

## **Computational Modeling of Single Neuron Extracellular Electric Potentials and Network Local Field Potentials Using LFPsim**

**Harilal Parasuram and Shyam Diwakar**

School of Biotechnology, Computational Neuroscience Laboratory, Amrita University, India.

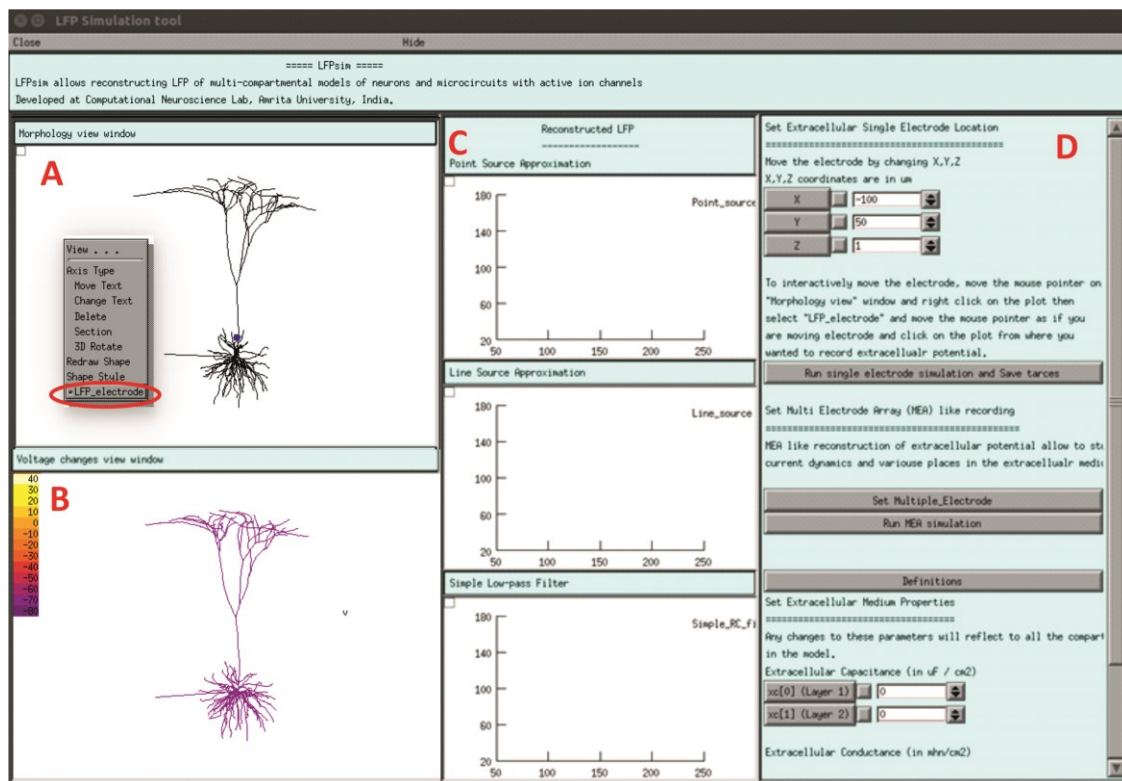
[harilalp@am.amrita.edu](mailto:harilalp@am.amrita.edu) ; [shyam@amrita.edu](mailto:shyam@amrita.edu)

### **1 LFP NEURON tool**

LFP simulation tool is a plug-in for NEURON simulation environment to reconstruct LFP from biophysical models of neurons and networks. LFP simulation tool uses NEURON's inherent extracellular mechanism to calculate total ionic currents from neuronal compartments at each time step (dt). The extracellular potential at a given point (x,y,z) was calculated by setting pointers to lfp.mod and for multiple recording points mea.mod. Point Source Approximation (PSA), Line Source Approximation (LSA) and Simple RC filter techniques were effectively implemented in the tool to calculate extracellular potential of a single cell and LFP of network models.

