A Brief User Guide for NeuroSim-TM-2.2 Simulator

1. Introductory Overview

The custom-made software NeuroSim-TM-2.2 written in the C programming language is used for simulation of spiking dynamics of generative networks composed of Leaky Integrate-and-Fire (LIF) point-like neurons with synaptic plasticity. The software has been specifically designed for numerical studies of spatiotemporal properties of population spikes (or population bursts) [1].

Synaptic plasticity may be only the short-term one, according to the Tsodyks-Uziel-Markram (TUM) model [2], or it can be complemented by 'long-term' Spike-Timing-Dependent Plasticity (STDP). Ordinary differential equations for the dynamics of neuron potentials and synaptic variables are solved using the standard Euler method. The default initial conditions are that all neurons have the same 'resting' value of the membrane potential, and all synapses have the same initial values of synaptic variables.

Both metric (i.e. spatially dependent) and metric-free network connectomes can be generated. For the metric networks, the software allows various spatial arrangements of neurons. In this case, the probability of forming a unilateral connection between every two neurons decreases exponentially with increasing their relative distance. The maximum size of the generated network is limited by the amount of operative memory available to a single-thread program, as multi-thread parallelization is not yet implemented.

After compilation with a standard C compiler (e.g., GCC), the executable file for NeuroSim-TM-2.2 can be used for all available variants of simulation without recompiling. All parameters required for choosing and performing simulations are set through the single input file input.txt, which should be placed in the same folder as the executable file.

The software also supports several protocols for specific numerical experiments on influence of various forms of neuron stimulation on network activity, as well as a simple model for global homeostasis. *These and other capabilities unused in the papers published so far will be omitted here.*

Based on the data in input.txt (see Table 1 below), the program simulates neuronal network dynamics during a specified time and writes the resulting data in a set of output files. All simulation parameters of individual neurons and synapses are also exported in the output files allowing an accurate reproducibility of the simulation, except for the optional mode of stochastic spontaneous spike generation. In total, there are 18 output files (including 4 files in subfolder \syn_resources_dynamics). There are three sorts of these files: primary output files of network dynamics, files of parameters of neuronal network (connectome, etc.) that are required for reproducing the simulation, and auxiliary files made for fast analysis of the results and other purposes.

The *primary output files* are as follows:

- activity.txt contains normalized spiking activity of the network neurons as a function of chunked time,
- raster.txt contains all spike generation times of individual neurons,
- x.txt, y.txt, z.txt, u.txt (in subfolder \syn_resources_dynamics) contain the dynamics of network-averaged fractions of synaptic resources in the TUM model [2].

The *files of neuronal network parameters* are as follows:

- coordinates.txt contains spatial Cartesian coordinates of neurons on two-dimensional plane,
- connections.txt contains the network connectome (a directed and unweighted graph), i.e. complete information on all connections between neurons,
- synaptic_parameters_distribution.txt contains the parameters of every synapse of the network,
- exc_I_distribution.txt and inh_I_distribution.txt contain the values of constant 'background' current (which determines neuronal excitability and the fraction of steady pacemakers among the neurons) for every excitatory and inhibitory neuron, respectively,
- or, alternatively to the last, p_sp_distribution.txt contains the values of the probability of spontaneous spike generation for every neuron.

Finally, the *auxiliary files* are as follows: active_connections.txt, M.txt, w_initital.txt,

- connections_per_neuron.txt contains the number of outgoing synapses for a neuron with the given ID (the neuron IDs range from zero to N-1, where N is the total number of neurons), i.e. there are two integer numbers per row.
- burst_times.txt contains the population spike (or population burst, PB) times, if the PB amplitude exceeds the threshold value burst_threshold stated in input.txt,
- IBI.txt contains successive time intervals between the detected PBs,
- info.txt contains the overview of the mode and key parameters for the particular simulation run.

To interactively control the network activity during the simulation, Gnuplot scripts plot_activity.plt and, for small networks, plot_raster.plt have been used. These scripts visualize the current content of the output files activity.txt and raster.txt, respectively, which are updated regularly during the simulation.

[1]: A.V. Paraskevov, D.K. Zendrikov, A spatially resolved network spike in model neuronal cultures reveals nucleation centers, circular traveling waves and drifting spiral waves, Phys. Biol. 14 (2017) 026003.

