

Flysim User Guide

Version 0.8.11

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1. Overview

Computer simulation plays an important role in examining hypotheses and dynamics as well as in the analysis of neural networks. We developed a neural network simulator named Flysim to fulfil these purposes. Our simulator contains many synapse models, which can not only be defined by experimental constraints or by computational hypothesis, but can also be flexibly programmed during simulations. Using the simulator, users can easily and intuitively simulate neural networks and find desirable dynamics in their simulations.

1.1 Biological and program model definition

A map from a biological neuron to the program model is shown below:

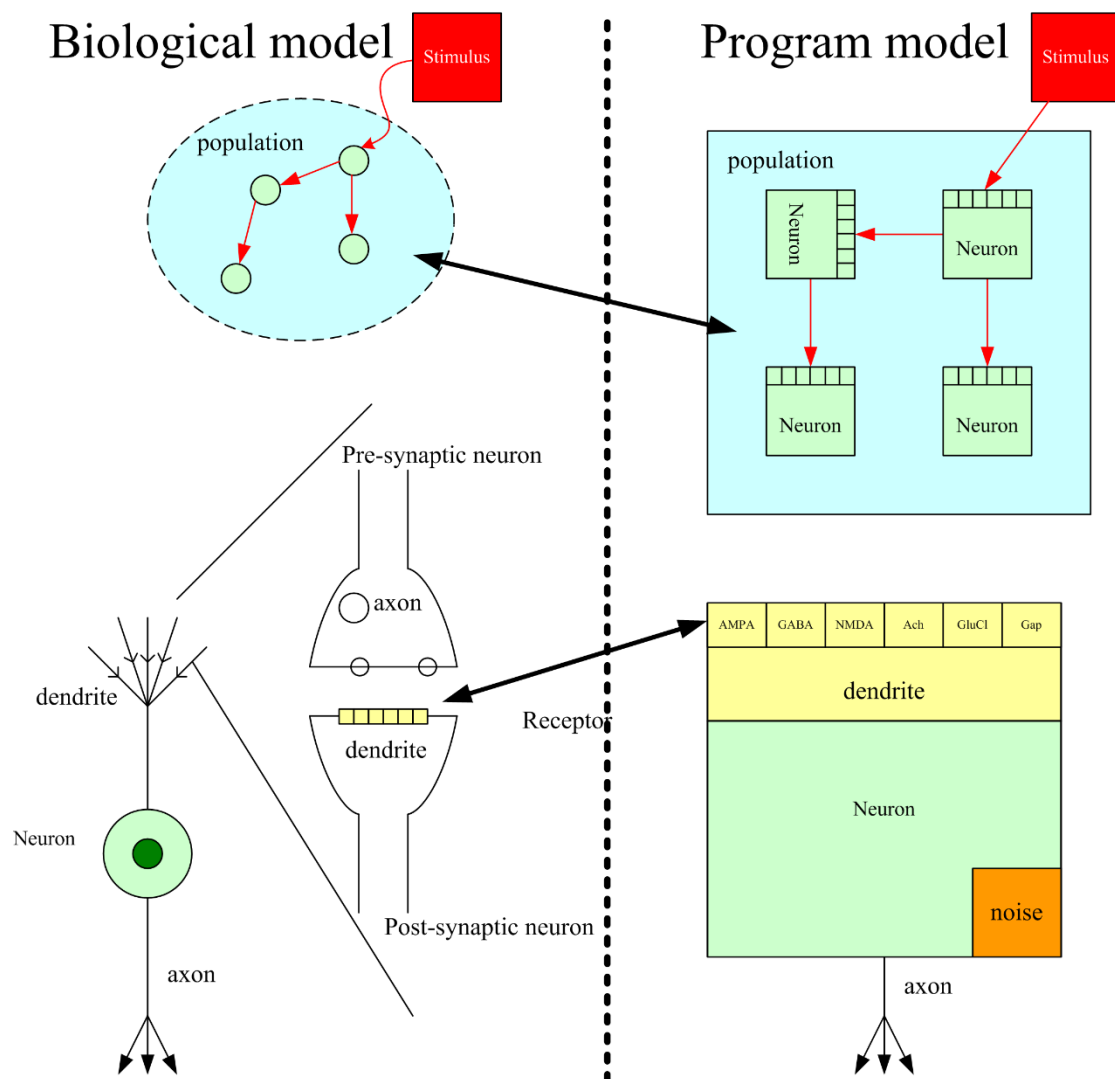


Figure 1 The intuitive map of a biological model to the program model

Every biological model parameter is mapped one to one onto the program model definition. Hence, we can describe parameters of all neurons with the same population of membrane and same synapse models. Flysim supports the leaky integrate and fire (LIF) model for membrane potential dynamics, and synapse models with exponential decay calculations for six different receptor types: AMPA, GABA, NMDA, Ach, GluCL and gap junctions. The axon model uses a simple time delay, approximating action potential transmission.

1.2 Flysim command options

Table 1 shows online command options used with Flysim `-h`. These commands are most commonly used. `-pro` assign an experiment protocol file, `-conf` assigns a network definition file, `-rp` shows how many times the experiment repeats, `-t` is for using multi-thread methods by the simulator to speed up simulation, `-dt` defines the fundamental time step in unit of ms, `-nmodel` specifies what membrane and synapse model to run in the simulation. When we want to experiment with the same neuron network but a different protocol, flysim uses three commands: `-om`, `-os`, `-or` for batch operation. `-daemon` is an experimental command only for our in-house tool “hanitu,” it is a low-level communication operation. Running the command “./flysim” without any other option will by default read the example network.pro and network.conf in the same directory and display the simulation results.