#### **1.1 Getting familiar with tool Interface**

LFP simulation tool interface was created using NEURON's in-build graphics components. Interface mainly consisted of Morphology view window (A), Voltage changes view window (B), Reconstructed LFP view panel (C), Electrode parameters (D), extracellular medium properties set panel (D).



**Figure 1. LFP simulation tool interface.** A, *Morphology view window* is basically NEURON's shape plot which helps to visualize neuron morphology and extracellular electrode location (shown in blue). Right click of mouse on this window give user to interactively select LFP electrode location by selecting "LFP\_electrode" menu (red circled). Right click of mouse on this window will also give couple of option to user including view the model at different angles. B, *Voltage changes view window* is basically NEURON's space plot which helps to visualize voltages changes across the neuron during the activity. Voltage range from -70 mV to +40 mV was defined as colormap. C, *Reconstructed LFP view panel*, allow user to view the reconstructed LFP in three different method. D, *Simulation controls*, which includes controls for setting electrode parameters, extracellular medium properties and running simulation.

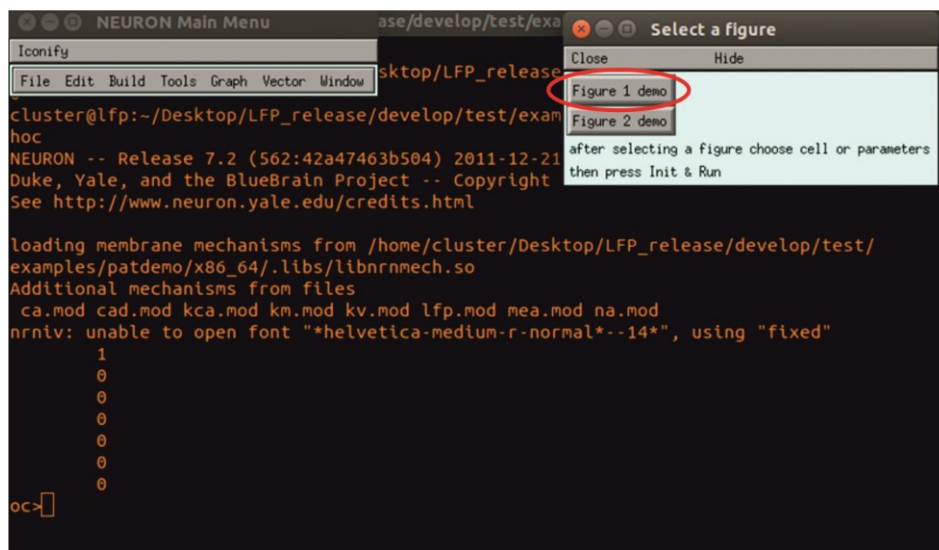
## 1.2 Reconstructing LFP of detailed neuron models

How to execute the tool and stepwise procedure including detailed explanations and screenshots give below. Please visit NEURON's website if you need any help for installing the simulation environment.

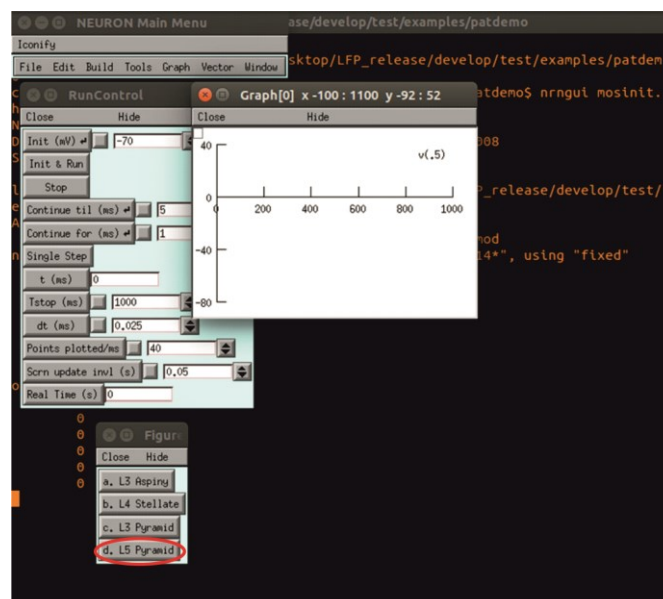
**Follow steps from 1 to 14 to run single electrode LFP simulation.**