[2]: M. Tsodyks, A. Uziel, H. Markram, Synchrony generation in recurrent networks with frequency-dependent synapses, J. Neurosci. 20 (2000) RC50.

2. Compiling the simulator

The software can be standardly compiled with the GCC compiler in both Windows and Linux operating systems using console command:

```
gcc NeuroSim-TM.c -o NeuroSim-TM
```

In Linux systems, the option -lm is sometimes needed for successful compilation.

3. Starting the simulation

A copy of the executable file should be placed in the directory of a particular run. It will search there for the input files with specific names and generate its output.

The input settings are specified in the file input.txt. The syntax of the input file is PARAMETER_NAME=VALUE at the beginning of a new line without spaces. All other symbols are discarded as comments. The parameters can be specified in any order. The list of parameters is presented in Table 1.

If some of the parameters are not found in input.txt, the default values from NeuroSim-TM-2.2.c (see lines 486-581 there) are used. Before the simulation starts, the user is prompted to check if the values imported from the input file are correct and to type 'Y' (yes) for confirmation.

After that, the static parameters of the neuronal network are generated (or loaded from the previously saved files; see details below) and are written in the output files:

- coordinates.txt with coordinates *X* and *Y* of one neuron per row, in units of *L*,
- connections.txt with the indices of pre- and post-synaptic neurons, and the generated random value from the uniform distribution that should be greater than the connection probability for this pair of neurons (i.e, there are three numbers, two integers and one real, per row),
- synaptic_parameters_distribution.txt with pre- and post-synaptic neuron indices, and the values of synaptic parameters in the TUM model [2] (*A>0* if presynaptic neuron is excitatory one, and *A<0* if it is inhibitory one), *U*, *tau_I*, *tau_rec*, *tau_facil* for one synapse per row,
- exc_I_distribution.txt with an excitatory neuron index and the value of its constant background current per row,
- inh_I_distribution.txt with an inhibitory neuron index and the value of its constant background current per row (if the neuronal network does not contain inhibitory neurons, the file is empty),
- p_sp_distribution.txt with a neuron index and the value of probability of spontaneous spike generation (per time step *dt*) by the neuron per row.

These files are then closed at the beginning of the simulation (indicated by the console message 'Network is created successfully') and can be used for the analysis of neuronal network realization, for performing other runs with this realization, and for reproducing the simulations.

During a simulation, the program prints in its console window the spike times and indices of spiking neurons, and the number of population spikes detected by crossing the population activity threshold burst_threshold stated in input.txt. At the same time, the dynamical data are periodically written to the output files and can be accessed from there (e.g., by Gnuplot scripts for plotting graphs of network activity and raster of spikes), even if the simulation is still running.

After a simulation is completed, its results are exported to the above-mentioned output files in the simulation folder:

- activity.txt containing (per row) the timestamp and the normalized network activity averaged over AVG_TIME time chunk stated in input.txt,
- raster.txt containing (per row) spiking neuron index, i.e. neuron ID, and the corresponding spike time,
- x.txt, y.txt, z.txt, u.txt in subfolder \syn_resources_dynamics contain (per row) the timestamp and the corresponding fractions *x*, *y*, *z*, *u* of synaptic resources in the TUM model of short-term synaptic plasticity [2], averaged over all synapses of the network and over the time chunk AVG_TIME.

Note: As the output data are event-driven (the events are neuronal spikes), the simulation may run without any messages about spikes in the console window. That happens (e.g., during some time after the beginning of simulation) if all neurons are in sub-threshold regime, i.e. for some time they do not receive enough input excitation to generate a spike. In this case, the simulation is still running, and the program window should not be closed until the message 'Releasing memory... Done' indicating the end of the simulation.

4. Reproduction of simulation results

To use previously generated components of the neuronal network realization, please carry out the following sequence:

1. Copy all existing files of neuronal network parameters described in the previous section, and input.txt, from the folder with the accomplished simulation to the folder of a new ‘reproducing’ simulation, where the executable file NeuroSim-TM-2.2 is placed.