Table 1 Flysim command options

examples:	
<code>-pro network.pro</code>	# read protocol file: default=network.pro
<code>-conf network.conf</code>	# read configuration file: default=network.conf
<code>-om my_membrane.dat</code>	# for batch operation: output membrane potential file
<code>-os my_spike.dat</code>	# for batch operation: output spikes file
<code>-or my_rate.dat</code>	# for batch operation: output firing rate: default rate window=50ms, print out=100ms
<code>-rp 1</code>	# set repeat times: default=1
<code>-t 4</code>	# set multithreading: default=1
<code>-s accurate</code>	# for -nmodel GNL, numerical error level of solver: accurate(RK4), moderate(improved Euler), rough(default, Euler)
<code>-daemon port</code>	# Flysim as daemon(experiment): port number
<code>-dt 0.1</code>	# time step(default=0.1ms)
<code>-udfsed 1</code>	# user define random seed:0~2 ³² -1
<code>-STP</code>	# use short term plasticity synapse
<code>-STD</code>	# use short term depression synapse and this option is disabled when -STP used
<code>-LTP</code>	# use long term plasticity synapse(STDP)
<code>-SodCH</code>	# Sodium channel(experiment), only used in LIF
<code>-nmodel LIF</code>	# neuron model: # sim06: capable mode of sim06_10 leaky integrate and fire model # sim07: capable mode of sim07_21 leaky integrate and fire model # LIF(default): classical leaky integrate and fire model # HH: Hodgkin-Huxley model

2. Network definition file and description

Fysim reads .conf and .pro files for network definition and experimental protocol. Table 2 shows a toy example that has two populations: Exc1 and Exc2. Each population has 20 neurons with all to all connections; Exc1 only receives background stimulation and excites Exc2. Exc2 is also stimulated by background stimulation but not connected to another downstream population. In the example in table 2, the code between NeuralPopulation:Exc1 and EndNeuralPopulation defines all of neuron population Exc1's membrane and connection parameters, where N=20 stands for 20 neurons in this population and C=0.5 means each one has a membrane capacitance of 0.5nF. Taum=20 sets the membrane time constant to 20 ms, RestPot=-70 sets the resting potential to -70 mV, ResrPot=-55 sets the reset potential to -55 mV and Threshold=-50 sets the action potential threshold to -50 mV. The code from Receptor:AMPA to EndReceptor defines the receptor dynamic as AMPA (there are 5 type receptor can be defined here but gap junction), Tau=2 sets the receptor decay time constant to 2 ms, RevPot=0 sets the reversal potential to 0 mV, FreqExt=0 defines the external background stimulation frequency at 0Hz, MeanExtEff=2.1 sets the external stimulation strength at 2.1nS, received by each neuron in the population. We also need to assign connections between different populations. TargetPopulation: Exc2 defines Exc1 connection to Exc2 with mean efficacy of 4.2 nS (MeanEff=4.2). After defining Exc1 population, Exc2 is defined by similar keywords and variables but with no connection to any other population.

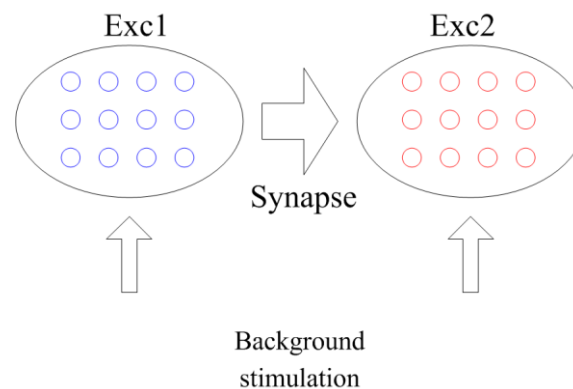


Figure 2 This toy example is only used to show a basic flysim script description, not for the purpose of any scientific investigation.

Table 2 Network.conf example

NeuralPopulation: Exc1 N=20 C=0.5 Tau=20 RestPot=-70 ResetPot=-55 Threshold=-50	NeuralPopulation: Exc2 N=20 C=0.5 Tau=20 RestPot=-70 ResetPot=-55 Threshold=-50
Receptor: AMPA Tau=2 RevPot=0 FreqExt=0 MeanExtEff=2.1 MeanExtCon=1 EndReceptor	Receptor: AMPA Tau=2 RevPot=0 FreqExt=0 MeanExtEff=2.1 MeanExtCon=1 EndReceptor
Receptor: GABA Tau=5 RevPot=-90 FreqExt=0 MeanExtEff=0.0 MeanExtCon=800.0 EndReceptor	Receptor: GABA Tau=5 RevPot=-90 FreqExt=0 MeanExtEff=0.0 MeanExtCon=800.0 EndReceptor
Receptor: NMDA Tau=100 RevPot=0 FreqExt=0 MeanExtEff=0 MeanExtCon=0 EndReceptor	Receptor: NMDA Tau=100 RevPot=0 FreqExt=0 MeanExtEff=0 MeanExtCon=0 EndReceptor
TargetPopulation: Exc2 TargetReceptor=AMPA MeanEff=4.2 EndTargetPopulation	EndNeuralPopulation
EndNeuralPopulation	

2.1 Short term plasticity

Flysim supports short-term facilitation and short-term depression (STF/STD) as shown in figure 3. This type of plasticity influences the millisecond to hundreds of millisecond time-scale of the dynamics of synapse. Using option –STP to perform this mechanism, which then calculates $\frac{ds}{dt} = D * F * \sum_k \delta(t - t^k) - \frac{s}{\tau_s}$ instead of (3) and $\frac{dx}{dt} = D * F * \sum_k \delta(t - t^k) - \frac{x}{\tau_x}$ instead of (4). The other option –STD is used for only STD, at F is set to 1 all of the time.

