According to the project specifications, the first version of a GPU-based large scale network simulation software package (LSNS) is developed. This simulation environment is currently used for multiscale modeling and consists of:

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 is able to perform 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 <…>.

**LSNS simulation engine (version 1.0)**

**Cells model**

The simulation engine supports the computation of the conductance-based single-compartment model of neuron in the Hodgkin–Huxley style. The dynamic of neuronal membrane potential (V) is defined by a set of membrane ionic currents as describes as:

(1)

where: is 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 type of ion channels and classified by gate variables. The current version of LSNS package supports: (i) v*oltage-gated* ion channels which open or close depending on the voltage gradient across the membrane, (ii) *other-gated* ion channels like calcium-dependent potassium channels, leak channel; (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:

(2)

where: is maximal conductance; and are gate variables (activation and inactivation); and are power for activation and inactivation, correspondingly; is membrane potential and is reversal potential of the corresponding channels .

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

(3)

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

***Voltage-gated ion channels***.

These types of ions channels open or close depending on the membrane potential of the cell and are described as follow:

1) The *generic description* of the gate variable (activation or inactivation) is defined as [#ref]:

(4)

where is membrane potential, is half-voltage and is 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 half-voltages for time constants; , are slopes for time constants; is threshold.

2) The  *description* of the gate variable (activation or inactivation) is defined as [#ref]:

,

where: ; is membrane potential; is half-voltage; is slope; and are free parameters which specify either alpha or beta variable. 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* channels are also described according to (3). The steady states and time constants for these types of ion channels for gate variables are [#ref]:

1. ,

The time constants are: or

1. , ,

The time constants are: or

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

The *leak current* approximates the passive properties of the cell and is describes as:

(5)

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

***Ligand-gated ion channels (synapses)***

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

(6)

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 membrane potential for post-synaptic neuron; is reversal potential for *j*-th synapse.

Let suppose that , are equal for *N* synapses ( *= 1,..N*), then the equation (6) cab be rewritten as:

(7)

According to (7) the total synaptic current for postsynaptic neuron for all similar synapses (*j* = 1..N) is calculating as:

(8)

The current version of the package is supported three types of synapses which are:

1. *Weighted sum* synapse*.*

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

(9)

where: is rate of transmitter release; and are weight of connection and input signal between post-synaptic neuron and non-spiking element of the network (like drive, output, feedback, etc). The total transmitter release for all similar synapses can be written then as:

10

1. *Instant* synapse*.*

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

(11)

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 are half-voltage and slope for instant synapse. The total transmitter release for instant synapses is:

where: (12)

1. *Pulse model* of synapse.

The model of transmitter release for pulse synapse is written as recurrence equation for -th integration step:

(13)

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 (which is equal to 1 then spike is generated by presynaptic neuron or 0 otherwise); – the membrane potential of presynaptic neuron; =0. The total transmitter release then can be written as:

(14)

The mechanism for synaptic plasticity that 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 LSNS package. It represents the magnesium block for *NMDA-type* of synapse and is calculating as:

(15)

Finally, the equation (8) for total synaptic current for all similar synapses (*j* = 1..N) can be written as:

(16)

where: the total transmitter release can be defined as linear recurrence equation - , is rate of transmitter release; 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 ions dynamics**.

The reversal potentials of correspondent ions are calculated according the follow equation:

(17)

where: ;; , 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:

(18)

where: is time constant for ions dynamics; In the right part of this 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.

The current version of the LSNS package supports follow descriptions of ion pumps:

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

(19)

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

1. the Ca pump (I) is taken from <…> and writes as:

(20)

where: is the maximal pump current; is equilibrium intracellular Ca concentration

1. the Ca pump (II) is taken from <…> and writes as:

(20)

where: is the maximal pump current; is equilibrium intracellular Ca concentration

Network units

a) drives;

b) outputs;

c) feedbacks.

**Model translator for LSNS simulation engine (version 1.0)**

<…>

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