Sequence generation in arbitrary temporal patterns from theta-nested gamma oscillations: a model of the basal ganglia–thalamo-cortical loops

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Abstract

A computational model that is able to generate sequences at arbitrary rates in a given serial order is presented for the cortico-basal ganglia (BG)–thalamic neural circuitry. Upon generating a sequence, this model stores information on the serial order of components in a cortical buffer by means of theta-nested gamma frequency oscillations observed experimentally in cortico-striatal neurons. This model assumes the existence of at least two functionally different classes of striatal spiny neurons. One class of striatal projection neurons (S-cells) select the first component in the cortical buffer through a temporal winner-take-all mechanism implemented by lateral inhibition. The inhibition should last for at least a few hundred milliseconds. In reality, it may be mediated by GABA\textsubscript{B} receptors at the presynaptic terminals of the cortico-striatal projection. The other class of striatal projection neurons (M-cells) retain the currently executed component in a cortico-BG–thalamic loop, for which the strong nonlinearity in transitions between up and down states of striatal neurons is crucial. For sequence generation at the level of striatum, the cortical neurons encoding the component selected for execution are inactivated by the feedback from the activated cortico-BG–thalamic loop. This model predicts that the transition to next component is triggered by a single external signal, i.e. the subthalamic input to the globus pallidum. This input gives a neural substrate for adjusting the rate of sequence generation.

Keywords: Temporal sequence; The basal ganglia; Temporal coding; Theta oscillation; Gamma-frequency oscillation; Subthalamic nucleus; Computational model

Nomenclature

Pyramidal cells

\begin{align*}
N_{\text{pyr}} & \text{ the number of pyramidal cells} \\
V_i & \text{ membrane potentials of the } i\text{th pyramidal cell} \\
\tau & \text{ membrane time constant} \\
V_{\text{rest}} & \text{ resting potential} \\
V_{\text{theta}} & \text{ theta-oscillatory input} \\
V_{\text{theta}} & \text{ the amplitude of } V_{\text{theta}} \\
f & \text{ the frequency of } V_{\text{theta}} \\
V_{\text{GABA}} & \text{ GABAergic feedback} \\
V_{\text{GABA}} & \text{ the amplitude of } V_{\text{GABA}} \\
\tau_{\text{GABA}} & \text{ the time constant for } V_{\text{GABA}} \\
C_{\text{ADP}} & \text{ source for after-depolarization} \\
\tau_{\text{ADP}} & \text{ the time constant for } V_{\text{ADP}} \\
V_{\text{in}}^{(i)} & \text{ input for encoding components} \\
V_{\text{ext}}^{(i)} & \text{ input for eliminating components} \\
V_{\text{th}} & \text{ the amplitude of } V_{\text{ext}}^{(i)} \\
f & \text{ firing time of the } i\text{th pyramidal cell} \\
\end{align*}

S-cells

\begin{align*}
M_{\text{SC}} & \text{ the number of S-cells and basal ganglia–thalamo-cortical loops} \\
V_{\text{S}}^{(i)} & \text{ membrane potentials of the } i\text{th S-cell} \\
\tau_{\text{S}} & \text{ membrane time constant} \\
V_{\text{S}}^{(i)} & \text{ resting potential} \\
V_{\text{aff}}^{(i)} & \text{ cortical input to the } i\text{th S-cell} \\
V_{\text{aff}}^{(i)} & \text{ the amplitude of } V_{\text{aff}}^{(i)} \\
\tau_{\text{aff}} & \text{ decay and rise time constant of } V_{\text{aff}}^{(i)} \\
r_{\text{S}} & \text{ the transmission rate of cortical input to the } i\text{th S-cell} \\
\Phi_{\text{S}} & \text{ the ensemble of pyramidal cells projecting to the } i\text{th S-cell} \\
\end{align*}

Basal ganglia–thalamo-cortical loops

\begin{align*}
x_{\text{M}} & \text{ mean firing rate of M-cell in the } i\text{th loop} \\
y_{\text{GPi}} & \text{ mean firing rate of GPi cell in the } i\text{th loop} \\
\tilde{y}_{\text{GPe}} & \text{ mean firing rate of GPe cell in the } i\text{th loop} \\
o_{\text{i}} & \text{ mean firing rate of thalamic cell in the } i\text{th loop} \\
\end{align*}

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Temporal sequence processing gives a basis for higher information processing by the brain such as memory, motor, cognitive or language processing. Some experimental results showed that striatal and pallidal neurons fire in relation to the sequence in which different movements are generated. For instance, the activity of a pallidal neuron changes when a particular arm movement is generated in a sequence (Mushiake & Strick, 1995). In the striatum, some spiny neurons are activated during a particular movement, while others are activated in preparation for next movement in a sequence (Cools, 1980; Graybiel, 1995; Kermadi and Joseph, 1995; Kimura, Kato, Shimazaki & Watanabe, 1996). This suggests that the basal ganglia are engaged in processing temporal sequence. There is some evidence that species-specific stereotyped action sequences, such as grooming action syntax of rats, are coded in the striatum (Cromwell & Berridge, 1996). However, it is widely considered that the activation of striatal neurons requires cortical driving inputs and, moreover, many neurons in motor-related frontal cortices of monkey show various activities which encode sequence information (Barone & Joseph, 1989; Hikosaka, Sakai, Miyauchi, Takino, Sasaki & Pütz, 1996; Shima, Mushiake, Saito & Tanji, 1996; Tanji and Shima, 1994). Therefore, it is likely that, at least in monkeys, generic action sequences are encoded in the cortex rather than the striatum. In this study, we model the cortico-basal ganglia (BG)–thalamic neural network to show how the basal ganglia are able to decode sequences from a cortical memory repository. We show that the basal ganglia have the anatomical and physiological characteristics which particularly suit for this purpose.