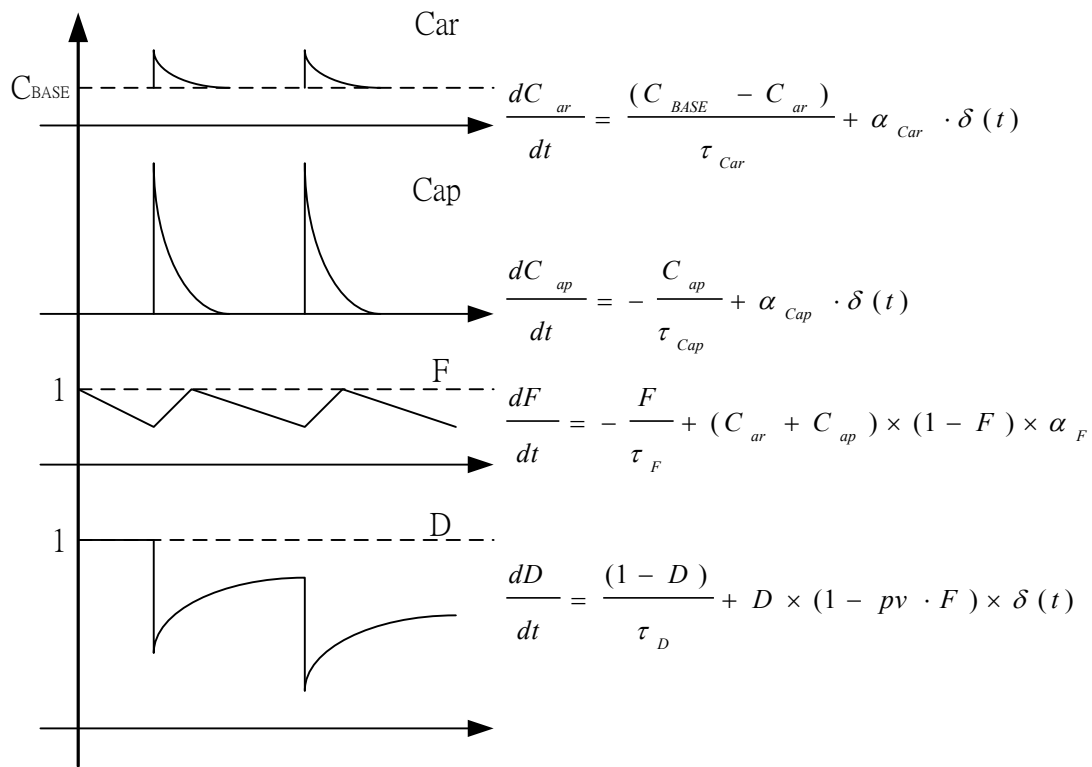


Figure 3 short term plasticity are compressed facilitation F and depression D affected by calcium dynamics.

2.2 Long term plasticity

Spike timing dependent plasticity (STDP) is a well-studied type of long-term synaptic plasticity, and flysim implements STDP for synapse conductance changes, on a time scale of tens of seconds to tens of minutes. As shown in figure 4, we use an additive rule for long term potentiation and a multiplicative rule for depression.

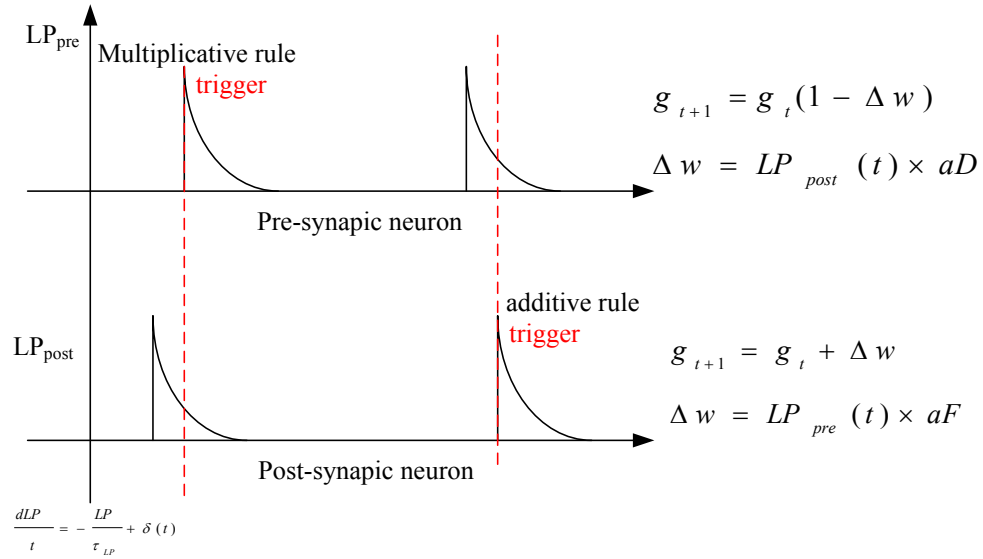


Figure 4 long term plasticity is measured between spike pair, each spike has a single exponential decay variable LP. Additive rule is used when post-synaptic neuron firing, and multiplicative rule decrease conductance when pre-synaptic neuron firing.

