Synchronous Rhythms in a Model for the Indirect Pathway of the Basal Ganglia

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D. Terman[1], J.E. Rubin[2], A.C. Yew[1], and C.J. Wilson[3]

[1]Department of Mathematics, The Ohio State University
231 West 18th Avenue, Columbus, OH 43210, USA

[2]Department of Mathematics, University of Pittsburgh
301 Thackeray Hall, Pittsburgh, PA 15260

[3]Division of Life Sciences, University of Texas at San Antonio
6900 N. Loop 1604 West, San Antonio, TX 78249, USA

Abstract

By developing and analyzing a conductance-based network model for interactions of the external segment of the globus pallidus and the subthalamic nucleus in the basal ganglia, we test hypotheses on the origin of tremor-related synchronous activity in parkinsonian states. We find that in a "parkinsonian" regime, the network robustly generates two synchronous rhythms. In one rhythm, isolated episodes of full-population synchronized bursting arise and repeat at 1-2Hz. In the other rhythm, the cells split into synchronized clusters that alternate firing. We explore the mechanisms behind these rhythms as well as modulations that eliminate synchronous oscillations in the network.

Keywords: basal ganglia, subthalamic nucleus, globus pallidus, synchronous oscillations, Parkinson's disease

1 Introduction

Numerous studies have emphasized the crucial role played by the basal ganglia in the generation of movement disorders associated with Parkinson's disease. Structures within the basal ganglia are, in fact, the target of surgical procedures including pallidotomy, lesioning of the subthalamic nucleus, and deep brain stimulation. However, the precise nature of the basal ganglia's role in movement control, as well as movement disorders, remains mysterious.

The basal ganglia consists of several complex and highly interconnected nuclei. Cortical information is first processed by the striatum and is then transmitted to both the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). These are the output nuclei of the basal ganglia. According to the model first proposed by Albin *et al* [1], the cortical information flows through the basal ganglia via two distinct circuits: the so-called 'direct' and 'indirect' pathways. That is, motor information is either sent directly from the striatum to the output nuclei or indirectly via the external segment of the globus pallidus (GPe) and the subthalamic nucleus (STN). The only excitatory connections in the basal ganglia are those arising from STN. According to this model, the indirect pathway becomes overly activated during the parkinsonian state. Increased activity of STN leads to increased activity of GPi which in turn leads to an inhibition of neurons in the thalamic target region of the basal ganglia.

Recent experiments have demonstrated that resting tremor is associated with synchronous neuronal activity within both the internal and external segments of the globus pallidus and the subthalamic nucleus [2, 7]. However, neither the origins of this synchronous activity nor the neuronal mechanisms which underlie this activity are understood. Tremor-related activity may, for example, originate from synchronous rhythms in the motor thalamus and then be transmitted to the globus pallidus [12]. Another possibility is that synchronized oscillatory bursts are generated within the basal ganglia [3]. It has been suggested that the excitatory STN and inhibitory GPe form a feedback system that produces synchronized bursts; this system constitutes a central pacemaker modulated by striatal inhibition of GPe neurons. To test this proposal, Plenz and Kitai developed an *in vitro* model in which both the STN and GPe were co-cultured with the cortex and striatum. They demonstrated that neurons in the STN and GPe spontaneously produced synchronized oscillatory bursts at low frequencies [13].

A primary goal of this paper is the development of computational models to test hypotheses associated with the origin and mechanisms of tremor-related synchronous activity. The first step in our analysis is to develop conductance-based models for both the STN and GPe neurons. We then consider a network of synaptically coupled STN and GPe neurons and seek conditions under which the network exhibits synchronous oscillations. Since the precise details of how these cells are connected are poorly understood, we explore networks with different architectures and coupling parameters.

A brief description of our model and its behavior is presented in the Section 2. We find two classes of synchronous activity, and explore how these rhythms change with respect to changes in network parameters, to test the hypothesis that network behavior is modulated by striatal inhibition to GPe. In Section 3 we discuss the neuronal mechanisms which underlie the synchronous rhythms and speculate on possible insights the computational model may give on the origin of parkinsonian symptoms.

