**RESEARCH PROJECT – PROJECT REPORT**

**SUBMISSION GUIDELINES/INSTRUCTIONS**

1. Name of Research Institution Conducting Research Project:

**Drexel University**

2. Name of Principal Investigator/Co-Principal Investigator:

(a) Principal Investigator:

**Ilya A. Rybak**

(b) Co-Principal Investigator:

**Sergey N. Markin; Yaroslav I. Molkov**

3. Research Project Title/Research Project Record Identification Number:

(a) Research Project Title:

**Computational Modeling of the Primate Motor Control System for Subsequent Simulation Studies of Huntington's Disease**

Research Project Record Identification Number:

**A-8427**

4. Research Project Reporting Period:

[**04/01/15**] through [**09/30/15**]

5. Is the Research Project on track to be completed by the End Date specified in the Research Agreement?

Yes: [\_\_X\_\_] No: [\_\_\_\_\_].

6. Is the Research Project on track to substantially achieve each of the original Milestones set forth in the Research Agreement?

Yes: [\_\_X\_\_] No: [\_\_\_\_\_].

7. Do you anticipate any changes to the personnel (including the level of effort) approved for this project?

Yes: [\_\_\_\_\_] No: [\_\_X\_\_].

8. Research Project Milestones: Set forth below are each of the milestones for the research project that were to be accomplished during the reporting period covered by this progress report.

1. **A model augmented by the Basal Ganglia (BG) compartment controlling the thalamo-cortical relay network capable of efficiently discriminating between competing motor instructions (action selection). [specific aim 2.2]**
2. **Incorporation of synaptic plasticity for reinforcement learning in cortico-striatal network. [specific aim 2.2]**
3. **Complete and deliver the Large Scale Network Simulation Software that the Foundation has found acceptable, including debugging; ALL PREVIOUS AND SUBSEQUENT MODELS will be re-cast into the Large Scale Network Simulation Software environment. Provide Large Scale Network Simulation Software demonstration and benchmarking to the Foundation. [specific aim 4.3]**

9. Research Project – Project Report:

a) Please provide (i) a reasonably detailed description of the status and progress of your research project (including an analysis of the progress towards each of the milestones listed above (whether achieved or not achieved)) and (ii) any other additional or relevant information related to the research project that you would like to share with the foundation's science team. If not included as part of your description below, please provide a copy of all results and underlying data as a separate document(s).

**I. A model augmented by the Basal Ganglia (BG) compartment controlling the thalamo-cortical relay network capable of efficiently discriminating between competing motor instructions (action selection).**

Specific Aim 2.2: Modeling BG circuits:

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| --- |
|  |
| **Figure 1.** Basal ganglia model involved in action selection, synaptic plasticity and reinforcement learning.  PFC=Pre-Frontal Cortex; PMC=Pre-Motor Cortex; MSN=Medium Spiny Neuron; GPi=Globus Pallidus internal; GPe=Globus Pallidus external; SNc=Substantia Nigra pars compacta; STN=Sub-Thalamic Nucleus. |

We developed a model of the BG which contains both direct and indirect pathways. The model is composed of direct and indirect pathway striatal medium spiny neurons (MSN), internal segment of the globus pallidus (GPi), external segment of the globus pallidus (GPe), a substantia nigra pars compacta (SNc), and a subthalamic nucleus (STN). Striatal neurons of the BG model receive sensory information through the prefrontal cortex (PFC) network; they also receive information about active motor commands from the thalamus. BG output is delivered back to the thalamus through the GPi. Direct pathway striatal neurons inhibit corresponding GPi neurons, which in turn disinhibit corresponding thalamic neurons. Direct pathway striatal neurons also exhibit recurrent lateral inhibition, where each neuron projects an inhibitory synapse on all other neurons with a 0.3 connection weight. In contrast, indirect pathway striatal neurons inhibit corresponding GPe neurons, which in turn disinhibit corresponding GPi neurons. Connection weights between the different neuron populations included in the model are given in **Table 1.1** for glutamatergic connections and **Table 1.2** for GABAergic connections. GPi, GPe and thalamic neurons also receive tonic drives which set their base activity level, the weights of tonic drive connections are given in **Table 1.3**. Dopaminergic output from the SNc influences synaptic plasticity of cortico-striatal connections between the PFC and direct and indirect pathway striatal neurons. STN output induces variability in the activity of GPe neurons, necessary for exploring the motor response space. **Figure 1** shows a schematic of the overall BG model described in this report.

