All initial simulations in this project (~1st year) will be performed using a neural simulation package NSM-3.0 developed at Drexel by Drs. S. N. Markin, N. A. Shevtsova, and I. A. Rybak. This simulation environment has been specially developed and is currently used (see our previous models) 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). The periphery model will be included in the package (see above). NSM-3.0 has special tools for simulation of various in vivo and in vitro experimental approaches (suppression of different ionic channels and transmitter systems, lesions, transections, various stimulations applied to particular neural populations, etc.) An important advantage of the package is that a user can build models by a top-down approach. For example, a model can be explicitly built at the population level by defining average values and variances of neuronal parameters within populations and weights of synaptic connections between populations. The program then defines the individual parameters of neurons and connections using a random generator and the assigned average values and variances. NSM 3.0 allows simulation of about a hundred neural populations with 20-50 neurons in each population with reasonable processing time. The package will be distributed among all project participants and they will be able to use the model in its current state.

Starting at the beginning of the project, a GPU-based large scale network simulation software package (LSNS) will be developed and completed in about one year. All models will run on the LSNS environment, enabling a free-standing, inexpensive, computationally-efficient means of simulating the activity of large networks of synaptically-connected, biophysically-relevant neurons.

The core of openLSNS is developed and includes:

General information,

Architecture,

Kernels,

Interactions.

According to the project specifications, the first version of a GPU-based large scale network simulation software package (LSNS) is developed and includes:

1) The simulation engine (the core of LSNS package that provides the basic abilities to perform computational simulations of neural networks of Hodgkin-Huxley type neurons). The simulation engine includes: 1. Cells model that may consist of: (a) synaptic model; (b) ions dynamics; (c) ions current (including synapses); (d) membrane potential. 2. Network units which are (a) drives; (b) outputs; (c) feedbacks.

2) The translator.

**Cells model.**

**Synaptic model**

***General information***

Synaptic current for postsynaptic neuron that generated by j-th synapse is calculated according to [Ermentrout&Terman, 2010, Destexhe et al., 1994, Destexhe&Mainen, 1994, Destexhe et al., 1998]:

(1)

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

Let suppose (for simplicity) that , are equal for N synapses (*j* = 1…N) and =1, then

(2)

According to (2) the synaptic current for postsynaptic neuron from all similar synapses (*j* = 1..N) is calculating as:

(3)

Three types of synapses are implemented in the current version of the package.

***Weighted sum***

(4)

Total synaptic current for postsynaptic neuron is:

(5)

where:

(6)

is j-th input from non-spiking network element like drive, output, feedback etc.

***Instant synapse***

The simplest model of transmitter release at *j*-th synapse between post- and pre- synaptic neurons is modeling by sigmoid function and is described as follow:

(7)

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

Total synaptic current for postsynaptic neuron is:

(8)

where:

(9)

***Pulse model of synapse (fast synapse)***

The model of transmitter release for fast synapse at *i*-th integration step [##ref] is described as:

(10)

where: - integration step; T - time constant; – rate of transmitter release; - weight of connection for *j*-th synapse between post- and pre- synaptic neurons; – Dirac function (1 then spike generated by presynaptic neuron; 0 otherwise); – the membrane potential of presynaptic neuron; =0; *i*=1…L.

Total synaptic current for postsynaptic neuron is:

(11)

where:

(12)

The proposed model can be used as rough approximation for the model of AMPA/GABA(a/b) synapses. The advantage of the proposed model of a synapse is that it is not necessary to store intermediate results of synaptic summation () into the local memory which improve the performance of synaptic computing.

**Implementation**

The equations (6, 9 and 12) could be rewritten as linear recurrence equation:

(13)

where:

; *k* = 1..L

=0

*Blah-blah-blah*

***Model of NMDA synapse.***

***General information.***

The synaptic current for postsynaptic neuron that generated by j-th NMDA synapse is calculated similar to equation (1) [Destexhe&Mainen, 1994, Ermentrout&Terman, 2010]

(11)

where is maximal conductance; is gate variable that characterizes the transmitter release, is reversal potential for *j*-th synapse; z(V) represents the magnesium block and is calculating as:

(25)

The model of transmitter release [Destexhe et al., 1994, Destexhe&Mainen, 1994, Destexhe et al., 1998] described similar to the model of transmitter release for AMPA/GABA(a) synapses (see eq. 10-12).

**Implementation**

The implementation of simplified model of synaptic current of NMDA synapse is similar to the model of AMPA/GABA(a) synapses (see eq. 13, 14). The magnesium block is calculating according to (eq. 25).

The more complicated model of the synapse (see 26, 27) might be implemented similar to implementation of GABA(b) synapses.

1. **Presynaptic inhibition**

***General information***

The presynaptic inhibition affects to the rate of transmitter release in synaptic vesicles (parameter in all equation for calculating of the dynamics of transmitter release, see eq(s) 4, 9, 17 etc). Then the simplest model of presynaptic inhibition can be written as follow:

(28)

where: is maximal rate of transmitter release; is presynaptic inhibition.

**Implementation**

The model of modulation will be implemented if necessary

1. **Synaptic plasticity**

***General information***

**Implementation**

n/a

Ions current are described according to follow equation:

()

where and are gate variables (activation and inactivation); and are …; is maximal conductance; is membrane potential and is reversal potential.

In general, the gate variables () are described as follow:

()

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

Voltage dependent currents:

Implemented several types of description of gate variables:

**Generic description**

The steady state value is describes as follow:

The time constants of different subtypes of gate variables are describes as follow:

1) instant:

;

2) generic description:

;

3) modified generic description:

;

4) modified generic for A-current:

**Alpha-Beta model of ion current**

The steady state value is describes as follow:

, where:

1) instant

2) generic description

**Z-channels (DeShutter&Bauer)**

// activated ion channel. T\*d[M/H]/dt = [M/H]inf-[M/H];

//-----------------------------------------------------------------------------

// 3) 'zgate3' instant alpha/beta description (time constant is 0):

//=========================== zgate1 ==========================================

**Leakage**

<..... non specific model, specific model>

Ions dynamics.

Reversal potential (E = RT/Fz\*ln[Out]/[In])

Dynamics:

Ca-ions

Na-ions

Cells description

differential equation for membrane potential; definition of spike onsets.

()

Network units

a) drives;

b) outputs;

c) feedbacks.

Biomechanics

a) muscles;

b) arm model.

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