2 Results

2.1 Model STN and GPe Neurons

Biophysical models for single STN neurons are constructed according to recent voltage-clamp and current-clamp data [4]. The single-compartment model includes spike-producing currents (I_K and I_{Na}), a low-threshold T-type Ca^{2+}-current (I_T), a Ca^{2+}-activated, voltage-independent "after-hyperpolarization" K^+ current (I_{AHP}), a high-threshold Ca^{2+}-current (I_{Ca}) and a leak current (I_L).

The model STN neurons are spontaneously active with a firing rate of approximately 3 Hz. When current is injected, the cells achieve firing rates on the order of 200 Hz with little change in the voltage range of the membrane potential traversed by the action potentials. The STN neurons display a strong afterhyperpolarization following a period of high frequency spikes, and this afterhyperpolarization increases smoothly over a wide range of firing rates during the pulses. Rebound bursts can be elicited following the removal of negative current, and their duration depends on the degree of hyperpolarization. These rebound bursts typically last up to 200 ms and are then followed by spontaneous firing.

The single-compartment model for the GPe neurons includes currents similar to those for the STN neurons. The GPe neurons display high-frequency repetitive firing that does not show strong accommodation and is followed by a strong hyperpolarization. Under small hyperpolarizing current injections, the model GPe neurons exhibit oscillations in which a period of spiking alternates with a silent phase of near resting behavior. Termination of active phases is caused by activation of the outward K^+ current I_{AHP} as calcium accumulates in the cell. These model GPe cells display properties similar to the "Type 2" neurons described by Nambu and Llinas [11], the repetitive firing neurons described by Kita and Kitai [8], and the "high-frequency discharge with pause" neurons described by DeLong [5].

2.2 Synchronous population rhythms

In our model STN-GPe network, each STN cell receives inhibitory input from a subpopulation of GPe cells, and each GPe cell receives excitatory input from a subpopulation of STN cells. We also include inhibitory pallidopallidal coupling [9], and model inhibitory input from the striatum to the GPe as an applied current I_{app}.

We discovered two classes of synchronous oscillations in the model network. The first class, shown in Fig. 1, is characterized by isolated events of bursting activity that repeat at a slow frequency of 1–2 Hz. Every cell participates during each event; however, there may be little synchrony between individual spikes generated by different cells. Considerable variation may arise in the durations of different cells' active phases within a single event as well as in the durations of a single cell's active phases over multiple events. The bursting activity of STN cells in general lasts longer than that of GPe cells. This type of oscillatory network behavior will be referred to as the *episodic* rhythm.

The second class of synchronous rhythms, shown in Fig. 2 is characterized by a faster population rhythm of up to 6 Hz in which both the GPe and STN cells break up into two or more subpopulations or "clusters" that take turns firing. Neurons within each cluster burst in a tightly synchronized fashion, while cells belonging to different clusters burst out of phase. This kind of behavior will be referred to as the *clustered* rhythm.

2.3 Modulation of network behavior

Synchronous neuronal activity is associated with a pathological state of the basal ganglia, believed to result from the reduction of dopamine in the striatum. Details of how the loss of dopamine leads to pathological behavior are unknown. It has been suggested that decreased dopamine leads to an increased level of inhibition sent from the striatum to GPe (e.g. [6]). Another suggestion is that dopamine affects $\mathrm{GABA_A}$ among inter-GPe collaterals [14]. We use our computational model to test these hypotheses.

Fig. 3 shows the evolution of voltages of STN cells in a simulation of the network with precisely the same parameter values as those for Fig. 1 except that maximal pallidopallidal synaptic conductance $g_{G\to G}$ has been increased from 0 to 0.3 nS/μm^2 and I_{app} to GPe has been changed from -1.2 to 0 pA/μm^2. These correspond to increasing $\mathrm{GABA_A}$ among inter-GPe collaterals and decreasing input to GPe from the striatum. Note that the solution shown in Fig. 3 displays little synchronized or bursting activity. Each neuron spikes irregularly and there is little correlation among any of the neurons. This asynchronous rhythm can perhaps be viewed as corresponding to the "normal" resting behavior of neurons within the GPe and STN.