2. Append prefix saved_ to the corresponding files described in the previous section. In other words, rename coordinates.txt into saved_coordinates.txt, connections.txt into saved_connections.txt, synaptic_parameters_distribution.txt into saved_synaptic_parameters_distribution.txt etc. However, the file input.txt should not be renamed.

3. In the file input.txt, change values of the flags listed below from 0 to 1:

3.1. Set use_saved_coordinates=1 to use spatial coordinates of neurons from the file saved_coordinates.txt for the new simulation, instead of generating new coordinates in the case if use_saved_coordinates=0.

3.2. Set use_saved_topology=1 to use network connectome graph from the file saved_connections.txt. If a spatial neuronal network is simulated, then one must previously set use_saved_coordinates=1 for consistency (there will be an error message otherwise). If use_saved_topology=0, new network connectome graph will be generated based on the loaded or generated coordinates of neurons.

3.3. Set use_saved_synaptic_parameters=1 to use the synaptic parameters from the file saved_synaptic_parameters_distribution.txt. Again, one must previously set use_saved_topology=1 for consistency. If use_saved_synaptic_parameters=0, a new set of synaptic parameters will be generated for the loaded or newly-generated network connectome graph.

3.4. Set use_saved_stimulation_data=1 to use either the values of constant background currents of neurons loaded from the pair of files saved_exc_I_distribution.txt and saved_inh_I_distribution.txt or the corresponding values of the probability of spontaneous spike generation loaded from the file saved_p_sp_distribution.txt. The number of neurons must be consistent with that stated in the input.txt and implied in the data loaded from all relevant files. If use_saved_stimulation_data=0, the corresponding values will be generated anew.

Notes: 1) Due to deterministic nature of the neuron and synapse models, simulations can be reproduced with exact spike times given the same input files (except for the modes of spontaneous stochastic neuronal spiking). 2) If any inconsistencies between the input files are detected, such as mismatch in overall number of neurons, excitatory/inhibitory types of neurons etc., the simulation will not be started and the corresponding error message will be shown.

Table 1: List of simulation parameters in the input file input.txt

Parameter name	Default value	Possible values	Description
use_saved_coordinates	0	0 for No 1 for Yes	Flag to import neuron coordinates from saved_coordinates.txt
use_saved_topology	0	0 for No 1 for Yes	Flag to import graph of connections from saved_connections.txt
use_saved_stimulation_data	0	0 for No 1 for Yes	Flag to import stimulation parameters from the files saved_exc_I_distribution.txt and saved_inh_I_distribution.txt for Stimulation_type=1 and 2 or saved_p_sp_distribution.txt for Stimulation_type=3 and 4 (see below)
use_saved_synaptic_parameters	0	0 for No 1 for Yes	Flag to import synaptic parameters from saved_synaptic_parameters_distribution.txt. This option is only available with use_saved_topology=1
Main simulation settings			
N	50000	1 to 10^6	Number of neurons
Inh_neurons_fraction	0.2	0 to 1	Fraction of inhibitory neurons
dt	0.1 ms		Simulation time step
AVG_TIME	2 ms		Time interval ('chunk') for averaging dynamic output values
SIM_TIME	10000 ms	>AVG_TIME	Overall simulation time
burst_threshold	0.2	0 to 1	Population burst detection threshold for network activity
Topology (connectome) parameters			
spatial_layer_type	1	0 1 2 3 4 5 6 7	<u>Metric-free (binomial) topology</u> with connection probability P_CON between two neurons <u>Spatial distributions of neurons over the *LxL* square with neuron density patterns:</u> Uniform Square lattice 3 vertical stripes with variable density Bell-shaped Gradient Two counter gradients Barbell
P_CON	0.1	0 to 1	Probability of creating a directional connection between each pair of neurons in metric-free topology (spatial_layer_type=0)
force_binomial_topology	0	0 or 1	Flag to use the metric-free connectivity using P_CON while still placing the neurons spatially (spatial_layer_type!=0)
lambda	0.01 L	0 to sqrt(2)*L	Exponential decay length of spatially-dependent probability of connecting a pair of neurons
max_conn_length	1.415 L		Hard maximum limit on the possible connection length in spatially dependent connectomes
spike_speed	0.2 L/ms		Spike speed for spatially dependent connectomes with the connections considered as straight lines
tau_delay	0.2 ms		minimal spike-propagation delay
LIF neuron model parameters			
TAU_M	20 ms		Typical relaxation time of the membrane potential
R_IN	1 GOhm		Membrane resistance
V_REST	0 mV		Membrane resting potential
V_RESET	13.5 mV		Reset value of the membrane potential after spiking