Normally, neurons in the internal globus pallidum (GPI), the output station of the basal ganglia, tonically inhibit thalamic relay neurons (Parent & Hazrati, 1995). On the contrary, the striatum, the input station of the basal ganglia, is normally silent and inhibits both GPe and the external globus pallidum (GPe) on receiving cortical stimuli. As in other models of the basal ganglia (Beiser & Houk, 1998; Berns & Sejnowski, 1998; Dominey, 1995), we assume that the thalamo-cortical neural circuits that govern motor execution are kept inhibited by the pallidal activity. Therefore, to execute sequential movements, the tonic inhibition on the thalamic cell responsible for producing each component movement must be removed sequentially. In order to produce sequence efficiently, it is further assumed that the removal of tonic inhibition is retained during each movement. In the present model, this is achieved by the positive feedback via motor cortices from the thalamic neurons to the striatal neurons that disinhibited the same thalamic neurons (Hikosaka, 1989). In other words, these cortico-BG–thalamic loop circuits, which will be identified later with the closed circuitry connecting the supplementary motor area (SMA), the basal ganglia and the ventral lateral thalamic nucleus, function as working memory for the current status of sequence processing. To this end, this model requires a precise wiring connecting particular striatal, pallidal, thalamic and cortical neurons and thus prefers a parallel architecture (Albin, Young, & Penny, 1989) to an open-mixed architecture (Joel & Weiner, 1994) for the cortico-BG–thalamic neural circuitry. The necessity of working memory for sequence processing was also suggested by Berns and Sejnowski (1998), who proposed the loops between GPe and the subthalamic nucleus as working memory.

This model focuses on two important issues in biological sequence processing, to which much attention has not been paid in previous experimental and modeling studies. First, it is speculated that the brain has some neural mechanism which underlies an immediate sequence generation without intensive learning. In many computational models, sequence information is embedded into spatial memory representations. For instance in Dominey (1995) or Beiser and Houk (1998), sequence information is encoded into the wiring patterns of modifiable synapses at the cortico-striatal projection. Learning sequence information in this way makes the execution of sequence efficient, however, on the contrary the flexibility in modifying sequence will be reduced, as the modifications should require drastic changes in the wiring patterns. A solution to this problem is obtained if the brain has a short-term repository in which sequence information is easily encoded and renewed, when necessary. In this model, we assume that the cortex employs such a short-term memory repository in storing the serial order of components.

In particular, we employ theta-nested gamma oscillations proposed by Lisman and Idiart (1995) as a possible neural substrate for this short-term memory. Dual oscillations are typically seen in the hippocampus and entorhinal cortex (Buzsaki & Chrobak, 1995), where the population activity of pyramidal cells show fast oscillations in the gamma frequency range (~40 Hz) that are modulated by slow theta rhythm (~5–6 Hz). In their model, the origin of dual oscillations was explained as follows: pyramidal cells fire periodically in every theta cycle, but the relative phases of firing in a theta cycle can differ for different cells by integer multiples of gamma-frequency subcycles. As

\[ f_B(x) \] sigmoid response function of slope \( \beta \)

\[ \theta^+(x) \] threshold linear response function

\[ J_{ox} \] synaptic connection from \( o \)-cells to \( x \)-cells

\[ J_{yx} \] synaptic connection from \( x \)-cells to \( y \)-cells

\[ J_{xy} \] synaptic connection from \( x \)-cells to \( y \)-cells

\[ I_f \] input from S-cell to GPi cell in the \( f \)th loop

\[ I_{sw} \] a single subthalamic input to GPi cells

\[ K \] thalamic lateral inhibitory connections

\[ h_o \] threshold for \( x \)-cells

\[ h_T, \tilde{h}_T \] sources for tonic GPi and GPe activity

\[ \epsilon \] minimal activity for losers in winner-take-all competition

1. Introduction
reviewed later, the serial order of components can be immediately stored as the temporal order in which coding neurons fire at different gamma-frequency subcycles. At present, no direct evidence in behaving animals is known for the functional roles of cortical dual oscillations. It is however pointed out that they were found in the activity patterns of cortico-striatal neurons in anesthetized animals (Cowen & Wilson, 1994) and organotypic cultures (Plenz & Kitai, 1996). During the present sequence generation, the first component in short-term memory is selected by the striatum to prepare for its execution by the cortico-BG–thalamic loops.

Second, a plausible model of sequence processing by the brain should have a neural mechanism for assigning arbitrary duration to each component. There is an infinite variety of temporal patterns in which the same movements are produced in the same serial order. However, most computational models based on recurrent neural networks of formal neurons (Dehaene, Changeux & Nadal, 1987; Kleinfeld 1986; Sompolinsky & Kanter, 1986), bursting neurons (Aoyagi, 1992) or neural oscillators (Fukai, 1995a) generate a learned sequence only in a fixed temporal pattern. It is efficient if two sequences producing the same serial order in different temporal patterns can be treated as the same sequence. To this end, this model assumes that sequence generation undergoes two different stages (Tamori & Tanaka, 1993). At the first stage, information on the serial order of components is retained in the short-term memory buffer explained above. At the second stage, an actual sequence is generated according to the stored order information: In this decoding process, arbitrary duration is assigned to each component by some mechanism implemented within known anatomical constraints of the basal ganglia.

In many behavioral experiments, learning a sequence establishes association between a sensory cue and a specific transition in movements or behavioral states. Thus the times of proceeding to different movements may be partially determined by sensory stimuli. The brain may achieve this by rewiring synaptic contacts such that each cue signal activates a particular neural circuit that is needed for making a desired transition (Beiser & Houk, 1998; Berns & Sejnowski, 1998; Dominey, 1995). This approach seems practical and robust, but the necessity of rewiring reduces the flexibility in reorganizing behavioral sequence. Also in some cases such sensory cues do not exist, hence, it is likely that a more basic mechanism exists. In this model, a possible mechanism is proposed: the movement transitions planned in the cortical buffer are achieved by a single external signal to the basal ganglia, i.e. the excitatory signal to GPe by the subthalamic nucleus. As the subthalamic nucleus receives short-latency cortical inputs (Parent & Hazrati, 1995), it is possible that this subthalamo-pallidal signal is originally generated in the cortex by sensory cues, or any feedback from the lower sensory-motor systems that inform completion of a movement. For efficient sequence production, two further assumptions are made. First, the component just executed should be eliminated from the cortical buffer to prepare for the next transition. This is done by an inhibitory feedback to the cortical buffer from the cortico-BG–thalamic loops. Second, the winner-take-all (WTA) competition operates among the loops for restricting the number of active loops to unity. This also prevents the occurrence of a planned transition before it is signaled by the subthalamic nucleus. As the basal ganglia and thalamus contain many sources of inhibition, the recurrent inhibitory networks necessary for the competition can be found at multiple subcortical sites.