3 Discussion

3.1 Mechanism for episodic subthalamopallidal rhythms

To understand the neuronal mechanism underlying the episodic rhythm, consider a simple network consisting of one STN and one GPe neuron. Suppose that STN fires an action potential. The resulting excitation induces GPe to respond with its own spike. This leads to hyperpolarization of STN which, in turn, activates the inward current I_T. The STN neuron then rebounds and this process continues, producing a volley of bursting activity.

The termination of bursting activity is due to activation of the outward current I_{AHP} in GPe as calcium builds up with each additional spike. Once I_{AHP} activates enough, the GPe neuron can no longer respond to excitation from STN. When GPe's activity terminates, STN fires one last burst of spikes due to rebound.

A similar mechanism accounts for the bursts of activity in a larger network of STN-GPe neurons. The spontaneous spike of one STN cell recruits several GPe cells and this, in turn, recruits other STN neurons due to rebound. The activity then spreads throughout the network. The event terminates when calcium has built up in all of the GPe cells sufficiently to activate I_{AHP} and silence these cells.

The time duration between events is determined primarily by the I_{AHP} current in STN neurons. During an event, STN neurons fire rapid action potentials resulting in an increase of their intracellular calcium. Once the event terminates, there is a prolonged afterhyperpolarization before the cells return to regular spiking and a new event is initiated.

The time duration of each event is determined by two factors. The first is how long it takes for calcium to build up and hyperpolarize GPe neurons so that they no longer respond to excitation from STN. This depends on the strength of STN $\rightarrow$ GPe synaptic excitation. The second factor is the duration of rapid spiking after STN neurons rebound, which is controlled by the inactivation rate of I_T in STN neurons.

The reason that there may be little synchrony among individual spikes corresponding to different neurons is because inhibition plays a dual role in the rhythm. Inhibition is needed so that STN neurons can rebound; however, it also acts to desynchronize spikes within each episode.

3.2 Mechanism for clustered subthalamopallidal rhythms

To understand the neuronal mechanism underlying the clustered rhythms, consider a simple case in which the network breaks up into two clusters (containing both STN and GPe cells). We begin with a group S_1 of STN cells firing a burst of action potentials. The resulting excitation elicits bursts from a subpopulation of GPe cells, say G_1. This, in turn, leads to tonic inhibition of another group S_2 of STN cells. S_2 is prevented from firing if the inhibition it receives is powerful enough.

Eventually, cells in S_2 'escape' their silent phase and fire a burst of action potentials. This induces another GPe subpopulation G_2 to become active and the resulting inhibition terminates S_1's activity. The roles of the S_1/G_1 and S_2/G_2 clusters are now reversed. The primary reason why S_2 cells are able to escape is that while they are hyperpolarized, their inward I_T currents deinactivate. A second reason is that S_1's firing rate experiences some adaptation, due to I_T inactivation, and this leads to a decrease in the level of inhibition received by S_2. The length of time for which one cluster can fire before another one takes over, and hence the population bursting frequency, is mostly set by the rate of deinactivation of I_T in inactive STN cells relative to the level of inhibition they receive. Spike frequency adaptation also contributes to the timing of the rhythm.

Details, such as the number of clusters, which neurons belong to the same cluster, and the exact bursting frequency, are heavily dependent on the network architecture and coupling parameters. The network will organize itself in such a way that inhibition to active STN clusters is considerably less powerful than inhibition to silent STN clusters. Note that here, as in the case of episodic rhythms, inhibition plays multiple roles. Active STN neurons need moderate levels of inhibition to deinactivate I_T and rebound, while silent neurons are suppressed because they receive more powerful tonic inhibition which completely deactivates I_T.

3.3 Differences between the rhythms

The primary factors which select between the two synchronous rhythms are the underlying network architecture and the strengths of synaptic input. Parameter values which determine properties of individual cells are nearly the same.

The topology of connectivity among STN and GPe neurons is considerably more structured for clustered rhythms. Here it is important that different clusters of STN cells receive different levels of inhibition at different times. In the episodic rhythm, every neuron participates in each episode of activity. For the solution shown in Fig. 1 we chose random connections among the neurons. This allowed for activity to spread efficiently throughout the network.