In an example shown in figure 5, only 10 timed spike pairs can change the synaptic conductance by over 20%, from 1.5nS increasing to 1.9nS, or decreasing to 1.1nS in the long term.

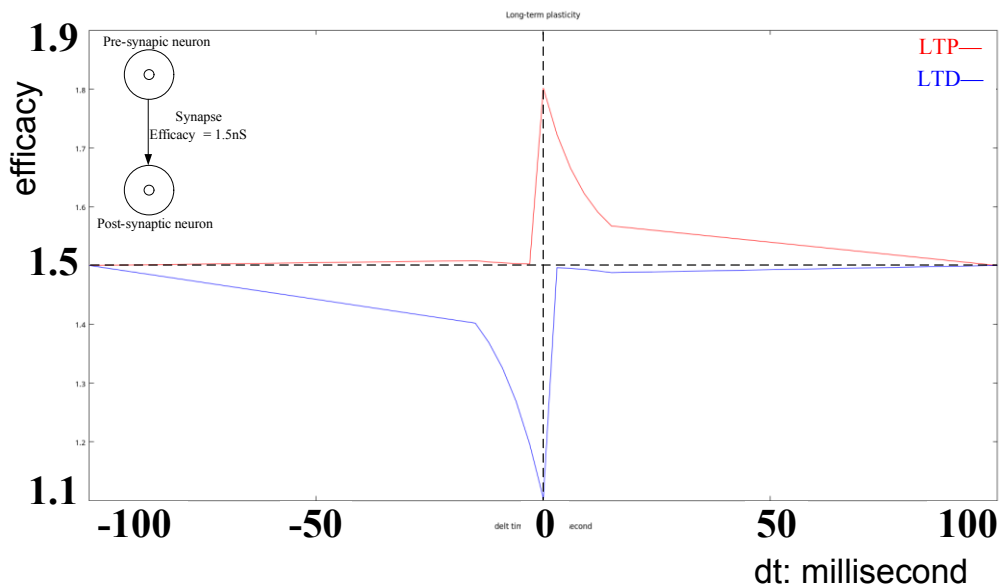


Figure 5: Curve showing conductance changes as a function of spike pair time differences during STP/STD.

2.3 Network definition script

We have previously shown some examples, and we now list all script definitions here. The default neural network definition file is network.conf, the protocol file is network.pro.

NeuralPopulation: Exc1

.....

EndNeuralPopulation //keyword: neuron population definition from NeuralPopulation to
EndNeuralPopulation is named Exc1 °

```
N=100           //there are 100 neurons in Exc1 population
C=0.5           //membrane capacitance is 0.5 nF
Taum=20         //membrane leay time constant is 20 ms
Threshold=-50   //action potential threshold voltage is -50 mV
RestPot=-70     //resting state membrane voltage is -70 mV
ResetPot=-55    //reversal potential is -55 mV
RefractoryPeriod=1.9 //refractory period is 1.9 ms
SpikeDly=0.3    //spike delay in axon transmission is 0.3 ms
STP_pv=0.6      //STP parameter: vesicle release ratio pv
STP_tD=300      //STP parameter: time constant of D factor
STP_aF=1.0      //STP parameter: scaling of F factor
STP_tF=7000     //STP parameter: time constant of F factor
STP_aCap=2.0    //STP parameter: scaling of peak calcium level
STP_tCap=100    //STP parameter: time constant of peak calcium level
STP_aCar=3.0    //STP parameter: scaling of resting calcium level
STP_tCar=70     //STP parameter: time constant resting calcium level
SelfConnection=true //auto-connection enable: default is false
```

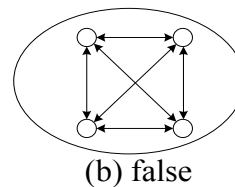
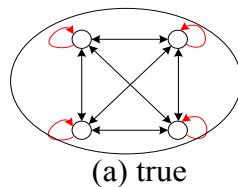


Figure 6. Absence or presence of post-synaptic population connection to itself, (a)
SelfConnection=true connects neuron in a population to itself, but
(b)SelfConnection=false disables self-connection.

```

Receptor:AMPA      // AMPA receptor parameters setting
Tau=5              //decay time constant=5ms
RevPot=-70         //reversal potential=-70mV
FreqExt=0.84375    //external stimulation=0.84375Hz
MeanExtEff=2.1     //external connection mean efficacy=2.1nS

EndReceptor        //end of receptor definition

```

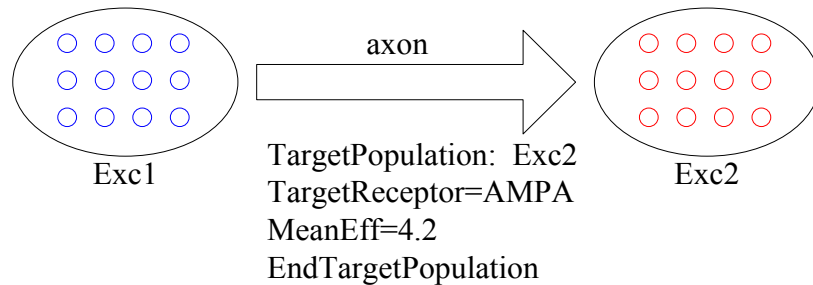


Figure 7 Connections between Exc1 and Exc2

```

TargetPopulation: Exc2 //post-synaptic population is Exc2
TargetReceptor=AMPA    //and connect to Exc2's AMPA receptor
MeanEff=4.2            //mean efficacy is 4.2nS
Connectivity=0.5        //connection ratio between Exc1 and Exc2, 0.5 means each neuron in Exc1
                        //has 10(20*0.5=10) post-synaptic neurons in the Exc2 population.

EndTargetPopulation     //end of connection