This work has been presented in an abstract form (Fukai, 1997).

2. Model

2.1. Cortical short-term memory buffer

Below, the model of short-term memory is briefly reviewed. The model consists of $N$ pyramidal neurons and an inhibitory interneuron and an inhibitory interneuron (Fig. 1(a)). The interneuron is not modeled explicitly. The pyramidal neurons are modeled by integrate-and-fire neurons and their membrane potentials obey

$$\frac{\text{d}V_j}{\text{d}t} = -V_j + V_{\text{rest}} + V_{\theta} + V_{\text{GABA}} + V_{\text{ADP}} + V^{(\text{ext})}_{\text{in}} + V^{(\text{ext})}_{\text{el}}$$

$$j = 1, \ldots, N.$$ (1)

An action potential is elicited whenever the membrane potential reaches threshold, and the potential is then reset to resting potential $V_{\text{rest}}$. $V_{\theta}$ is an oscillatory bias and $V_{\text{GABA}}$ is the inhibitory feedback from the interneuron:

$$V_{\theta}(t) = v_{\theta}(t) \cos(2\pi ft),$$ (2)

$$V_{\text{GABA}}(t) = -\frac{v_{\text{GABA}}}{N/M} \sum_{j=1}^{N} \left( t - t^{(\text{fire})}_{j} \right) \exp \left( \frac{-t - t^{(\text{fire})}_{j}}{\tau_{\text{GABA}}} \right),$$ (3)

where $t^{(\text{fire})}_{j}$ stands for the firing time of the $j$th pyramidal neuron and $M$ is the number of the neurons that fire synchronously at the same subcycle. The pyramidal neuron exhibits a ramp of depolarization after a spike during cholinergic or serotonergic modulation (Caeser, Brown, Gahwiler & Knopfel, 1993):

$$V_{\text{ADP}}(t) = \frac{V_{\text{ADP}}}{\tau_{\text{ADP}}} (t - t^{(\text{fire})}_{j}) \exp \left( \frac{-t - t^{(\text{fire})}_{j}}{\tau_{\text{ADP}}} \right).$$ (4)

Each time a neuron fires, $V_{\text{ADP}}$ is reset and starts to build up for that neuron. $V^{(\text{in})}_{\text{ext}}$ and $V^{(\text{el})}_{\text{ext}}$ stand for the external inputs that activate and inactivate pyramidal neurons, respectively. The values of parameters for the entire model are listed in the Appendix.

The input $V^{(\text{in})}_{\text{ext}}$, which was not in the original model by Lisman and Idiart (1995), is incorporated to feedback the
information on the current status of the basal ganglia in sequence generation. As mentioned previously, the feedback is used for eliminating the component just selected for execution by the striatal neural network. The input is defined later in terms of the thalamic activity (see Eq. (20)). For demonstrating the performance of the short-term memory buffer, the results of simulations conducted in the original paper are reproduced in Fig. 1(b) for $V_{\text{ext}}^\dagger$: If a subgroup of pyramidal neurons (here a subgroup consists of S-neurons) are activated by the instantaneous input $V_{\text{in}}^\dagger$, the neurons start to fire synchronously. Owing to the subthreshold oscillation generated by $V_{\text{theta}}$ and the after-depolarization, they show sustained periodic discharges at the frequency of theta oscillation. If another subgroup of neurons are excited, they also start to fire periodically. Owing to the effects of inhibitory feedback, the subgroups activated at different times fire at different gamma-frequency subcycles. Moreover, the activated subgroups start to fire in a sequence at the rising phases of every theta cycle. Therefore, if a new subgroup is activated at (preferably, slightly before) a trough of theta oscillation, its firing is advanced in successive theta cycles until it finally merges into the tail of sequence. Following this protocol proposed by those authors, the network can store the order of components in the serial order of neuronal firings in a theta cycle, as far as the number of stored components is less than $7 \pm 2$.

In the present model, dual oscillations are used to store only future components of the sequence generated. As mentioned previously, this enables the striatum to prepare for the next component. It is also remarked that this usage of short-term memory buffer makes its limited memory capacity fully available.

2.2. Neural network of the basal ganglia

To decode a sequence in variable temporal patterns, in this model the basal ganglia neural network performs: (i) selection of the first component in dual oscillations; (ii) retention of the selected component during a required period; and (iii) transition to the next component, or termination when no next component exists. To do these operations, the striatal neural network is modeled as an array of selection units (S-neurons) for performing operation (i), whereas operations (ii) and (iii) are accomplished by parallel cortico-BG–thalamic loops involving other striatal units (M-neurons). As we will see later, the transition to next component can be “broadcasted” by an external input to all loops, without specifying the loop that stores a current component.

We will see that different mathematical descriptions, integrate-and-fire neurons and formal processing units with sigmoidal output, are employed for describing the two classes of striatal projection neurons, S- and M-neurons, respectively. This is because the action potential timing is essential for the functional roles of S-neurons but not for those of M-neurons. The differences in their roles are considered due to the differences in the cortical inputs they receive.

2.2.1. The selection units

The selection process (i) can be accomplished by S-neurons through a temporal WTA mechanism similar to that proposed some time ago by researchers including the present author (Fukai 1995b; Thorpe, 1990). Detailed mathematical analysis of the temporal WTA mechanism was reported elsewhere (Fukai, 1996) and will not be repeated here. As we will see later, S-neurons exhibit preparatory activity for the next component. In experiments, striatal projection neurons showing such a type of responses are preferentially found in the anterior striatum (Kimura et al., 1996), which is projected to primarily by the cingulate (CMA) and pre-supplementary motor areas (pre-SMA). Therefore, it is speculated that S-neurons represent the
projection neurons of the anterior striatum and the short-term memory buffer exists somewhere in these motor cortices.