Another difference is that for the episodic rhythm, it is important that calcium in GPe can build up sufficiently so that the neurons are no longer able to respond to STN firing. This depends on the combined strength of excitation from STN to GPe and I_{app}, the level of hyperpolarizing input from the striatum to GPe. For clustered rhythms, on the other hand, GPe neurons must always be able to respond to STN firing; hence, synaptic STN$\to$GPe excitation is considerably stronger.

3.4 The role of the indirect pathway

Recent papers have questioned the role of the so-called indirect pathway in the generation of parkinsonian symptoms (e.g. [10]). The classical view holds that during parkinsonian states, an increased level of inhibition from the striatum to GPe causes a decrease in the activity of GPe. This in turn would send less inhibition to STN, thus increasing STN activity. Recent experiments, however, have demonstrated that GPe is not hypoactive in parkinsonian states [10]. Certain results suggest that GPe activity may even increase; others indicate that the overall level of $\mathrm{GABA_A}$ received by GPe cells may, in fact, hold steady or decrease [14].

The analysis and simulations given in this paper are consistent with these experiments. Indeed, our results suggest that to account for the new experiments, one does not need to diminish the role of the indirect pathway; instead, one needs to reinterpret the role played by inhibition in generating synchronous rhythms among the relevant cells. Our analysis demonstrates that inhibition may do more than simply regulate the firing rates of neurons. Inhibition may, in fact, play a variety of roles, sometimes increasing firing rates, sometimes helping to desynchronize activity, and at other times helping to synchronize activity.

In Fig. 4, we suggest an alternative interpretation of the roles of inhibition and excitation in allowing the indirect pathway to generate tremor-like activity. In the "normal" state, there is strong $\mathrm{GABA_A}$ activity among GPe neurons, while synaptic interactions between GPe and STN are weak. During parkinsonian conditions, the striatum sends an increased level of inhibition to GPe and inter-GPe connections are weakened. This allows the STN and GPe populations to be more responsive to each other. For instance, in both the episodic and clustered rhythms, hyperpolarizing striatal input (I_{app}) is strong enough to prevent spontaneous firing of GPe cells, but the GPe cells are then more sensitive to excitation from STN; they also, due to decreased pallidopallidal inhibition, send more coordinated input to the STN. These stronger mutual interactions between the populations lead to increased synchronous and phasic behavior, as well as higher STN activity in general.

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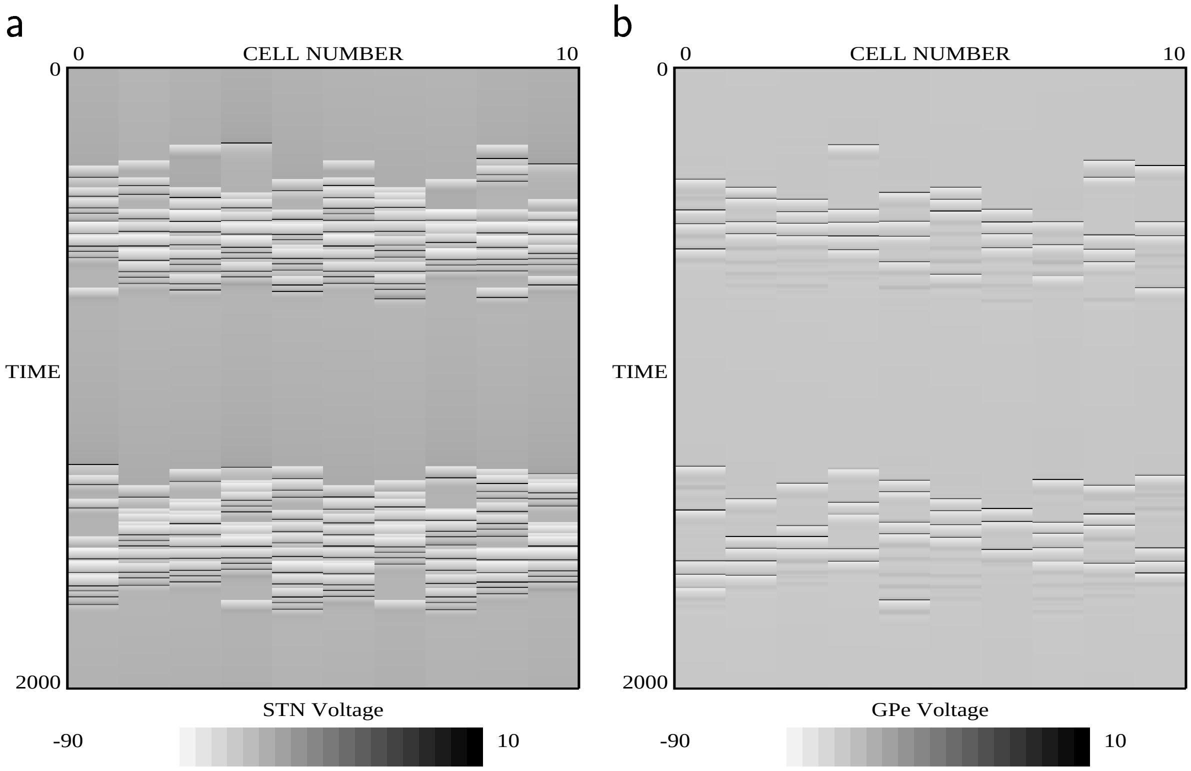