V_TH	15 mV		Spiking threshold of the membrane potential
TAU_REF_EXC	3 ms		Absolute refractory period for an excitatory neuron
TAU_REF_INH	2 ms		Absolute refractory period for an inhibitory neuron
Synapse model parameters (TUM model [2] of short-term synaptic plasticity)			
Aee	38 pA		Mean values for synaptic current amplitudes distributed normally* among synapses with the standard deviations ('sigmas') taken 0.5 of the mean.
Aei	54 pA		
Aie	-72 pA		
Aii	-72 pA		
Uee	0.5		Mean values for the corresponding coefficients distributed normally among synapses with sigma 0.5.
Uei	0.5		
Uie	0.04		
Uii	0.04		
tau_rec_ee	800 ms		Mean values for the corresponding time constants distributed normally among synapses with sigma 0.5.
tau_rec_ei	800 ms		
tau_rec_ie	100 ms		
tau_rec_ii	100 ms		
tau_facil_ie	1000 ms		Mean values for the corresponding time constants distributed normally among synapses with sigma 0.5.
tau_facil_ii	1000 ms		
tau_I	3 ms		Time constant of the fraction of synaptic resource in the active state; same for all synapses.
x_init	0.98		Initial fractions of synaptic resource for every synapse. Integrity condition *x + y + z = 1* must be always held.
y_init	0.01		
z_init	0.01		
Stimulation parameters			
Stimulation_type	1	1 2 3 4	Stimulation of neurons with normally distributed constant 'background' currents Two fixed values of constant currents Normally distributed probabilities of spontaneous spiking Two constant values of spontaneous spiking probability
I_bg_mean	7.7 pA		Constant (background) input current parameters for Stimulation_type=1
I_bg_sd	4.0 pA		
I_bg_min	0 pA		
I_bg_max	20 pA		
I_bg_1	2 pA		Two fixed values of input currents for Stimulation_type=2
I_bg_2	37 pA		
Fraction_of_neurons_with_I_bg_1	0.75	0 to 1	
P_SP_mean	0.0005		Spontaneous spiking probability (per time step dt) for Stimulation_type=3
P_SP_sd	0		
P_SP_min	0		
P_SP_max	0.001		
P_sp_1	0.005		Two constant values of spontaneous spiking probability for Stimulation_type=4
P_sp_2	0.00001		
Fraction_of_neurons_with_p_sp_1	0.25	0 to 1	

*: Hereafter, 'normally' means the non-negative and upper-bounded part of the normal distribution. By default, the upper bound (or lower one, if the parameter is always negative) has been taken as 4 of the mean, unless the parameter value is naturally restricted by 1.