|  |  |  |
| --- | --- | --- |
| **Table 1.1: Glutamatergic connection weights** | | |
| **Sources** | **Targets** | |
| D1-MSNi | D2-MSNi |
| Thalamusi | 1 | 1 |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Table 1.2: GABAergic connection weights** | | | | | |
| **Sources** | **Targets** | | | | |
| D1-MSNi | D2-MSNi | GPii | GPei | Thalamusi |
| PFCj | Varies1 | Varies1 |  |  | 0.452 |
| D1-MSNi |  |  | 2 |  |  |
| D2-MSNi |  |  |  | 2 |  |
| GPii |  |  |  |  | 1 |
| GPei |  |  | 1.5 |  |  |
| 1 connection weights are plastic, initially randomly set between 0 and 0.01, and vary trial-to-trial.  2 connection weight is 0.45 where j=i, otherwise weight is 0. | | | | | |

|  |  |  |  |
| --- | --- | --- | --- |
| **Table 1.3: Tonic drive connection weights** | | | |
| **Sources** | **Targets** | | |
| GPi | GPe | Thalamus |
| Tonic Drive | 2 | 1.3 | 0.5 |

In the current incarnation of the BG model, striatal, GPe, GPi and thalamic neurons are modeled as non-spiking neurons whose activation depends on the weighted sum of their inputs and is described by a sigmoidal function as follows:

(1.1)

where: is the output, or firing rate, of the neuron; and is the sum of weighted inputs.

Due to the nature of recurrent lateral inhibition between direct pathway striatal MSN, and the feedforward loop architecture of the circuit, the dynamics of direct pathway striatal MSN and thalamic neurons are described according to the Wilson-Cowan model. The time evolution of activity of neurons is described using a nonlinear sigmoidal function representing interactions between neurons, as follows:

(1.2)

where: is a neuron’s firing rate during the previous time step; is the weighted sum of inputs during the current time step; and is a time constant, equal to 1ms in this case.

The activation of other neurons in the model is considered instantaneous.

The current model accommodates different sensory cues at the PFC level, modeled as different PFC inputs to the striatum, and can produce different actions in response. Each action is represented by the activity of one thalamic neuron. In the initial implementation of the model we assumed that PFC sensory cues are mapped to thalamic actions in a one-to-one fashion, such that PFC neuron carrying sensory cue triggers thalamic neuron, associated with action, where and the weight of such one-to-one connection is 0.45; otherwise the connection weight for other cue-action pairs (PFC-thalamic neuron pairs), where , is 0. These sensory cues to action connections are direct and do not pass through any of the BG nuclei, thus representing pre-associated cue-response mapping.

Each of the BG nuclei, except the striatum and SNc, contains a population of neurons of the same size as possible actions, such that each neuron in a BG nuclei corresponds to one action. The striatum incorporates two neurons per action, one that is a direct pathway striatal MSN and the other an indirect pathway MSN. The SNc produces one common dopaminergic reward signal that influences the synaptic plasticity of connections between the PFC and striatal neurons, and is therefore modeled as a single signal.

PFC sensory output, corresponding to all possible sensory cues, is delivered to all direct and indirect pathway striatal neurons. Connection weights between PFC neurons and striatal MSN are initially set randomly between 0 and 0.01, but are plastic and therefore change trial-to-trial based on a reinforcement learning algorithm.