Figure 1: Network behavior in the episodic suthalamopallidal rhythm. A network of 10 STN cells and 10 GPe cells was simulated, with each GPe cell receiving input from two randomly chosen STN cells. (a) Voltages for STN cells (in mV) as they evolved over time (in ms). (b) Voltages for GPe cells (in mV) over time (in ms).

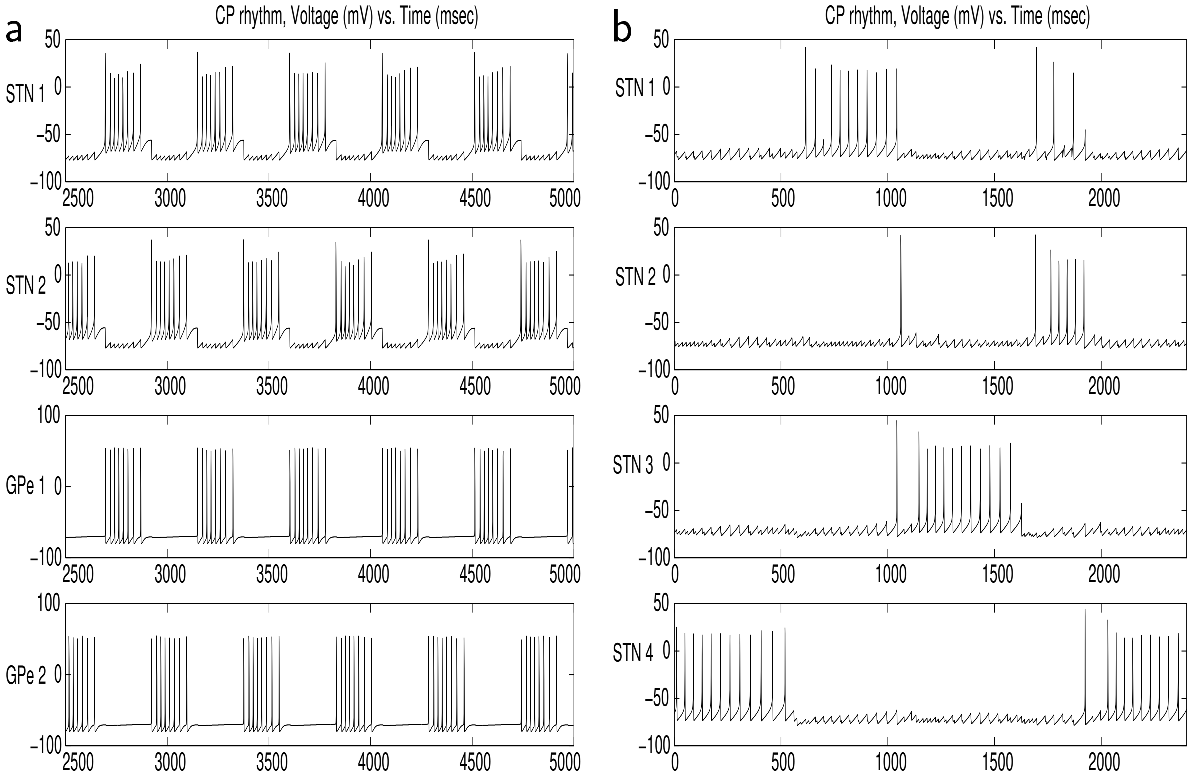

Figure 2: Clustered subthalamopallidal rhythms. Each trace shows the voltage for a diferent cell as a function of