```

3. Experiment protocol and description

3.1 External(background) stimulation

In the protocol definition, each neuron has 2 types of external stimulation, whereby one is the receptor type, and the other is the current type. Receptor types use Poisson spike trains to stimulate each neuron's virtual receptors, and currents injected into neurons are calculated from these. Type=ChangeExtFreq sets the receptor type for stimulation. Receptor:AMPA assign receptor type as AMPA (or GABA, NMDA, ACH, GCL, Gap) dynamics FreqExt=240 sets the AMPA receptor stimulation to 240 Hz. The stimulation frequency can be set to values from 0 to 10,000 Hz. If you do not want any stimulation to a neuron, then do not write anything regarding the stimulation to the neuron.

The other type is current injection, this type of stimulation directly injects current into a neural membrane, with a Gaussian distribution specified by mean and standard deviation.

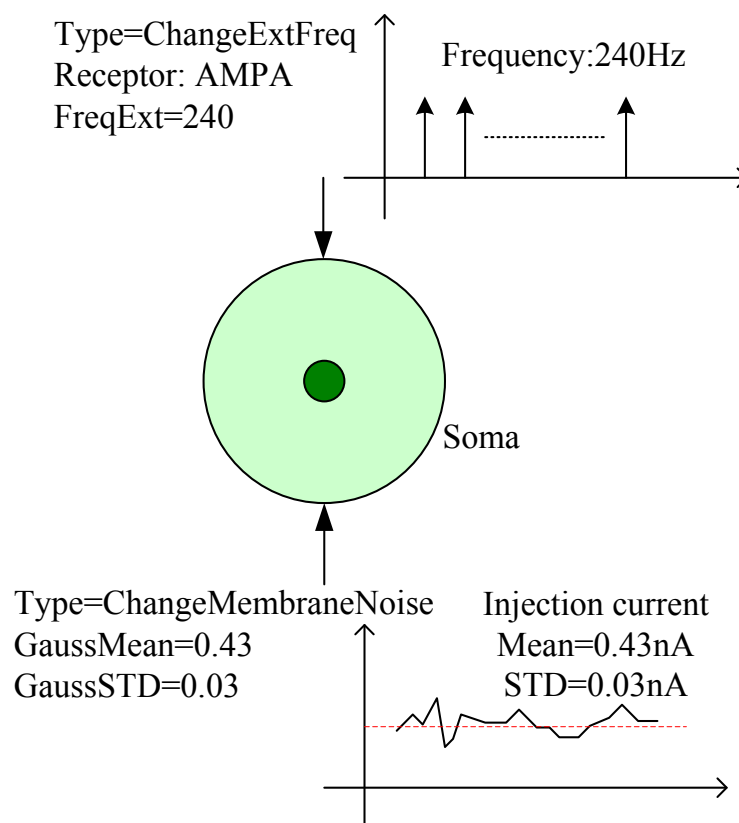


Figure 8 There are two types of stimulation mechanisms: receptor type and current injection type.

Type=ChangeMembraneNoise command establishes a current injection that will

change the membrane potential. GaussMean=0.43 sets the injected current to 0.43 nA (negative values hyperpolarize the neuron), and GaussSTD=0.03 generates a standard deviation= 0.03 nA.

We now introduce the procedure for writing an experiment protocol file. The file is based on time event triggers, with each event representing a population stimulation. In table 3, the code embedded in EventTime 3000.0 to EndEvent stimulates the model at the time 3000.0 ms; Type=ChangeExtFreq, Population:Exc1, Receptor:AMPA and FreqExt=240.0 set population Exc1 neuron's AMPA receptor type stimulation frequency to 240Hz. Label=#1#, the keyword "Label" combined with "#1#", is reserved for future developments. The other example event code is Type=ChangeMembraneNoise, GaussMean=0.43 and GaussSTD=0.03, which means that a Gaussian current with a mean=0.43 nA and a STD=0.03 A is injected into all neurons in the Exc1 population. Finally, Type=EndTrial ends the description of the experimental process.

3.2 File output control

As the last part in table 3, OutControl block defines three different dump data types, membrane potential (MemPot), neuron spike (Spike), and population firing rate (FiringRate). Inside the block, FileName: MemPot.dat, Type=MemPot, population:AllPopulation and EndOutputFile perform dumps of the membrane potential in all populations to MemPot.da, where "AllPopulation" is a special command asking flysim to print the value of every neuron in all populations. "AllPopulation" also can be replaced by Exc1 or Exc2, but not "Exc1,Exc2", depending on the network dynamics of interest. The second output file contains the neuron's spikes, by defining Type=Spike. If you want examine firing rate of neurons define Type=FiringRate, FiringRateWinodw=50 and PrintStep=10. In such a way, you can print out the average firing rate calculated with 50-ms time windows every 10 ms.

3.3 Macro

We also designed a useful program called Macro. Macro gathers many different populations in the sequence of their names listed, and can be used for different events which target the same neuron populations. Macros is defined in DefineMacro to EndDefineMacro. Inside the block, GroupName defines the Macro name, GroupMembers lists populations in sequence and EndGroupMembers ends a Macro definition. In table 3, macro Sti1 gathers Exc1,Exc2 but in a different sequence

compared to macro Sti2, which has two members, Exc2 and Exc1. Sometimes these sequencing options may help user to focus on certain dynamics.