The firing rate of each direct pathway MSN is driven by the differential equation:

(1.3)

where: is the firing rate of that MSN; is the weighted sum of inputs to that MSN; is the Wilson-Cowan time constant equal to 1ms; and is the index of the direct pathway MSN corresponding to a particular action.

The weighted sum of inputs to each direct pathway MSN during the current time step,, is defined as:

(1.4)

where: is the connection weight between PFC neuron, corresponding to cue between 1 and , and direct pathway MSN, this weight is plastic and changes trial-to-trial; is the firing rate of PFC neuron; is the connection weight between thalamic neuron and direct pathway MSN, corresponding to the same action, and is equal to 1; is the firing rate of thalamic neuron; and is the recurrent lateral inhibition connection weight between direct pathway MSN equal to 0.3.

The firing rate of each indirect pathway MSN,, is defined as:

(1.5)

where: is the connection weight between PFC neuron and indirect pathway MSN, this weight is plastic and changes trial-to-trial; and is the connection weight between thalamic neuron, and indirect pathway MSN, corresponding to the same action, and is equal to 1.

The firing rate of each GPe neuron,, is defined as:

(1.6)

where: is the tonic drive to GPe neurons, equal to 1.3; is the weight of the inhibitory connection between indirect pathway MSN and GPe neuron, corresponding to the same action, and is equal to 2; and is an exploratory signal generated by a corresponding STN neuron.

The STN is modeled as different outputs, each to a corresponding GPe neuron, where is the index of the corresponding action. The outputs’ magnitude, or firing rate, per output is a random positive value between 0 and 0.8, and varies trial-to-trial. The STN generates the exploratory signal which gives the BG its exploratory function to find better responses to sensory cues and correct for any perturbations:

. (1.7)

The firing rate of each GPi neurons,, is defined as:

(1.8)

where: is the tonic drive to GPi neurons, equal to 2;is the weight of the inhibitory connection between direct pathway MSN and GPi neuron, corresponding to the same action, and is equal to 2; andis the weight of the inhibitory connection between GPe neuron and GPi neuron, corresponding to the same action, and is equal to 1.5.

The firing rate of each thalamic neurons,, obeys the differential equation:

(1.9)

where: is the firing rate of thalamic neuron; is the weighted sum of inputs to thalamic neuron; and is the Wilson-Cowan time constant equal to 1ms.

The weighted sum of inputs to each thalamic neuron during the current time step,, is defined as:

(1.10)

where: is the tonic drive to thalamic neurons, equal to 0.5; is the connection weight between PFC neuron and thalamic neuron; andis the weight of the inhibitory connection between GPi neuron and thalamic neuron, corresponding to the same action, and is equal to 1.

Each experimental run, or simulation, consists of a predetermined number of consecutive trials, where each trial’s duration is 10ms, allowing Wilson-Cowan neurons to approximately reach steady state. The BG model learns, between trials, by modifying plastic synaptic connection weights between the PFC and striatal MSN based on a reinforcement learning algorithm.

**2.2.1 Action Selection:** In response to specific sensorimotor signals, the thalamus provides multiple candidate behaviors or motor commands to the BG due to the activation of specific thalamic neurons which correspond to the presented sensorimotor signals. The BG in turn receives additional sensorimotor input from the PFC and gates one or more of the thalamic motor commands while suppressing other competing responses. The BG output is conveyed through the GPi, which inhibits thalamic neurons and prevents inappropriate motor instructions from being executed by the motor cortex. The action selected for execution is determined by the cortico-striatal feedforward networks. The striatum is made up of two independent populations of medium spiny neurons (MSN) one of which sends inhibitory projections to the GPi (direct pathway), while the other projects to the GPe, which in turn inhibits the GPi (indirect pathway). Direct pathway striatal MSN contain recurrent inhibitory connections within the population, which permits the gated motor command to suppress weaker competing commands. Accordingly, there are two mechanisms of action selection. A direct pathway MSN, receiving the strongest excitation, will inhibit other direct pathway MSN, thus disinhibiting GPi neurons responsible for blocking corresponding competing motor commands. The GPi neuron that receives direct inhibition from the active direct pathway MSN will be inhibited and thus let the corresponding thalamic signal to pass through and initiate the movement. Activation of a direct pathway MSN represents an approval (GO) of the action. In contrast, the second mechanism of action selection occurs when an indirect pathway MSN is activated and inhibits a corresponding GPe neuron, which leads to the disinhibition of the corresponding GPi neuron and suppression of the corresponding motor command, thus preventing the action from being executed (NOGO). The state of cortico-striatal synaptic weights from the PFC to direct and indirect pathway MSN associates sensory cues which particular actions and permits the BG to determine a preferred action when multiple options are presented by the thalamus.