time. (a) Network of 2 STN cells and 2 GPe cells. (b) Network of 16 cells of each type; the STN cells formed our clusters, with a GPe cluster corresponding to each.

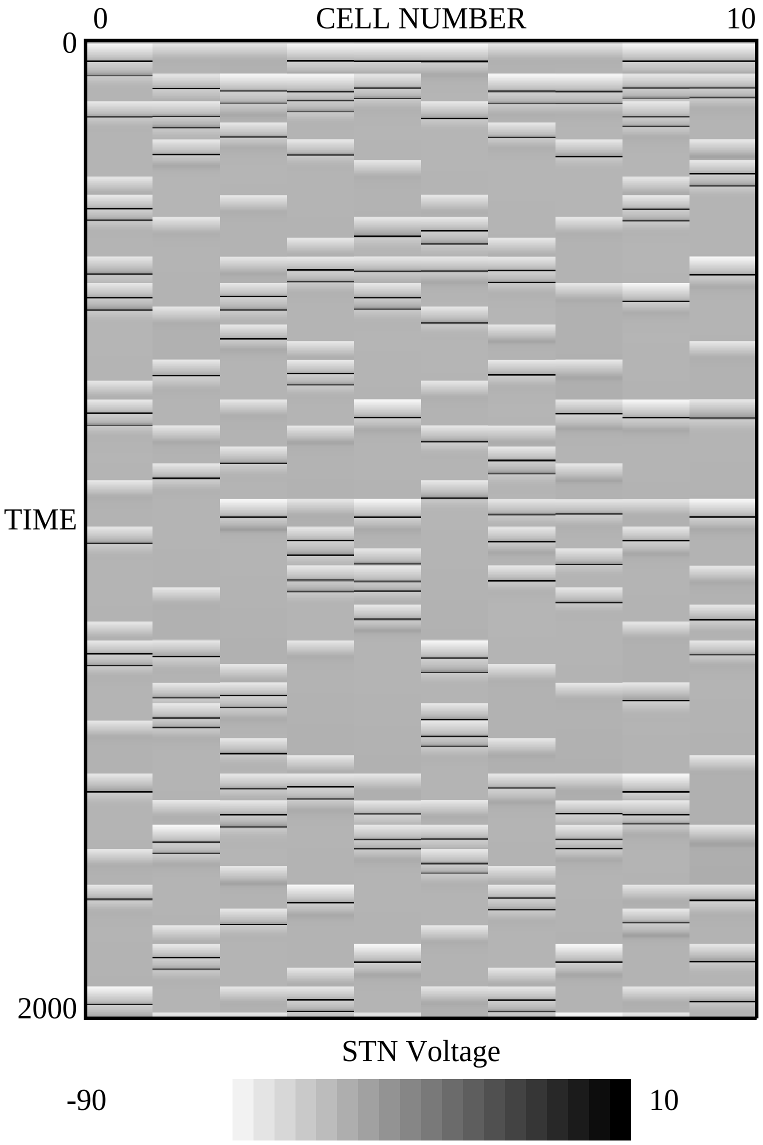

Figure 3: Normal resting STN behavior. After reduction of applied inhibitory current to GPe cells (representing striatal input reduction), the network switched from the episodic behavior of Figure 1 to this asynchronous, disorganized behavior. Voltages are in mV and time is in ms.

