterized by the loss of dopaminergic innervation of the striatum from the SNc. Early conceptual models (DeLong, 1990) diagrammed a "direct" and "indirect" circuit within the basal ganglia. These parallel circuits diverge according to their nigrostriatal targets; the direct pathway is said to preferentially target striatal $D_1$ receptors, whereas the indirect pathway is said to preferentially target $D_2$ receptors. These receptors modulate excitation and inhibition in the circuit, respectively. Ultimately, both pathways project to the cortex via the anterior thalamus (Fig. 1).

This simple model proved very useful in describing the motor effects of PD and helped guide treatment. However, recent experimental findings suggest that this model is incomplete. New PD treatments such as deep brain stimulation are difficult to reconcile within the classical model. Similarly, this model inadequately describes the role of the basal ganglia in learning, memory, language, and reward. Finally, there is mounting evidence that the $D_1/D_2$, direct/indirect segregation required by this model does not accurately describe the biology of the system. Indeed, as new experimental data are acquired, adjustments must be made to the conceptual and computational basal ganglia models. For example, Soares et al. (2004) showed that MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced parkinsonism in rhesus monkeys reduced GPe activity (and thus increased STN and GPi activity) as predicted. However, ablation of the GPe did not induce parkinsonian symptoms. The classical connectivity model dictates that GPe ablation would lead to STN disinhibition, and thus parkinsonian symptoms (Fig. 1). This finding is strong evidence that a more complex model of PD is needed.

To address the role the basal ganglia play in movement and movement disorders, Leblois et al. (2006) constructed a novel computational model of the basal ganglia to address the role of the direct and hyperdirect circuits in network function. In their recent paper in *The Journal of Neuroscience*, the authors highlight the competing role that both the direct and "hyperdirect" pathways play in motor control. Unlike the direct and indirect pathways, the hyperdirect pathway is a direct corticosubthalamic projection that bypasses the striatum.

The Leblois et al. model is founded on the simple premise wherein the network is composed of two parallel, closed-feedback circuits with five components each: cortex, STN, striatum, GPi, and thalamus [Leblois et al. (2006), their Fig. 1 (http://www.jneurosci.org/cgi/content/full/26/13/3567/F1)]. These two circuits remain segregated at all levels until they interact within the GPi; the hyperdirect subthalamopallidal connection is more divergent (less topographic) than the direct, striatopallidal connection, and their projections overlap with those from the striatum.

Given the enormous complexity of neural circuitry across five brain regions, many assumptions and simplifications must be made to create a computationally tractable model. As such, parameters used

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in neuronal circuit models are often adjusted to fit experimental electrophysiology data. For this reason, Leblois et al. (2006) have adjusted model parameters to replicate known experimental neuronal properties and connections. The authors seem to have taken great care to explicitly outline and cite experimental, anatomical, pharmacological, and electrophysiological support for the parameters of their model.

Although most basal ganglia models focus on constructing cortical feedforward circuits wherein the motor plan is formed within the cortex, the Leblois et al. (2006) model demonstrates the interesting property of symmetry breaking [their Fig. 3 (http://www.jneurosci.org/cgi/content/full/26/13/3567/F3)]. This property may underlie action selection within the basal ganglia system [Leblois et al. (2006), their Fig. 5 (http://www.jneurosci.org/cgi/content/full/26/13/3567/F5) and Fig. 8 (http://www.jneurosci.org/cgi/content/full/26/13/3567/F8)]. Symmetry breaking manifests when the two parallel circuits interact with one another within the GPi. Both loops are constructed such that they are acted on by homogenous "external" inputs to the cortex and striatum. Even when the external inputs to both structures are equal, symmetry breaking emerges; this occurs when one loop is continually amplified across iterations. As this amplification increases, the response of the other loop is more strongly depressed.

The question of whether symmetry breaking as modeled here occurs *in vitro* remains open. It is possible that this runaway amplification would be attenuated via lateral inhibitory connections within the basal ganglia. For example, a model proposed by Terman et al. (2002) sought to identify pathological oscillations seen within the indirect pathway. In the Terman et al. (2002) model, lateral inhibitory connections within the GPe are necessary for eliciting the pathological oscillations of PD.

Unlike previous basal ganglia models, the Leblois et al. (2006) model accurately models normal movement selection and pathological PD electrophysiology and dyskinesia without the need to segregate between direct and indirect pathways. The authors showed that pathological oscillatory activity emerges after dopamine (DA) depletion because of competition between the direct and hyperdirect loops [Leblois et al. (2006), their Fig. 12 (http://www.jneurosci.org/cgi/content/full/26/13/3567/F12)].

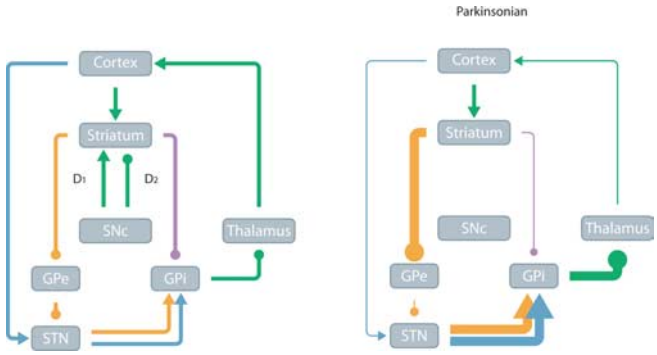


**Figure 1.** Diagram illustrating classical basal ganglia connectivity. Arrows indicate excitatory connections; dots indicate inhibitory connections. Arrow width indicates relative strength of connections. Striatal neurons of the direct pathway preferentially target the GPi, whereas neurons within the indirect pathway project to the GPe, then STN, and on to the GPi. The classical model states that $D_2$ receptors within the striatum are inhibitory, thus disinhibiting the GPe. In this model, PD would release the indirect pathway striatal inhibition and reduce direct pathway excitation. Both effects result in a hyperactive GPi, strongly inhibiting the thalamus and causing a reduction in cortical activity. Purple, Direct pathway; orange, indirect pathway; blue, hyperdirect pathway; green, ubiquitous connection.

Leblois et al. (2006) present a very convincing argument via an intricate, elegant model. Although their model seems incompatible with the Terman et al. (2002) model, the two may integrate well with one another. Both models show that oscillations are an emergent property of their networks after DA depletion. The Terman et al. (2002) model addresses the ameliorating effects of deep brain stimulation on PD dyskinesia, which Leblois et al. (2006) do not address.

Finally, Leblois et al. (2006) fail to address the role the basal ganglia play in cognitive processes. In a recent model, Frank (2005) outlined a network model that describes the effects of DA depletion and medicative DA restoration in PD. Similar to the model generated by Leblois et al. (2006), the Frank model does not incorporate lateral connections within nuclei. These separate basal ganglia models need to be brought together to formulate a more complete account of basal ganglia function and dysfunction. Experimental research can be guided by such models, and the models must continue to expand and integrate experimental findings.

Just as classical Newtonian mechanics adequately predict the motion of celestial bodies, so too does the classical connectivity model of the basal ganglia adequately represent their role in kinetic disorders. Unfortunately, Newtonian models break down when describing matter and energy at extreme densities, speeds, or scales. Similarly, the classical circuit representation of the basal ganglia appears to be an overly simplistic representation of basal ganglia function.

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