As the timing of action potentials is essential in that process, S-neurons are described by integrate-and-fire neurons as follows:

\[
\tau_s \frac{dV^{(S)}}{dt} = -r_i^{(S)} + V^{(S)}_{\text{rest}} + V^{(aff)}_i, \quad i = 1, \ldots, M, \tag{5}
\]

\[
V_i^{(aff)}(t) = \frac{v^{aff} r_i(t)}{(\tau_d/\tau_s)} - 1 \sum_{j \in \Phi_i} \left[ \exp \left( -\frac{t - t^{\text{fire}}_j}{\tau_d} \right) - \exp \left( -\frac{t - t^{\text{fire}}_j}{\tau_s} \right) \right], \tag{6}
\]

where \(V^{(S)}_{\text{rest}}\) is the resting potential and \(V^{(aff)}_i\) is the afferent input from short-term memory. The factor \(r_i(t)\) determines the instantaneous transmission rate at the synaptic connections of cortico-striatal fibers. In Eq. (6), \(\Phi_i\) stands for the ensemble of \(\eta = N/M\) pyramidal neurons that innervate the \(i\)th S-neuron. To activate the loop neural circuits, the S-neuron’s spiking activity should last for a sufficiently long time. To ensure this, an input spike to an S-neuron is assumed to generate a long-lasting depolarized state with short rise (\(\tau_s\)) and slow decay (\(\tau_d\)) constants. Striatal neurons in vivo show clearly-separable two states, down and up states, and they fire only in the up state which is just a few mV below firing threshold (Wilson, 1995). The above assumption does not seem to be unrealistic as the up state continues for tens of milliseconds–seconds in anesthetized animals.

For the selection of the first component, only the S-neuron stimulated earliest in every theta cycle should fire. To achieve this, firing of an S-neuron must abruptly suppress the activities of other S-neurons. Such competition among S-neurons seems to be reasonable, as the local axon collaterals of striatal projection neurons and interneurons are GABAergic (Groves, 1983; Kawaguchi, 1997). To avoid an accidental selection of late components, the suppression should last at least for a period of theta oscillation, which implies that the inhibitory effects should be mediated not only by GABA\(_A\) receptors, but also by GABA\(_B\) receptors. Recent experimental studies showed that GABA\(_B\) receptors exist at the presynaptic terminals of cortico-striatal fibers and that the activation of GABA\(_B\) receptors greatly suppresses the presynaptic glutamate release (Calabresi, Mercuri, Murtas & Bernardi, 1991). They also suggested that the GABA\(_B\) receptors are activated by GABA release from the collaterals of striatal neurons. Therefore we assume that firing of an S-neuron at time \(t_0\) abruptly suppresses the transmission rates \(r_j(t)\) for other S-neurons (Fig. 2(b)). The rates return to a normal value with a time constant \(\tau_{\text{FTA}}\):

\[
r_j(t) = \begin{cases} 1, & t < t_0 \\ 1 - \exp \left( -\frac{t - t_0}{\tau_{\text{FTA}}} \right), & t > t_0. \end{cases}
\]

Fig. 2. (a) The model neural network of the cortico-basal ganglia–thalamic loops. The essential part of the network consists of selection units (S-neurons) in the striatum (STR) and the parallel loop circuits formed by striatal M-neurons, GPI neurons and thalamic/cortical neurons, where the thalamic and cortical neurons in the loops are treated as single processing units (TH-CTX). An excitatory synaptic connection is drawn by symbol —, while an inhibitory synaptic connection by a small filled circle. The projections from M-neurons to GPe are drawn only for the first M-neuron. Both S-neurons and M-types have mutual inhibition, but the connections are not explicitly drawn. Mutual inhibition is implied by the dark shading of the related areas. All GPI neurons are stimulated by a common subthalamic input \(I_{\text{sw}}\). The connections with STM are one-to-one, as indicated by the numbers assigned to them. (b) The transmission rate \(r_j(t)\) for the cortico-striatal inputs to S-neurons are suppressed abruptly by firing of an S-neuron and then recover slowly with a time constant \(\tau_{\text{FTA}}\). The vertical arrow designates the firing time of the first S-neuron.

2.2.2. Basal ganglia–thalamo-cortical loops

Anatomically, the basal ganglia and the cortex form various loop neural circuits. In this model, the retention process (ii) is performed by the cortico-basal ganglia–thalamic loops that involve the so-called direct pathway from the
where $x_i$ and $y_i$ are the mean firing rates of neurons in the loops and GPe neurons, respectively.

The time evolution equations for the loops and GPe neurons are given as follows:

\[
\tau_i \frac{dx_i}{dt} = -x_i + \theta^+(J_{x_i}(o_i - h_i)),
\]

\[
\tau_i \frac{dy_i}{dt} = -y_i + \theta^+(h_T - J_{y_i}x_i - J_{y_i}y_i - I_i + I_{sw}),
\]

\[
\tau_i \frac{d\bar{y}_i}{dt} = -\bar{y}_i + \theta^+(h_T - J_{\bar{y}_i}\sum_{j \neq i} x_j),
\]

\[
\frac{d\theta_i}{dt} = o_i \left(1 - J_{\theta_i}y_i - o_i - K \sum_{j \neq i} o_j\right) + \epsilon, \quad i = 1, \ldots, M
\]

where $x_i$, $y_i$, $\bar{y}_i$, and $o_i$ represent the mean firing rates of striatal, GPi, GPe, and thalamic/cortical neurons. The rates are expressed in arbitrary units and may represent the activities of corresponding neural populations in reality (Wilson & Cowan, 1972). $f_{\theta}(x)$ and $\theta^+(x)$ are sigmoid and threshold-linear response functions, respectively:

\[
f_{\theta}(x) = \frac{1}{1 + e^{-\beta x}},
\]

\[
\theta^+(x) = \begin{cases} 
  x & \text{if } x > 0 \\
  0 & \text{if } x \leq 0.
\end{cases}
\]

All $J$s and $K$ stand for the weights of synaptic connections, $I_i$ for the input from the $i$th S-neuron, and $I_{sw}$ for a time-dependent subthalamic input. The projection from S-neurons to the loops is one-to-one (Fig. 2(a)). $h_0$, $h_T$, $h_T$ and $\epsilon$ are constants; $h_0$ is introduced to ensure $x_i = 0$ for $o_i = 0$; $h_T$ and $h_T$ are introduced to make pallidal neurons tonically active in the absence of inhibitory striatal inputs (see below for $\epsilon$).