**II. Incorporation of synaptic plasticity for reinforcement learning in cortico-striatal network**

**2.2.2. Synaptic plasticity and reinforcement learning in the BG:** Synaptic connections from the PFC to striatal MSN populations experience reward-based synaptic long term potentiation (LTP) and long term depression (LTD) implemented with a reinforcement learning rule. Striatal populations receive dopaminergic inputs from the SNc. These inputs represent a trial-to-trial reward/punishment system in the model. The differential effect of dopamine inputs on the populations of direct and indirect pathway striatal neurons is the result of the fact that D1 dopamine receptors are prevalent in direct pathway MSN while the MSN of the indirect pathway mostly express D2 receptors. Since D1 receptors are excitatory and D2 receptors are inhibitory, dopaminergic input from the SNc provides a facilitatory effect on the activity of D1 GO neurons in the direct pathway and an inhibitory effect on D2 NOGO neurons of the indirect pathway. Accordingly, phasic dopamine increases will lead to facilitation of LTP in the GO population and to suppression or even LTD in the NOGO counterpart. Similarly, dips in dopamine release potentiate synaptic connections in the indirect pathway and weaken ones in the direct pathway.

Cortical input to the SNc carries error signals, which are derived from the difference between the planned motor program and the outcome of its execution. This cortical input is used to determine the actual reward at the SNc. The SNc compares the actual reward with the expected reward, derived from previous experiences or trials, rewarding changes that lead to more desirable BG output and punishing changes that lead to larger errors. The SNc model assumes that the current trial will generate an error equivalent to that of the previous trial and any changes in the current trial’s error from that of the previous one causes a non-zero SNc output, which is either positive and thus reinforces random network changes that led to improved outcomes (smaller errors) or negative and thus discourages changes that led to worse outcomes (larger errors). Any complications in performing a reaching task (obstacles, perturbations etc.) will cause inaccurate motor program execution and thus reconfiguration of the action selection network in the striatum through reinforcement learning.

Synaptic plasticity and determination of the trial-to-trial changes in the connection weights in the model is implemented as follows:

(2.1)

(2.2)

where: is the synaptic connection weight between PFC neuronand direct pathway MSN for the previous trial; is the synaptic connection weight between PFC neuronand indirect pathway MSN for the previous trial; is the SNc dopaminergic reward/punishment signal; andis a synaptic depotentiation rate (synaptic scaling) parameter, equal to 0.08.

Note, weights and are positive, and therefore not allowed to drop below zero due to LTD or synaptic depotentiation.

, the SNc dopaminergic reward/punishment signal, is calculated by determining the difference between the previous trial error, which serves as the expected error for the current trial, and the actual error of the current trial and multiplying the difference by a learning rate parameter:

(2.3)

where is a learning rate parameter, equal to 100; is the error during the previous trial (expectation); and is the error during the current trial.

The error for each trial is calculated as follows:

(2.4)

where is the desired target action, and is the current selected action defined by the thalamic output.

As a result of action selection activity by the BG, multiple thalamic neurons, corresponding to several actions, may co-activate. In the current model implementation we define the selected action as an average index of all thalamic neuron activity. The thalamic output corresponding to the current selected action,, is determined by calculating the average index of all thalamic neurons representing all possible actions, as follows:

(2.5)

where is the action index between 1 and .