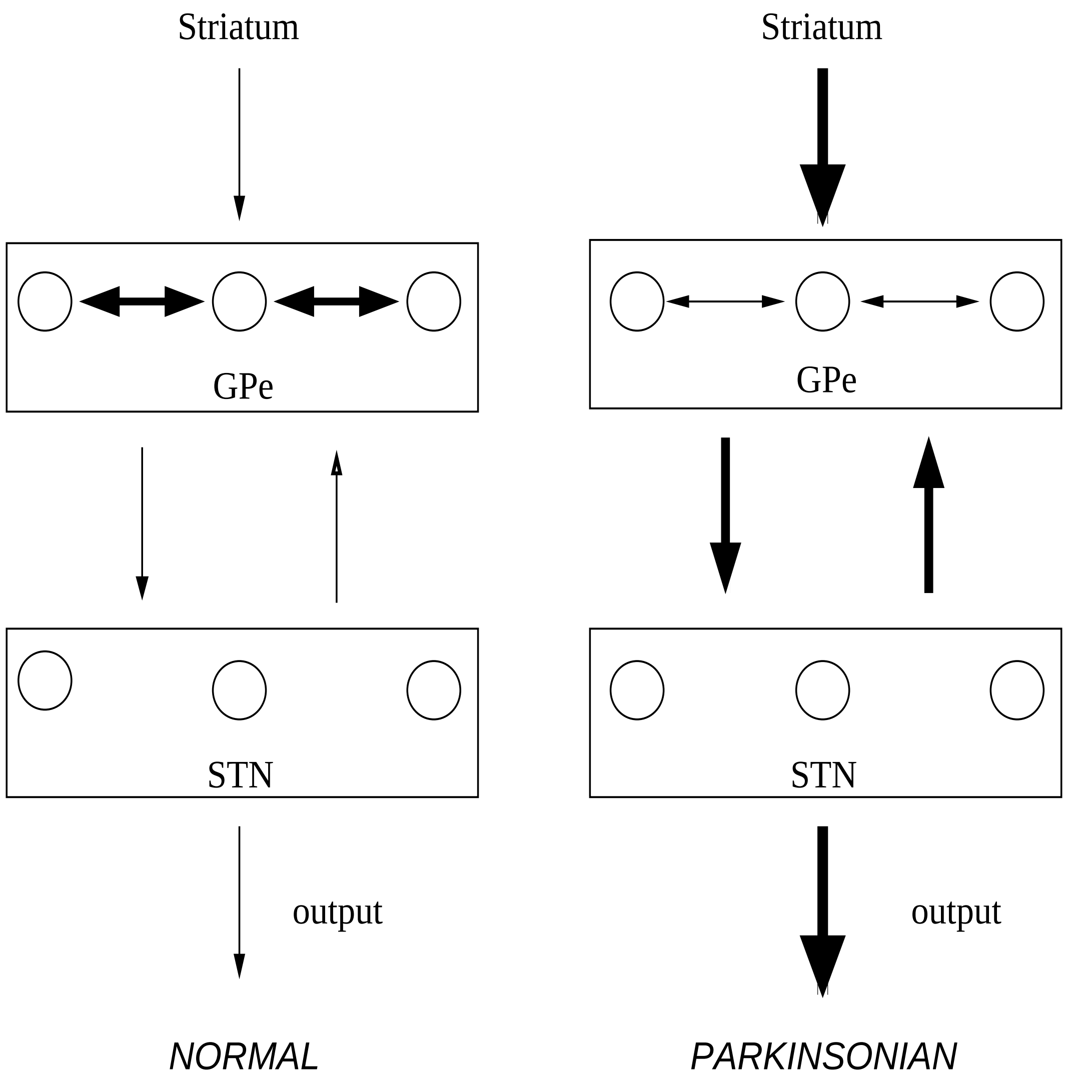

Figure 4: Schematic diagram of the indirect pathway connections in the basal ganglia in normal and parkinsonian states. In the parkinsonian regime, the combination of weakened inter-GPe connections and strengthened striatal input set the stage for synchronous GPe-STN rhythms and enhanced STN output.