The following points are noted in the above equations. (i) As striatal neurons exhibit a clear two-state character (Wilson, 1995), $x_i$ is assumed to have a sigmoid response function with a large slope. On the other hand, pallidal neurons $y_i$ and $\bar{y}_i$ have threshold linear response functions for simplicity. (ii) The thalamic part (or the thalamic/cortical part in the truncated description) is modeled as a WTA neural network. Thalamic relay neurons project to neurons in the reticular thalamic nucleus which in turn project back to the relay neurons. Although the detailed wiring between these neurons is not well known, indirect evidence suggested that a thalamic relay neuron exerts inhibitory influences on other relay neurons through the backprojection from the reticular nucleus (Sherman & Koch, 1986). Therefore, it is assumed that the WTA competition among the cortico-BG-thalamic loops stems from the lateral inhibitory effects among thalamic relay neurons. Such a competition is possibly found also among the striatal neurons (corresponding to M-neurons) or GPe neurons. These possibilities, however, will not be further considered in the present study. Eq. (11) can be derived from a membrane dynamics of lateral inhibitory neural networks with a sigmoid response function and describes the WTA competition among $o_S$ under the net input $1 - J_{\theta_i}y_i$. Hence, the removal of pallidal inhibition on a thalamic neuron allows it to be a winner. The behavior of the equation can be studied in an analytic manner (Fukai & Tanaka, 1997): if the strength $K$ of lateral inhibition is less than and close to the strength of self-inhibition, only a single $o_i$ with the largest input, i.e. the smallest $y_i$, is activated. The small constant $\epsilon$ arises from the sigmoid response characteristic of the original competitive neural networks and prevents $o_i$ from being trapped at zero. (iii) Compared with GPi, the functional roles of GPe are much less well known. In this model, it is assumed that each GPe neuron inhibits a GPi neuron in a loop and is inhibited by M-neurons in the other loops to enhance the WTA competition among the loops. Anatomical studies revealed the presence of massive and topographic inhibitory projection from GPe to GPi (Parent & Hazrati, 1995). However, whether the striato-GPe projection is organized in that particular way is not known at present. (iv) All GPi/SNr neurons in this model receive a common excitatory subthalamic input. It was suggested that the subthalamo-GPi/SNr projection is...
diffusive and innervates many pallidal neurons uniformly rather than exciting specific ones (Chesselet & Delfs, 1996; Parent & Hazrati, 1995). As the simplest possible case, a single subthalamic input is incorporated to raise the global activity level of GPi/SNr. The subthalamic input modeled here is considered to represent the effects of direct cortico-subthalamic projection. Although we model only a single array of cortico-BG–thalamic loops, in reality, there may be multiple arrays each of which receives a different subthalamic input. Having multiple output channels might be useful for executing compatible actions simultaneously. For instance, extending an arm simultaneously in different directions are incompatible, so the simultaneous release of motor mechanisms to execute these movements must be strictly inhibited. However, the combinations of compatible movements need not be inhibited. (v) The so-called indirect pathway from GPe to GPi via the subthalamic nucleus is not considered here. At present, the functional roles of this well-known pathway are not so clear. Some investigators even suggested the nonexistence of this pathway from detailed anatomical studies, claiming that the portion of subthalamic nucleus projecting to GPi differs from that projected to by GPe (Parent & Hazrati, 1995). Although this argument is controversial, the pathway is not incorporated into this model as its absence is nothing inconvenient for the present sequence generation.

Following a standard scenario for the direct pathway, the loops are expected to function in the following way (Hikosaka, 1989). GPi/SNr neurons normally suppress the thalamic activity by tonic inhibition. If somehow an S-neuron is excited cortically, the GPi/SNr output is inhibited in the loop projected to by that neuron, and accordingly the thalamic activity is released from the inhibition by GPi/SNr. This “self-active” state is assumed to continue while the component corresponding to the loop is kept excited by the released thalamic activity. This “self-active” state is assumed to continue while the component corresponding to the loop is generated.

3. Results
3.1. The dynamical properties of competing loops

The array of competing loops has some dynamical properties which a conventional competitive neural network does not have. These properties are analyzed, before numerical simulations are conducted for sequence generation by the entire neural network. In order to focus on the most essential points, $y_s$ are neglected for the time being. Also the subthalamic input $I_{sw}$ is set equal to zero.

The cortico-BG–thalamic loops exhibit two different activity patterns. In the absence of external input $I_s$, all $x_s$ are inactive and all $y_s$ are active owing to the constant bias $h_T$, and accordingly all $o_s$ are inhibited. This activity pattern represents the “resting state” of the loops:

$$x_i = f_T(-J_{ox} h_0) = 0, \quad y_i = h_T, \quad o_i = O(e) = 0.$$  

(14)

The value of $h_0$ was adjusted so as to make $x_i$ almost vanishing in this state. On the contrary, if some $I_s$ activates $x_i$, $y_i$ is inhibited and $o_i$ is released from the inhibition to become active, which in turn leads to the sustained activation of $x_s$. As $x_i$ inhibits $y_i$, this activity pattern (self-active state) may remain stable even after $I_s$ is reset to 0. Due to the WTA inhibition among $o_s$, more than one $o_s$ cannot be simultaneously active, which implies that more than one loop cannot be simultaneously in the self-active state. The activity of a winner loop is given by

$$x_i = f_T(J_{ox}(o_i - h_0)) = 1, \quad y_i = h_T - J_{yx} x_i \approx 0, \quad o_i = 1 - y_i \approx 1.$$  