Example of the input file input.txt (may be copy-pasted)

```
Important: Input format doesn't intend space between equality sign and a name
of a parameter.
Parameters may appear in any order.
If some parameters are not written in this file they are chosen by default.

*****Use saved data (0 for NO, 1 for YES)*****

use_saved_topology=0
use_saved_stimulation_data=0
use_saved_synaptic_parameters=0
use_saved_coordinates=0

*****General*****

Number of neurons:
N=50000
Inh_neurons_fraction=0.2

*****Simulation parameters*****

dt=0.1 ms
AVG_TIME=2 ms
SIM_TIME=10000 ms
burst_threshold=0.2 - threshold of activity when a PB is registered

*****Neuron model parameters*****

neuron_model=1 (0 - PERFECT INTEGRATE-AND-FIRE (PIF),
                1 - LEAKY INTEGRATE-AND-FIRE (LIF))

V_REST=0 mV
V_RESET=13.5 mV
V_TH=15 mV

TAU_REF_EXC=3 ms, refractory period of excitatory neurons
TAU_REF_INH=2 ms, refractory period of inhibitory neurons

TAU_M=20 ms (Used for LIF)
R_IN=1 Gohm (Used for LIF)
C_M=20 pF (Used for PIF)

limited_spiking_resource_mode=0 (0 - disabled,
                                 1 - enabled for NPM neurons only,
                                 2 - enabled for both PM and NPM neurons)
max_spikes_per_neuron=50

*****Synaptic parameters*****

x_init=0.98
y_init=0.01
z_init=0.01

Aee=38 pA
Aei=54 pA
Aie=-72 pA
Aii=-72 pA

Uee=0.5
Uei=0.5
Uie=0.04
Uii=0.04
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```
tau_rec_ee=800 ms
tau_rec_ei=800 ms
tau_rec_ie=100 ms
tau_rec_ii=100 ms

tau_facil_ie=1000 ms
tau_facil_ii=1000 ms

tau_I=3 ms

limited_synaptic_transmission_resource_mode=0 (0 - disabled,
                                               1 - enabled for connections with
presynaptic NPM neurons only,
                                               2 - enabled for all synapses)
max_pulses_per_synapse=10
syn_pulse_detection_threshold=0.1 pA

*****Topology parameters*****

spatial_layer_type=1   (0 for BINOMIAL,
                        1 for UNIFORM,
                        2 for SQUARE LATTICE,
                        3 for STRIPED,
                        4 for BELL,
                        5 for RAMP,
                        6 for DOUBLE RAMP,
                        7 for BARBELL)

force_binomial_topology=0

P_con=0.1 (used for BINOMIAL layer type)

Parameters for spatially-dependent topology:

B_exc=1
B_inh=1
lambda_exc=0.01 L
lambda_inh=0.01 L
max_conn_length=1.5 L
spike_speed=0.2 L/ms
tau_delay=0.2 ms

*****Stimulation parameters*****

Stimulation_type=1 (1 for gaussian background current distribution,
                    2 for two values of background current,
                    3 for gaussian spontaneous spiking probability
distribution,
                    4 for two values of spontaneous spiking probability)

I_bg_mean_exc=7.7 pA
I_bg_sd_exc=4.0 pA
I_bg_min_exc=0 pA
I_bg_max_exc=20 pA

I_bg_mean_inh=7.7 pA
I_bg_sd_inh=4.0 pA
I_bg_min_inh=0 pA
I_bg_max_inh=20 pA

I_bg_multiplier=1

I_bg_1=2 pA                         (used in case Stimulation_type = 2)
I_bg_2=37 pA                        (used in case Stimulation_type = 2)
Fraction_of_neurons_with_I_bg_1=0.75      (used in case Stimulation_type = 2)
```

```
P_sp_mean=0.0005
P_sp_sd=0
P_sp_min=0
P_sp_max=0.001

P_sp_1=0.005                        (used in case Stimulation_type = 4)
P_sp_2=0.00001                      (used in case Stimulation_type = 4)
Fraction_of_neurons_with_p_sp_1=1   (used in case Stimulation_type = 4)

*****Additional mechanisms*****

>>>Background current noise<<<

I_bg_noise_mode=0 (0 for OFF
                   1 for ON)
I_bg_noise_sd=3.5 pA

>>>Stimulation disabling<<<

stim_disable_protocol=0 (0 for no turning stimulation off,
                         1 for turning stimulation off when overcoming the
given activity threshold after <pb_number-1> PBs
                         2 for turning stimulation off at a certain time
                         3 for applying filters 1 and 2 together)
pb_number=1
activity_threshold=0.08
stim_off_time=2169 (ms - moment to turn off the stimulation)

inh_off_time=0 (ms - moment in simulation to force inhibitory neurons' membrane
potential maintain V_REST; set to -1 to disable the feature)

>>>STDP<<<

STDP parameters:

STDP_status=0  (0 for OFF,
                1 for MULTIPLICATIVE,
                2 for ADDITIVE)

W_OUTPUT_PERIOD=1000 (period of exporting synaptic weights if STDP is ON)

A_plus=0.01
A_minus=0.01
w_initial=0.5
tau_plus_corr=20
tau_minus_corr=20

>>>Homeostasis<<<

Homeostasis parameters:

Homeostasis_status=0 (0 for OFF
                      1 for ON)
b=0 (by default b = 1/N, unless it is set here)
M_max=1
```