Note, the current BG model is not yet coupled to action execution, so the definition of the selected action does not seem natural. However, the interpretation we have in mind (and will implement on the next stages of the project) is that every thalamic neuron represents a motor program performing reaching movement in a particular direction. The thalamic neurons relay signals from PMC to MC according to their firing rates. Accordingly, in the first order approximation the selected motor program and the resulting movement direction can be calculated as a weighted average of all possible programs with weights defined by the firing rates of the relay thalamic neurons, which is captured by Eq. 2.5.

**2.2.3. Exploration function of BG:** In addition to reinforcement learning functions of the direct GO and indirect NOGO pathways, the indirect pathway is involved in exploration of the alternative actions space. This is particularly important for quick learning when the system is required to switch from an established action selection pattern to a new one due to environment changes (e.g. perturbation, or appearance of an obstacle). To account for such a mechanism the model incorporates an exploratory signal generated by the STN, which excites GPe neurons and induces variable fluctuations in their activity. In case of uncertainty about action choices, GPe neurons can spontaneously suppress corresponding GPi neurons and permit corresponding actions to be executed. If a favorable outcome is realized, the action that generated the more desirable outcome will be learned by the striatal network and associated with the current sensory PFC input, resulting in the deliberate execution of this action in the future if similar sensory cues are presented. In contrast, if the outcome is undesirable, the next time similar cues are presented to the striatum, this action will be suppressed, which increases the probability of some other learned or spontaneous action to be executed under similar sensory conditions.**III. Complete and deliver the Large Scale Network Simulation Software that the Foundation has found acceptable, including debugging; ALL PREVIOUS AND SUBSEQUENT MODELS will be re-cast into the Large Scale Network Simulation Software environment. Provide Large Scale Network Simulation Software demonstration and benchmarking to the Foundation.**

Specific Aim 4.3: Simulation tools:

According to the project specifications, the first version of a GPU-based Large Scale Network Simulation (LSNS) software package is developed. <module structure> This simulation environment is currently used for multiscale modeling and consists of the following modules:

1) *The simulation engine*. This is the core of the LSNS package that provides the basic abilities to perform computational simulations of neural networks of Hodgkin-Huxley type neurons. The simulation engine is able to perform calculations for multiscale modeling and computational analysis of cross-level integration of: (a) the intrinsic biophysical properties of single neurons (at the level of ionic channel kinetics, dynamical changes of ionic concentrations, synaptic processes); (b) population properties (synaptic interactions between neurons within populations with random distributions of neuronal parameters); (c) network properties (connectivity and type of synaptic interactions between populations with random distribution of connections), (d) morpho-physiological structure (organization in interacting modules/compartments).

2) *The translator*.

3) *The model convertor.* This is a standalone utility which is developed to convert ASCII files of model descriptions from an old format (which were created by a previous simulation package NSM) to the new format (that is supported by the new LSNS simulation package).

**LSNS simulation engine**

**Neuron model:** The simulation engine supports the computation of the conductance-based single-compartment model of neurons in the Hodgkin–Huxley style. The dynamics of neuronal membrane potential (V) is defined by a set of membrane ionic currents and described as follow:

(3.1)

where is the neuronal membrane capacitance; are currents of ion channels; are synaptic currents; are pump currents.

The synaptic currents and currents of ion channels which are implemented by the LSNS core are considered as different types of ion channels and classified by gate variables. The current version of the LSNS package supports: (i) v*oltage-gated* ion channels which open or close depending on membrane potential, (ii) *other-gated* ion channels like calcium-dependent potassium channels, leak channel, etc; (iii) *ligand-gated* (synapses) ion channels open or close depending on binding of ligands to the channel.

**Implementation of ion channels:** All ion channels (including ligand-gated ion channels) are implemented according to follow formula:

(3.2)

where is the maximal conductance; and are gate variables (activation and inactivation, respectively); and are powers of activation and inactivation, correspondingly; is the membrane potential and the reversal potential of the corresponding channel.