(15)

The self-active state exists for sufficiently large values of $\beta$. This is easily understood from the consistency equation derived from Eq. (15):

$$x_i = f_T(J_{ox} J_{oy} J_{yx} x_i - J_{yo} (J_{oy} h_T + h_0 - 1)).$$  

(16)

This equation in general has two stable solutions in the vicinities of $x_i = 0$ (resting) and $x_i = 1$ (self-active), but the latter exists only when $\beta$ is greater than a certain critical value (Fig. 3(a)). Also a linear stability analysis at large values of $\beta$ shows that the fixed point near $x_i = 1$ is stable if

$$\beta e^{-\beta A} < 1,$$  

(17)

is satisfied for $A = J_{ox} J_{oy} J_{yx} - J_{yo} (J_{oy} h_T + h_0 - 1) > 0$. This is indeed the case for large values of $\beta$. Thus, $x_s$ must have almost a step-function-like response characteristic to obtain stable self-active states. This situation is numerically demonstrated in Fig. 3(b). In the simulations, a loop was initially put in the self-active state by setting $o_1(t) = 1$ for $0 \leq t \leq 200$ ms, and then all loops were set to evolve according to Eqs. (8)–(11) with $I_s = 0$. The figure shows that the loop remains active up to $t \to \infty$, if $\beta > \beta_c \approx 4.02$ for the parameter values used.

Now we consider the dynamical effects of input $I_s$, assuming that all $I_s$ have the same amplitude and frequency. In a wide range of parameter values, the winner loop once selected by an input remains activated, even after the input is removed and a different loop starts to receive a new input. In other words, an additional input is required for inactivating a previous winner by overwhelming the self-stabilization effects. To show this, numerical simulations were conducted under two different conditions with the following periodic input:

$$I_1(t) = V_s \left( \frac{t - t_k}{\tau} \right) \exp \left( - \frac{t - t_k}{\tau} \right), I_2(t) = \cdot = I_3(t) = 0,$$  

(18)
Namely, for the values of $b$, which were required in each condition for activating loop 1 from loop 1 was initially active. The minimum values of $V$ from loop 1 were initially active. The minimum values of $V$ value. (c) The lower bounds of $V_i$ (see Eq. (18)) for setting a loop in the self-active state at various values of $\beta$. For both $M = 10$ and 30, the solid curves represent the lower bounds in the condition that all loops are initially in the resting states, while the dashed curves represent those in the condition that a different loop is initially in the self-active state.

where $\tau = 4$ ms, $t_s = Tm$ ($m = 0, 1, \ldots$) and the frequency $1/T = 20$ Hz. In the first condition, all loops were initially inactive, whereas in the second condition a loop different from loop 1 was initially active. The minimum values of $V_i$ which were required in each condition for activating loop 1 are plotted against $\beta$ (Fig. 3(c)). For $\beta > \beta_c$, the minimum values are larger in the second condition than in the first one. Namely, for the values of $\beta$ and $V_i$ in the region between the solid and dashed curves, an active loop remains active even if a different loop is stimulated. The two curves merge to one another at $\beta = \beta_c$. At the critical point, the self-active states are barely stable and destabilized even by an indefinitely small perturbation. As seen in the figure, the value of $\beta_c$ becomes larger as $M$ is increased, as losers have small but nonzero activities of $O(\epsilon)$ that can compete with the winner.

Finally, it is remarked that a brief application of $I_{sw}$ resets the self-active state of a loop to the resting state, as it reactivates the inactive $y_i$.

### 3.2. Sequence generation by the entire neural network

For conducting numerical simulations of the entire neural network, the way the cortical memory buffer and cortico-BG–thalamic loops interact with one another needs to be determined. The interaction is described as follows. An action potential elicited from the $i$th S-neuron at $t = t_{\text{fire}}^{i}$ generates the postsynaptic current

$$I_i(t) = \left( \frac{t - t_{\text{fire}}^{i}}{\tau_y} \right) \exp\left( -\frac{t - t_{\text{fire}}^{i}}{\tau_y} \right), \quad i = 1, \ldots, M$$

in pallidal neuron $y_i$. Given this, the size of afferent input to S-neurons from the memory buffer, i.e. the value of $v_{\text{aff}}$ in Eq. (6), is fixed such that the firing rate of S-neuron is sufficient for raising a cortico-BG–thalamic loop to the self-active state when others are in the resting state, but it is insufficient for doing so when a different loop is active.

To eliminate the component just introduced into a loop from the cortical buffer, each pyramidal neuron in the cortical memory buffer is assumed to receive inhibitory feedback from the loop it projects to:

$$V_{\text{ext}}^{j}(t) = -v_{\text{th}}a_{Lj}(t), \quad j = 1, \ldots, N$$

where $L_j$ stands for the loop projected to by the $j$th pyramidal neuron (Figs. 1(a) and 2(a)). In the brain, this inhibitory feedback may be delivered by thalamic relay neurons or cortical neurons in SMA through inhibitory interneurons. If the thalamic part of the loops is VLo, the latter case is more likely as VLo does not have massive projections to pre-SMA and CMA, which are most probable cortical sites for the memory buffer.

As the number of active loops at any instance is at most one, the performance of the model remains qualitatively unchanged for different sizes of the model. Hence the results of simulations are shown below only for $N = 20$ and $M = 4$. In this case, each component is encoded in short-term memory by synchronous firing of five pyramidal neurons.