3.4 Protocol options

We have shown some simple examples previously, and list all keywords below. The absence of `–pro` assign protocol file means that flysim will run the default settings (network.pro).

```
DefineMacro          //This keyword combines with 與 EndDefineMacro to form a macro block,
we
                    define many macro inside block.

.....
GroupName:Sti2       // GroupName,GroupMembers and EndGroupMembers three keywords
                    Format a macro block.
GroupMembers:Exc2,Exc1 //population list in sequence
EndGroupMembers
.....
EndDefineMacro
EventTime 3000.0      //Event trigger at time 3000.0 ms
Type=ChangeExtFreq    //stimulation is receptor type
Label=#1#            //reserved descript
Population: Exc1      //target population is Exc1
Receptor: AMPA        //target receptor is AMPA type
FreqExt=240.0         //stands for 240Hz frequency stimulation to AMPA receptor type
EndEvent
.....
EventTime 6500.0
Type=ChangeMembraneNoise //current injection type stimulation
Label=#1#
Population: Exc1
GaussMean=0.43        //Gaussian mean = 0.43 nA
GaussSTD=0.03         //Gaussian STD = 0.03 nA
EndEvent
.....
EventTime 10100.00
Type=EndTrial         //EndTrial 10100.00 ms means that the experiment stops at time 10100
```

```

ms
Label=End_of_the_trial
EndEvent
%------
OutControl          //OutControl for dumping neural network variables
FileName:MemPot.dat  //Define FileName is MemPot.dat
Type=MemPot          //dump membrane potential to file
population:AllPopulation //dump all population
EndOutputFile

FileName:Spikes.dat
Type=Spike           //dump neuron spikes to file
population:Sti2       //output population is Sti2 macro which in Exc2, Exc1 sequence
EndOutputFile

FileName:FRates.dat
Type=FiringRate       //dump population firing rate to file
FiringRateWinodw=50   //average firing rate window is 50 ms
PrintStep=10          //every 10 ms dump data to file
population:Exc2
EndOutputFile
EndOutControl

```

Table 3 network.pro example

DefineMacro	EventTime 9000.0
GroupName:Sti1	Type=ChangeExtFreq
GroupMembers:Exc1,Exc2	Label=#1#
EndGroupMembers	Population: Sti2
	Receptor: AMPA
	FreqExt=700
	EndEvent
GroupName:Sti2	%-----
GroupMembers:Exc2,Exc1	EventTime 10100.00
EndGroupMembers	Type=EndTrial
EndDefineMacro	Label=End_of_the_trial
EventTime 3000.0	EndEvent
Type=ChangeExtFreq	%-----
Label=#1#	OutControl
Population: Exc1	
Receptor: AMPA	FileName:MemPot.dat
FreqExt=240.0	Type=MemPot
EndEvent	population:AllPopulation
	EndOutputFile
EventTime 6500.0	
Type=ChangeMembraneNoise	FileName:Spikes.dat
Label=#1#	Type=Spike
Population: Exc1	population:Sti2
GaussMean=0.43	EndOutputFile
GaussSTD=0.03	
EndEvent	FileName:FRates.dat
	Type=FiringRate
EventTime 7000.0	FiringRateWinodw=50
Type=ChangeExtFreq	PrintStep=10
Label=#1#	population:Exc2
Population: Sti1	EndOutputFile
Receptor: AMPA	
FreqExt=1000	
EndEvent	EndOutControl

4 Examples

In section 2 and 3, we have explained network definitions and experiment definition scripts. Next, we will describe a FI/FF curve example in below paragraph below. Table 4 describes the FF curve example, where we define only one neuronal network as network_n1.conf file and write network_n1.pro file as the protocol file, recording only the firing rate output. Then we change FreqExt=0~9000 in network_n1.pro, and the neuron response changes from low to high activity as shown in Figure 9. In table 5, the other example sets Type=ChangeMembraneNoise, and changes GaussMean=0~3nA, hence we get the neuronal activity shown in figure 10.

Table 4 FF curve experiment protocol

EventTime 1.0 Type=ChangeExtFreq Label=#1# Population: Exc1 Receptor: AMPA FreqExt=240.0 EndEvent %----- EventTime 10000 Type=EndTrial Label=End_of_the_trial EndEvent	OutControl FileName=MemPot.dat Type=MemPot population=AllPopulation EndOutputFile FileName=FRate.dat Type=FiringRate population=AllPopulation FiringRateWindow=100 PrintStep=10 EndOutputFile FileName=Spike.dat Type=Spike population=AllPopulation EndOutputFile EndOutControl
---	---