In general, the gate variables () for ion channels (excluding synapses) are described as:

(3.3)

where is a time constant, is the steady-state value of the correspondent gate variable (activation or inactivation, respectively).

**Voltage-gated ion channels:** These types of ion channels open or close depending on the membrane potential of the cell and are described as follows:

1) The *generic description* [see Butera et al, 1999] of the gate variable (activation or inactivation) is defined as:

(3.4)

where is the membrane potential, is the half-voltage and is the slope. The time constants of different subtypes of gate variables are:

1. instant current: ;
2. generic current: ;
3. modified generic current: ;
4. modified generic A-current:

where: , , are time constants; , are the half-voltages of the time constants; , are the slopes of the time constants; and is a threshold.

2) The  *description* [see potassium delayed-rectifier channel description in McCormick & Huguenard, 1992] of the gate variable (activation or inactivation) is defined as:

,

where: ; is the membrane potential; is the half-voltage; is the slope; and are free parameters which specify either alpha or beta variables. The time constants of different subtypes of gate variables are:

1. instant current:
2. current

**Other-gated ion channels:** The dynamics of gate variables for *Ca-activated potassium* [Mifflin et al. 1985] channels are also described according to (10). The steady states and time constants for these types of ion channels’ gate variables are:

1. ,

The time constants are: or

1. , ,

The time constants are: or

where: is the membrane potential; is the half-voltage; is the slope. The variables and are free parameters which specify the dynamics of the gate variable.

The *leak current* approximates the passive properties of the neuron and is described as:

(3.5)

where: is the membrane potential and is the reversal potential of the leak current.

**Ligand-gated ion channels (synapses):** Postsynaptic current [Ermentrout&Terman, 2010, Destexhe et al., 1994, Destexhe&Mainen, 1994, Destexhe et al., 1998] generated by the j-th synapse is calculated as follows:

(3.6)

where: is the maximal conductance; is the gate variable that characterizes the transmitter release; is the factor that defines how effectively the post-synaptic cell responds to neurotransmitters (=1 for most synapses, except those where the mechanism of synaptic plasticity is implemented); is the membrane potential of the post-synaptic neuron; is the reversal potential of the *j*-th synapse.

Suppose that and are equal for *N* synapses ( *= 1,..N*), then equation (13) can be rewritten as:

(3.7)

According to (14) the total postsynaptic current for similar synapses at a neuron (*j* = 1..N) is calculated as follows:

(3.8)

The current version of the package supports three types of synapses, which are:

1. *Weighted sum* synapse:

The neural transmitter release for this type of synapse is modeled as the weighted sum of all input signals at the synapse, and can be written as:

(3.9)

where: is the transmitter release rate; and are the connection weight and input signal between a post-synaptic neuron and a non-spiking element in the network (such as drive, output, feedbacks; see section **network units**), respectively. The total transmitter release for all similar synapses can be written then as:

(3.10)

1. *Instant* synapse:

The simplest model of transmitter release at the *j*-th synapse between post- and pre- synaptic non-spiking neurons is modeled as a sigmoid function and is described as follows:

(3.11)

where: is the transmitter release rate; is the connection weight of the *j*-th synapse between post- and pre- synaptic neurons; is the membrane potential of the presynaptic neuron; and are the half-voltage and slope of the instant synapse. The total transmitter release for instant synapses is given by:

where: (3.12)

1. *Pulse model* of synapse:

The transmitter release for pulse synapses is modelled as a recurrence equation for the   
-th integration step:

(3.13)

where: is the integration step; T is the time constant of the synapse; is the transmitter release rate; is the connection weight of the *j*-th synapse between post- and pre- synaptic neurons; is the Dirac function (which is equal to 1 when a spike is generated by a presynaptic neuron or 0 otherwise); is the membrane potential of the presynaptic neuron; =0. The total transmitter release can be written as:

(3.14)