In Fig. 4(a), the activity of pyramidal neurons, S-neurons and $o_{S}$ are shown for the retrieval of a sequence of four components C1–C4. $I_{sw}$ is shown at the bottom. As explained previously, the components are introduced into the cortical memory buffer at the troughs of theta oscillation which are designated by vertical arrows. Immediately after C1 is introduced to pyramidal neurons, they activate the first S-neuron, which in turn sets the first loop in the self-active state. Then the inhibitory feedback from the activated loop eliminates component C1 automatically from the cortical...
Fig. 4. Performance of the entire neuronal network during the retrieval of four components C1–C4. Short-term memory consists of twenty pyramidal neurons, and each S-neuron is innervated by five pyramidal neurons. (a) The loops are raised to the self-active state according to the serial order stored by the cortical memory buffer. When a component is registered by a loop, the component is eliminated from short-term memory by the inhibitory feedback from the loop. A self-active state continues until $I_{sw}$ signals the renewal of the component retained in the competing loops. Note that S-neurons prepare for the next component. (b) A stored sequence is changed during the retrieval. The components C3 and C4 are eliminated at the theta cycle designated by the horizontal bar and then restored in the reversed order. These changes can be completed in short-term memory without affecting the output of the loops. (c) Sequence generation without the WTA competition among the loops ($K = 0$). In this case, each loop is activated immediately after a new component is introduced in short-term memory.
memory buffer. After that, the buffer retains the components C2–C4, and the network of S-neurons selects the first component C2 as the next component to be executed. At this moment, the active S-neuron coding C2 is inhibiting GPi neurons in the second loop. However, owing to the self-stabilization of the first loop and the WTA competition in the thalamus, the second component is not executed at this stage. As discussed previously with Fig. 3(c), this behavior appears only if appropriate values are chosen for $\beta$ and $v_{\text{aff}}$. The effects of the WTA competition will be discussed later in detail.

Now we see the effects of the subthalamic input. When $I_{\text{sw}}$ stimulates all $y_i$s, it reactivates $y_1$ and resets the self-active state of the first loop to the resting state. $I_{\text{sw}}$ has noticeable dynamical effects only on the inactive $y_i$. As the activity of the first loop has been turned off, now the second loop can be set in the self-active state as a new winner and component C2 is executed. The activation of the second loop automatically eliminates C2 from the cortical memory buffer, and C3 comes to the first component and is selected by S-neurons. However, as in the previous case, execution of C3 starts only after the next arrival of $I_{\text{sw}}$. The sequential activation of cortico-BG–thalamic loops is repeated until $I_{\text{sw}}$ reactivates $y_4$. In this case, no next component exists in the cortical buffer and accordingly the fourth loop returns to the resting state. Thus, the subthalamic input implies the termination of sequence generation, when a future plan is absent in the cortical memory buffer.

The second example demonstrates the separation of cortical memory process from the cortico-subcortical execution process in the present framework of sequence generation. In Fig. 4(b), future components C3 and C4 are reversed at $t = 2s$ while C2 is still generated. This can be done simply by inhibiting all pyramidal neurons in the cortical memory buffer for about a theta cycle and reintroducing the same components in the reversed order. As the loop retaining the currently executed component remains in the self-active state until the next delivery of $I_{\text{sw}}$, the above on-line modifications of the activity patterns in the cortical memory buffer do not affect the output of the loops, and the reorganized sequence can be decoded successfully.

To see the dynamical behaviors of this model in the absence of the WTA competition among the cortico-BG–thalamic loops, the results of simulations for the case with $K = 0$ are shown in Fig. 4(c). As we can see from the figure, as soon as a component is introduced into the cortical memory buffer, it is executed by the cortico-BG–thalamic loops. Such a memory system is useless for the temporary storage of future components. Accordingly, the only expected functional role of subthalamic input is the termination of sequence generation, as shown in the figure. It is noticed that the activation of a new loop is followed by the automatic termination of a preceding loop. This is because the activation of M-neurons in the new loop disinhibits GPi neurons in the preceding loop through the striato-GPe-GPi connections assumed in this model.

Simulations similar to those shown in Fig. 4(a) were repeated varying the length of sequences, the times and oscillation phases at which $I_{\text{sw}}$ is given, and the size of neural network up to $M = 30$. The results were qualitatively unchanged and the target sequences were always generated in the correct orders.

4. Discussion

In the present study, the cortico-basal ganglia–thalamic neural network was constructed to decode sequence from a cortical memory buffer. This cortical buffer was assumed to use theta-nested gamma oscillations (Lisman & Idiart, 1995) for the storage of serial order of components. Using dual oscillations for that purpose enables the neural network to store the information on several future movements ahead for smooth execution of sequential movements. However, it puts some limitation on the performance of this model. (i) The capacity of short-term memory, i.e., the number of gamma subcycles that can be accommodated in a theta cycle, is only $7 \pm 2$. This does not seem to be a severe constraint since information on all future components is not necessary at any moment during sequence generation. (ii) A sequence which involves the same component more than once cannot be stored in dual oscillations. Simple repetitions such as locomotive motions might be treated as a single unified component. But real difficulties arise when neural networks deal with more complex sequences involving different branching patterns from the same component. Such a complex sequence always raises some difficulties in many computational models. To deal with the complex sequences in sequence learning, we may include time delays in neural dynamics to make it nonMarkovian (Dominey, 1995), possibly with higher order (many-body) synaptic interactions (Guyon, Personnaz, Nadal & Dreyfus, 1988). However, the validity of these solutions is limited in the temporal patterns and complexity of learnable sequence, and the problem is open for further studies.

The existence of two functionally-different classes of striatal spiny neurons, S-neurons and M-neurons, was assumed in this model. S-neurons select the first component in the cortical buffer for execution through a temporal WTA mechanism. M-neurons are involved in the cortico-BG–thalamic loops to retain the just executed component. For this purpose, M-neurons use a nonlinearity in the transitions between up and down states at a single neuron level. If the component just selected for execution by the basal ganglia is eliminated from the cortical buffer, as in the present case, the activity of an S-neuron becomes selective to the component executed next. On the contrary, the activity of a M-neuron is selective to the component executed currently. Movement-preparatory and movement-related striatal activities were indeed found in the experiments that require animals to perform sequential arm movements (Kimura et al., 1996). The former type of striatal projection neurons,
which may correspond to S-neurons, were preferentially found in the anterior striatum, whereas the letter type, which may correspond to M-neurons, in the posterior striatum. As the primary cortical projections to the anterior striatum are from CMA and pre-SMA, the short-term memory buffer is expected to exist in these motor cortices. On the contrary, the cortico-BG–thalamic loops for component retention are presumably identified with the SMA-BG–VLo-SMA neural circuitry (Matelli & Luppino, 1993; Sakai et al., 1996; Takada et al., 1998).