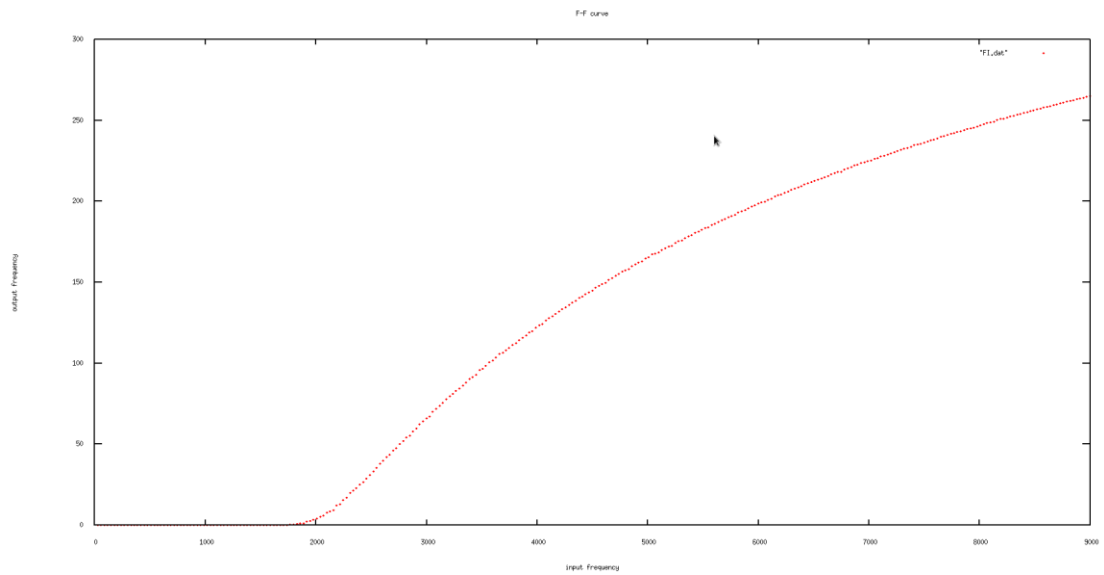


Figure 9 FF curve

Table 5 FI curve experiment protocol

EventTime 1.0 Type=ChangeMembraneNoise Population: Exc1 GaussMean=0.85 GaussSTD=0.3 EndEvent %----- EventTime 10000 Type=EndTrial Label=End_of_the_trial EndEvent	OutControl FileName=MemPot.dat Type=MemPot population=AllPopulation EndOutputFile FileName=FRate.dat Type=FiringRate population=AllPopulation FiringRateWindow=100 PrintStep=10 EndOutputFile FileName=Spike.dat Type=Spike population=AllPopulation EndOutputFile EndOutControl
---	---

