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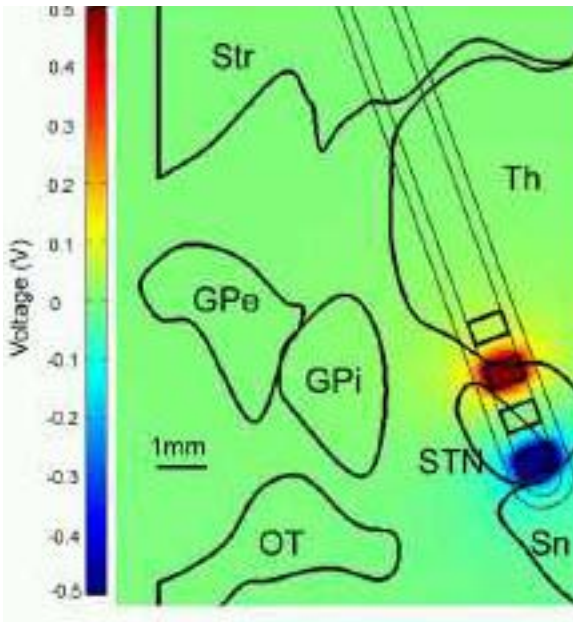
Neuronal Dynamics and the Basal Ganglia

By David Terman and Jonathan E. Rubin

Oscillations and other rhythmic patterns of neuronal activity arise throughout the central nervous system. Such oscillations have been implicated in the generation of sleep rhythms, epilepsy, parkinsonian tremor, sensory processing, and learning. Oscillatory behavior also arises in such physiological processes as respiration, movement, and secretion.

Researchers have made tremendous efforts to understand the cellular mechanisms responsible for these activity patterns. Numerous mathematical models have been developed, often based on the Hodgkin–Huxley formalism. Some of these models exhibit a rich mix of dynamic behaviors. (See, for example, the review articles [2,3].) The behavior of even a single cell can be quite complicated; an individual cell might fire, for example, repetitive action potentials or bursts of action potentials separated by silent phases of nearly quiescent behavior. Populations of cells can produce synchronized or partially synchronized oscillations, or spatially localized bumps of asynchronous activity. More complex population rhythms are also possible. For example, activity might propagate through a network in a wave-like manner or might show chaotic dynamics.

Mathematical modeling of neuronal networks has relied mainly on computational studies, with little mathematical analysis. This is so because realistic models typically consist of very large systems of nonlinear differential equations. As pointed out above, even a single cell can have very complicated dynamics. In addition, the synaptic coupling between cells can be either excitatory or inhibitory, and can include dynamics on multiple time scales. Because a neuronal system can involve combinations of different types of cells and different types of coupling, it is easy to understand why models for these systems lead to extremely challenging mathematical problems.



Even as researchers study the mechanism and effects of deep brain stimulation, it is being used in the treatment of Parkinson's disease and other disorders characterized by tremors. In DBS, an electrode implanted in the brain delivers continuous high-frequency stimulation.
The structures shown here are GP, globus pallidus (external and internal); STN, subthalamic nucleus; Sn, substantia nigra; and Str, striatum—all within the basal ganglia. Also shown are the thalamus (Th) and optic tract (OT). Used with permission from S. Miocinovic, M. Parent, C.R. Butson, P.J. Hahn, G.S. Russo, J.L. Vitek, and C.C. McIntyre, "Computational Analysis of Subthalamic Nucleus and Lenticular Fasciculus Activation During Therapeutic Deep Brain Stimulation," J. Neurophysiol., 96:3 (2006), 1569–80.

To describe how mathematical modeling and analysis have been used to address issues arising in neuroscience, we consider a concrete system: the basal ganglia [1]. The basal ganglia lie deep inside the brain and comprise several nuclei thought to play an important role in the control of movement. The basal ganglia have also been implicated in cognition, motivation, and emotion. Dysfunction of the basal ganglia is associated with movement disorders, such as Parkinson's disease (PD) and Huntington's disease.