The temporal selection mechanism requires that the lateral inhibition of striatal neurons lasts at least for one cycle of theta rhythm and hence should be mediated by GABA<sub>B</sub>-receptors. The activation of GABA<sub>B</sub>-receptors at the presynaptic terminals of cortico-striatal fibers greatly suppresses the glutamate release from the terminals (Calabresi et al., 1991). To obtain a mechanism for the required lateral inhibition, this model assumed that the GABA<sub>B</sub>-receptor activation is caused by GABA release from the axon collaterals of spiny neurons. In the striatum, these axon collaterals mainly target the cell bodies or primary dendrites of spiny neurons rather than the dendritic spines at which the cortico-striatal fibers terminate. Nevertheless, the above assumption does not seem to be unrealistic. First, if the presynaptic GABA<sub>B</sub>-receptors play any role, it is difficult to consider the existence of other release sites of GABA that activates these receptors. Second, GABA which is released from the collaterals near the cell body possibly activates the GABA<sub>B</sub>-receptors at the dendritic spines, since the dendritic fields of spiny neurons are not very large. It is remarked that the spiny neurons showing preparatory activity may preferentially have the presynaptic GABA<sub>B</sub>-receptors, if their functional role is as proposed here.

Since the activation of GABA<sub>B</sub>-receptors is in general slow, the onset of temporal WTA competition may not be fast enough to suppress the second or third cortical input in a theta cycle. From purely dynamical point of view, the temporal WTA mechanism can be similarly accomplished by recurrent inhibition (Fukai, 1995b; Fukai, 1996). As the intrastrial recurrent inhibition is mainly mediated by GABA<sub>A</sub>-receptors (Groves, 1983; Kawaguchi, 1997), it is desirable that GABA<sub>A</sub>-receptor-mediated fast inhibition cooperates for the onset of competition. However, physiological evidence for a WTA competition through the intrastrial recurrent inhibition is very weak (Jaeger, Kita & Wilson, 1994; Kita, 1995; Park, Lighthall & Kitai, 1980; Plenz & Aertsen, 1996; Rebec & Curtis, 1988). Further studies are needed to clarify the functional roles of striatal GABAergic systems.

Owing to the self-activation in the loops and the firing-rate-based WTA competition in the thalamus, a new cortico-BG–thalamic loop can be activated only after a previous one is inactivated. The former is needed for a sustained inhibition of the GPi neuron in an active loop, while the latter is mainly for limiting the number of active loops. The competition also prevents the next loop from being activated solely by the preparatory activity of S-neurons (see Fig. 4(c)). Using this property of the competing cortico-BG–thalamic loops, we could control the rate of sequence generation with a single external input, i.e. the subthalamic input to GPi neurons. The diffusive and nontopographic anatomical organization of the subthalamo-pallidal projection (Parent & Hazrati, 1995) makes the subthalamic nucleus particularly suitable for that purpose. It is noted that the activity of subthalamic neurons engaged in the proposed function should be selective to neither current nor next component: The subthalamic input implies a simple command “proceed to the next movement” rather than a more specific command, say “proceed to movement B after A”.

The WTA competition becomes essentially temporal among the loop neural circuits, as mentioned above. Nevertheless, S-neurons are still required for activating the next loop correctly for arbitrarily timed $I_{in}$. If the first component in cortical oscillations was not selected by S-neurons prior to its execution, the component introduced next into the cortico-BG–thalamic loops would be the one which arrives first after the inactivation of a previous loop. Thus selected component is not necessarily the next component planned in the sequence.

In the present model, the competition among the cortico-BG–thalamic loops was realized at the thalamus, since thalamic relay neurons are considered to exert inhibitory influences on each other through the backprojection from reticular thalamic neurons (Sherman & Koch, 1986). However, the desired lateral inhibition can also occur at GPi and the striatum, as competition among M-neurons in the latter case, as both anatomical sites are rich in GABAergic projection neurons and interneurons. In any case, all the results obtained in this paper should be reproduced without much difficulties.

Broad functions of the basal ganglia have not been fully clarified, and many points discussed here must be still tested by experiments. In particular, further experiments for clarifying the cooperation between the basal ganglia and cortical oscillations in sequence processing in vivo are awaited.

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Appendix A

The values of the model parameters are listed below.

A.1. Short-term memory:

\[ V_{\text{rest}} = -60 \text{ mV and firing threshold} = -50 \text{ mV}, \quad \Delta V_{\text{ADP}} = 30 \text{ mV}, \quad \Delta V_{\text{GABA}} = 10 \text{ mV}, \quad \theta = 5 \text{ mV and } \varphi = 3 \text{ mV}. \]

The time constants are \( \tau = 4\text{ ms and } \tau_{\text{ADP}} = 200 \text{ ms} \) (Storm, 1989). Frequency of theta oscillation \( f = 6 \text{ Hz} \).

A.2. S-neurons:

\[ V_{\text{SI}} = -70 \text{ mV and threshold for firing is } -50 \text{ mV} \] (Wilson & Kawaguchi, 1996). \( \tau_3 = 3 \text{ ms, } \tau_4 = 70 \text{ ms and } \tau_{\text{FTA}} = 150 \text{ ms. } \eta = 5 \text{ and } \varphi_{\text{aff}} = 130 \text{ mV}. \)

A.3. The competing loops:

The model neural network exhibits the desired behavior for a wide range of the parameter values. In the simulations, the values of parameters are fixed as \( J_{\text{ad}} = 1, \quad J_{\text{xy}} = 0.8, \quad J_{\text{st}} = 0.4, \quad J_{\text{xy}} = 0.4, \quad J_{\text{st}} = 1.5, \quad K = 0.9, \quad h_{\text{a}} = 1, \quad h_{\text{b}} = 0.8, \quad h_{\text{c}} = 0.5, \quad \varepsilon = 0.01 \text{ and } \beta = 5 \text{ unless otherwise stated. The time constants are } \tau_3 = \tau_4 = 4 \text{ ms.} \)

References