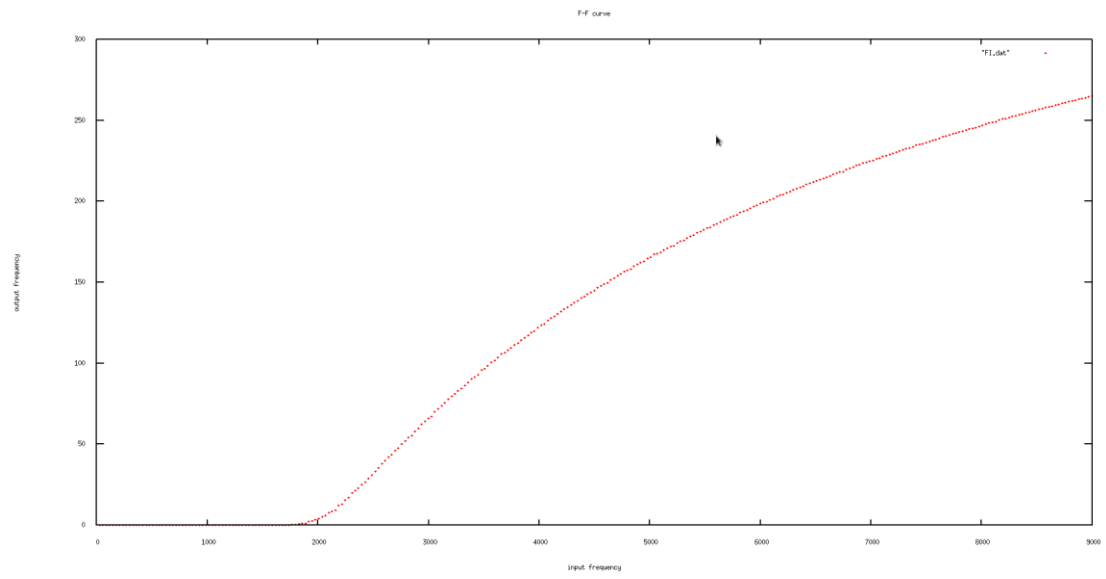


Figure 9. FF curve

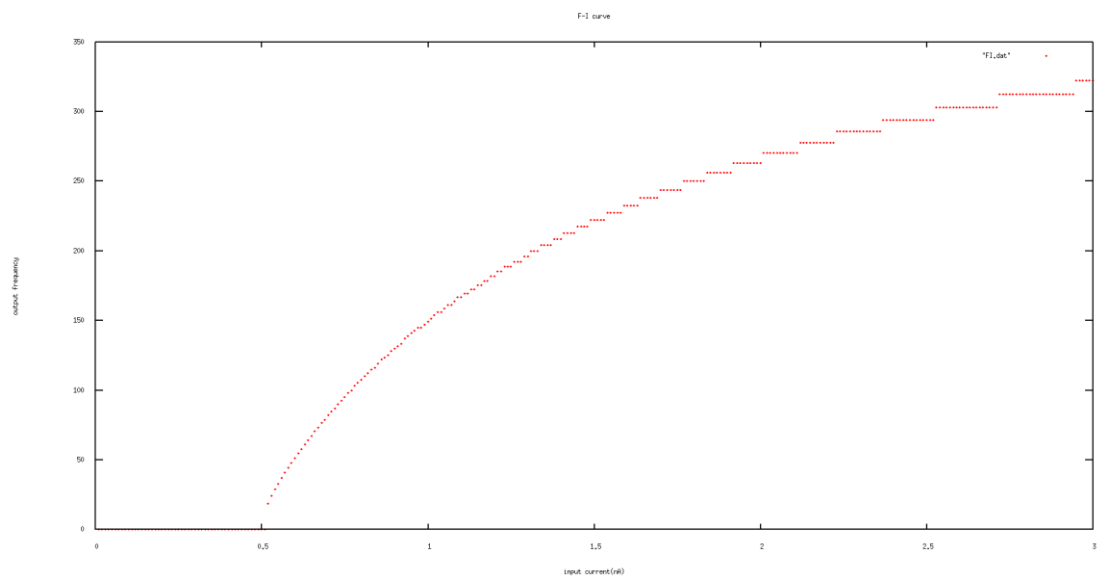


Figure 10. FI curve

Appendix:

A. Neuron models

A.1 LIF

In a sub threshold membrane potential regime, flysim uses the leaky integrated and fire mechanism. The membrane potential eq. (1) has a synapse current term including external stimulation and pre-synaptic neuron stimulation. Pre-synaptic neuron stimulations can come in 5 types of chemical synapse and 1 type of electrical synapse. Equation (3) is a single exponential time constant decay used in fast response receptor type, such as AMPA, GABA, Ach and GCL. These receptors only have different decay time constant and reversal potentials. NMDA receptor dynamics are more complex and given in eq. (3)(4), since the opening of this receptor is also influenced by magnesium ions. Gap junction between neurons are described by the last term in eq. (2).

$$C_m \frac{dV}{dt} = -g_L(V - V_L) + I_{syn} \dots (1)$$

$$I_{syn} = \sum g_{AMPA} s_{AMPA} (V - V_E) + \sum g_{GABA} s_{GABA} (V - V_E) + \sum \frac{g_{NMDA} s_{NMDA} (V - V_E)}{1 + [M_g^{2+}] \frac{e^{-0.062V}}{3.57}} + \sum g_{GAP} (V - V_{post}) \dots (2)$$

$$\frac{ds}{dt} = \sum_k \delta(t - t^k) - \frac{s}{\tau} \dots (3)$$

$$\frac{dx}{dt} = \sum_k \delta(t - t^k) - \frac{x}{\tau_x} \dots (4)$$

$$\frac{ds}{dt} = \alpha_s (1 - s)x - \frac{s}{\tau_s} \dots (5)$$

We solve eq.(1) to (5) with a first order exponential integrator (EI) approximation as numerical iteration in each time step. Eq. (6) is derived from (1) with EI form, Eq. (7) is derived from (3) with EI form and equation (4)(5) has the EI form (8)(9).

$$V = V * df_V + \frac{ef_V}{C_m} (g_L * V_L + I_{syn}), \tau_V = \frac{g_L}{C_m}, df_V = \exp\left(\frac{-dt}{\tau_V}\right), ef_V = \tau_V \left(1 - \exp\left(\frac{-dt}{\tau_V}\right)\right) \dots (6)$$

$$s = s * df_s + \delta(t - t^k), df_s = \exp\left(\frac{-dt}{\tau_s}\right) \dots (7)$$

$$x = x * df_x + \delta(t - t^k), df_x = \exp\left(\frac{-dt}{\tau_x}\right) \dots (8)$$

$$s = s * df_s + ef_s * \alpha_s * x * (1 - s), df_s = \exp\left(\frac{-dt}{\tau_s}\right), ef_s = \tau_s * \left(1 - \exp\left(\frac{-dt}{\tau_s}\right)\right) \dots (9)$$

A.2 sim06

This model uses the same LIF membrane potential model but eq. (1) to (5) use an Euler approximation as numerical iteration in each time step. With the option `-s rough`, (1) becomes (10).

$$V = V + dt \left(\frac{1}{C_m} (g_L * (V_L - V) + I_{syn}) \right) \dots (10)$$

(3) becomes:

If (presynaptic neuron firing)

$$s = s + 1 \dots (11)$$

else

$$s = s - dt \frac{s}{\tau_s} \dots (12)$$

(4) becomes:

If (presynaptic neuron firing)

$$x = x + 1 \dots (13)$$

else

$$x = x - dt \frac{x}{\tau_x} \dots (14)$$

(5) becomes:

$$s = s + dt \left(\alpha_s * x(1 - s) - \frac{s}{\tau_s} \right) \dots (15)$$

With the option `-s moderate`, equations (12),(14) and (15) use 2nd order Euler approximation, when the option changes to `-s accurate`, equations (12),(14) and (15) use a Runge-kKutta 4th order to approximation.

A.3 sim07

This model replaces eq. (12)(14) with the EI form (17)(19)

If (presynaptic neuron firing)

$$s = s + 1 \dots\dots\dots(16)$$

else

$$s = s * df_s \dots\dots\dots(17)$$

If (presynaptic neuron firing)

$$x = x + 1 \dots\dots\dots(18)$$

else

$$x = x * df_x \dots\dots\dots(19)$$

This model no longer supports the option -s.

Reference:

Hempel CM, Hartman KH, Wang XJ, Turrigiano GG, Nelson SB, Multiple forms of short-term plasticity at excitatory synapses in rat medial prefrontal cortex. *J Neurophysiol* 83:3031–3041.

Wang, X.-J. Synaptic basis of cortical persistent activity: the importance of NMDA receptors to working memory. *J. Neurosci.* 19: 9587–9603.