The mechanism of synaptic plasticity, which defines how effectively the post-synaptic cell responds to neurotransmitters and involves the NMDA receptors [Destexhe&Mainen, 1994, Ermentrout&Terman, 2010], is also implemented in the current version of the LSNS package. It represents the magnesium () blockade of *NMDA-type* synapses and is calculated as follows:

(3.15)

Finally, equation (15) for total synaptic current of all similar synapses (*j* = 1..N) can be written as:

(3.16)

where: the total transmitter release can be defined as a linear recurrence equation   
, is the transmitter release rate; for pulse model of the synapse or 0 otherwise; or or for different types of synapses; for *NMDA-type* of synapse or 1 otherwise.

**Implementation of ion dynamics:** The reversal potentials of ions are calculated according the following equation:

(3.17)

where: is the universal gas constant;is the temperature;   
 is the Faraday constant, and is the ionic charge which is: +1 for Na, +1 for K, +2 for Ca, -1 for Cl and +2 for Mg ions. The subscripts ‘out’ and ‘in’ indicate the concentrations of these ions outside and inside the cell, respectively.

The description of ions dynamics is written as:

(3.18)

where: is the time constant for ion dynamics; in the right part of the equation, the first term represents influx from the extracellular space through voltage-gated channels of correspondent ions, and the second term represents the membrane pump, which extrudes free intracellular ions from the cytoplasm. Parameters and define ion buffering and pump kinetics.

The current version of the LSNS package supports the following descriptions of ion pumps and currents of voltage-gated channels:

1. Sodium dynamics for the Na/K pump is taken from [Li et al. 1996], and defined as:

(3.19)

where: ; is the pump current rate; is the equilibrium intracellular concentration; and is the pump parameter.

1. The calcium dynamics for the Ca pump are defined as [see Booth et al. 1997&Rybak et al. 1997]:

(3.20)

where: is the pump current rate; is the equilibrium intracellular Ca concentration.

The Ca buffering parameter in equation (25) is described as either (i) [Booth et al. 1997] or (ii) , where are normalized coefficients [Rybak et al. 1997].

**Network units:** In additional to the neuron model, the simulation engine supports non-spiking network elements which emulate tonic activity (*drives*) from external parts of the nervous system, integrated nerve activity (*outputs*) produced by the network, and afferent signals from the sensory-motor system (*feedbacks*).

**Drives:** These network units generate constant signals and are used to emulate tonic excitatory and inhibitory external drives to network elements like neurons and outputs. The current version of the LSNS simulation engine provides the possibility to create drives and establish connections between drives and other network units such as populations of neurons and outputs.

**Outputs:** The outputs are non-spiking units which combine input signals from both spiking (neurons) and non-spiking (non-spiking neurons, drives, outputs and feedbacks) network elements, filter the weighted sum of these inputs and project the output signal through the network. The current version of the LSNS simulation engine provides the possibility to create outputs and establish connections between outputs and other units like populations and outputs. The integrated activity from all input elements can be written as follow:

(3.21)

where: , are time constants. The weighted sum of input signals () is defined as:   
(i) ; where is the output from any non-spiking element like drive, output or feedback; (ii) ; where for non-spiking neurons (see model of instant synapses); (iii) (see model of pulse synapses for details).

**Feedbacks:** The feedbacks collect information from the sensory-motor system and project the pre-processed input signals onto network elements (both spiking and non-spiking). The current version of the LSNS simulation engine implements primary and secondary afferent feedbacks from the motor system:

(3.22)

where: is the normalized muscle velocity; ; is the normalized muscle displacement; is the integrated activity of corresponding motoneurons; and are constant components; is the normalized muscle force; , , , , , are coefficients (see [Markin et al, 2010] for details).

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(b) Please provide a list of any separate documents you are providing along with this progress report (manuscripts, files, etc).

1. BG\_model.cc

Source code of basal ganglia model

1. Basal\_Ganglia\_Model\_Simulation\_Results.pdf

Basal Ganglia model sample simulation replicating published experimental data

1. X