Experiments have revealed complex firing patterns for neurons within the basal ganglia; moreover, patterns of neuronal activity, both spatial and temporal, differ between normal and pathological states. During normal resting conditions, neurons in the basal ganglia typically discharge in a tonic and irregular mode; little correlation is seen in the spiking patterns of different neurons. In parkinsonian states, these neurons display higher degrees of rhythmic bursting activity. Experiments have also demonstrated that resting tremor is associated with synchronous activity among neurons within the basal ganglia. Neither the origins of these firing patterns nor the specific neuronal mechanisms that cause them to change in pathological states are understood. As experiments have continued to demonstrate the importance of temporal and spatial dynamics for function and dysfunction of the basal ganglia, the need for realistic, biophysically based models has become increasingly clear.

Working closely with experimentalists, we constructed a mathematical model for neurons within the so-called indirect pathway of the basal ganglia [5]. Our focus on the indirect pathway was motivated in part by experiments demonstrating a drastic increase in correlated activity within the indirect pathway both in parkinsonian animal models and in human subjects with Parkinson's disease. Experiments also indicate that the pathological rhythms seen in PD may originate from abnormal interactions within the indirect pathway.

In computer simulations, our model exhibits a very rich set of dynamic behaviors. In particular, the network generates both correlated rhythmic activity and irregular uncorrelated spiking, depending on the tuning of certain network features. Mathematical analysis of the model, based on dynamical systems and, specifically, geometric singular perturbation methods, has elucidated mechanisms underlying these firing patterns. This has led to hypotheses about an important puzzle: How can the depletion of the neurotransmitter dopamine, as occurs in parkinsonian states, lead to an increase in correlated, burst-like activity?

We have extended our model to test hypotheses about the mechanisms underlying the effects of deep brain stimulation (DBS), a therapeutic intervention for PD and other disorders featuring pathological tremors. In DBS, an electrode is surgically implanted in a carefully targeted area of the brain, where it provides continuous delivery of high-frequency stimulation. DBS has come into wide use in the treatment of PD and other neurological disorders, but the basic mechanisms responsible for its effectiveness remain mysterious.

Researchers continue to explore one fundamental issue: What is the primary effect of DBS on neuronal activity in and near the site where it is applied? Various arguments support the idea that DBS primarily suppresses neuronal activity. According to one such argument, because the clinical effects of DBS are similar to those of ablative surgeries, in which areas of the brain are actually removed, the mechanisms underlying

these treatments must be similar as well. Several recent experimental papers, however, suggest that DBS actually enhances neuronal activity. This seems contradictory: Given that PD is associated with increased firing of the basal ganglia output nuclei, how could DBS ameliorate motor symptoms of PD by further increasing this firing? In [4], we demonstrate, with a computational model, why these findings are not contradictory, but rather a natural consequence of interactions between the *i*ntrinsic and synaptic properties of the cells involved. A key aspect of the mechanism that we analyze is the regularization of pathologically rhythmic activity, an insight that could be achieved only through a consideration of the dynamical features of network behavior.

The basal ganglia are one of many neuronal systems that offer tremendous opportunities for mathematicians to work closely with experimentalists on important problems. Mathematical modeling and analysis provide an effective way to formulate and test new hypotheses about mechanisms underlying observed firing patterns; however, close collaboration with experimentalists is crucially important to ensure that model development is appropriately constrained by experimental data. Novel mathematical methods are also needed for the analysis of complex models of neuronal systems. Such analysis is necessary if we are to develop an understanding of how experimentally observed firing patterns depend on complex interactions between the intrinsic, synaptic, and network properties of the system. Much of the analysis done so far has considered small networks with simple network architectures. Understanding how more complicated network topologies influence population rhythms represents one particularly important challenge that will need to be tackled as the mathematical study of neuronal networks advances.

References

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David Terman is a professor of mathematics at Ohio State University. Jonathan E. Rubin is a professor of mathematics, and a member of the Center for Neuroscience, at the University of Pittsburgh.