Simulations of pharmacological actions in the basal ganglia circuit
Ichiro Sakurai (P)1, Kenichi Sato2, and Michio Niwano1
1 Department of Electronic Engineering, Graduate School of Engineering, Tohoku University
2 Information Science Center, Tohoku Pharmaceutical University
E-mail: denko@riec.tohoku.ac.jp

Abstract—We have carried out computational simulations to investigate pharmacological effects in the basal ganglia (BG). Results of our simulations showed that dopamine depletion induces a time delay of the saccade eye movements and an oscillatory behavior of the neuronal activity in the BG. We also suggest that the oscillatory behavior is originated from formation of closed loop circuits in the BG.

Keywords—Basal ganglia, Saccade, Dopamine depletion, Oscillation, Closed loop circuit

1. Introduction
It is reported that injection of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydro-pyridine (MPTP) into animal brains reduces the dopamine concentration in the whole brain [1]. Delay of eye movements in a saccade and oscillatory behaviors of the neuronal activity in the BG are also reported [2][3]. In the present work, we simulate the delay in saccade eye movements and the oscillation in the BG on the basis of a computational model developed by Brown et al [4]. We also discuss the mechanism for the appearance of oscillatory behaviors in the BG neuronal activity.

2. Method
2.1. TELOS model
We have carried out simulations by using a neural network model, named “TELOS model”. TELOS is from the ancient Greek telos for goal, end, or completion of a plan, but is also an acronym for TElencephalic Laminar Objective Selector. This model was developed by Brown et al. to explain how the brain learns different types of eye movement, and deals with the neural circuits of versatility including basal ganglia, cortex, thalamus and superior colliculus [4]. In TELOS model, phasic dopaminergic signal affects some neurons and synapses: the activity of striatal cells and synaptic weights related to the basal ganglia changes, depending on the dopamine concentration in the brain. The TELOS model has the following advantages: Firstly, we can calculate directly the neuronal activity. Secondly, we can adjust the dopamine concentration and the intensity of stimulus to neurons. Therefore, the TELOS model is appropriate for simulating the effects of dopamine depletion that would be induced by MPTP injection into the basal ganglia. Among 14 hypotheses in the TELOS model, two hypotheses, thalamo-striatal feedback hypothesis and dopamine hypothesis, play a crucial role in our present investigation. The former one is that the pathway (feedback) from the thalamus to the striatum cannot be neglected, and the latter one is that the dopamine concentration depends on whether the eye movement is executed correctly or not.

2.2. Simulation method
It is well known that MPTP injection causes destruction of dopamine neurons, resulting in a decrease in the dopamine concentration in the brain [1]. As mentioned above, dopaminergic signals affect some neurons and synapses. One typical equation in the TELOS model representing effects of dopamine depletion is given by the equation:

\[ \frac{d}{dt} G_{xy}^{(SI)} = 30 \left[ (1 - G_{xy}^{(SI)}) N S_{xy} - (G_{xy}^{(SI)} + 0.58) \right] \quad (1) \]

where \( G_{xy}^{(SI)} \) is the activity of striatal neuron, \( S_{xy} \) is the activity of superior colliculus and \( N \) is the parameter that depends on the amount of dopamine. This equation, which corresponds to Eq. (30) in ref. [4], represents a temporal change of \( G_{xy}^{(SI)} \) that depends on the value of \( N \). When the model circuits show no changes in the dopamine concentration, \( N \) is set at zero, and when the dopamine concentration is depleted, \( N \) becomes non-zero. We can thus represent MPTP injection into animal brains as non-zero values of \( N \). In order to investigate the effects of dopamine depletion, we used other equations in ref. [4] that contain parameter \( N \); for example, eqs. (34), (52), and (53) given in ref. [4].

Time tables of the saccade task and the simulation we have performed to investigate pharmacological effects are depicted in Fig. 1. Saccade tasks are performed twice; without and with MPTP injection. In the saccade task, the first optical stimulus (fixation point) is given to the center of the retina. After 200 ms, the second stimulus (target
point) is given to a different locus and the first stimulus is shut off, as is shown in Fig. 2. The eyes will begin to move toward the target point more than 200 ms after the second stimulus is given. In the simulation for the investigation of pharmacological effects, two sequential tasks are carried out. The first task with no MPTP injection is performed from 0 s to 1 s. For this task $\bar{N}$ is set at zero. Subsequently, $\bar{N}$ is fixed at a non-zero positive value until 81 s. This duration corresponds to a waiting time after MPTP injection to animal brains in the conventional animal experiment. After this waiting, the second saccade task is performed for 1 s.

3. Simulation results

3.1. Delay of eye movement

Activity of superior colliculus (SC) cell when dopamine is depleted is shown in Fig. 2.

These traces were obtained during 2nd task in Fig. 1. According to ref.[4], if activity of SC cell reaches 0.6, eye movement initiates. In Fig. 2, as $\bar{N}$ increases, delay of eye movement (delay of rise in each trace) increases. As shown in Fig. 1, the time target point is given is 0.2 s. Thus, when $\bar{N}$ is 2, delay of eye movement is about 82 ms.

Occurrence of eye movement is observed in animal experiment[2], thus our simulation reproduced this phenomena. In Fig. 1, maximum value of each trace is also decreased. In TELOS model, only whether activity of SC cell reaches 0.6 is important. Thus we neglect the change of the maximum value in each trace.

3.2. Oscillatory behaviour of neuronal activity

During 2nd saccade under dopamine depletion ($\bar{N} = 1$), some neurons around basal ganglia show oscillatory behavior. The oscillation of cells is shown in Fig. 3.

In Fig. 3, globus pallidus external segment (GPe), thalamus, striatum (STM), globus pallidus internal segment (GPI) show oscillatory behavior. Activity of subthalamic nucleus (STN) is not oscillatory.

To extract minimum indispensable components in the circuit for generating oscillation, first we omitted input neurons of TELOS model. The circuit for essential components for generating the oscillation is shown in Fig. 4.

4. Summary

In the computational model, we reproduce delay of eye movements and oscillatory behavior in basal ganglia during dopamine depletion. By our analysis, the origin of oscillation is the closed loop circuit.

References