1. Download the LFP simulation tool source code and biophysical model of neuron/network of your interest from model DB. LFP tool can be downloaded from: <https://senselab.med.yale.edu/ModelDB/showmodel.cshtml?model=190140>. In this example, Pyramidal Neuron models (Deep, Superficial, Aspiny, Stellate) published by (Mainen and Sejnowski 1996) was used, Accession ID: 2488.
2. Unzip or extract the LFP tool and model neuron/network.
3. Copy and paste all files and folder in the LFP tool folder to neuron/network model folder. Please note, lfp.mod and mea.mod should be placed along with model's mechanism (mod) files.

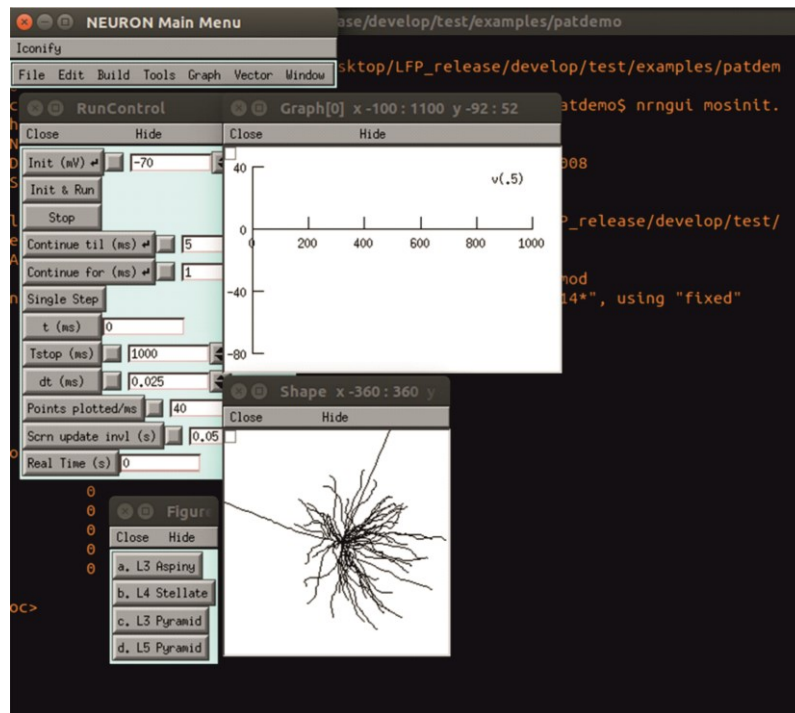
4. Please follow the model's "readme file" if there is any specific procedure for compiling the model in NEURON.
5. For Linux/Unix user, open a terminal and change present working directory to the neuron model folder, then run *nrnivmodl* to compile the model. If you have already compiled the model, then you may have to re-compile after you copy *lfp.mod* and *mea.mod* files to the model directory.
6. For Windows users, double click on "mknrndll" and set the path for where ".mod" files were placed in the model and click on "nrnmech.dll" button for compiling the mechanism files.
7. Please follow model's "read me file" to load the neuron model in NEURON. Here, in this example *mosinit.hoc* file was used to load neuron models. In terminal, type "*nrngui mosinit.hoc*" to load the model in Linux. For Windows users, just double click on *mosinit.hoc* file in the model. If the model is successfully loaded, you can see two NEURON window pop up as showed in the below screenshot. As specified in the neuron model's read me file, click on "Figure 1 demo" button to load the neuron.



Then click on "L5 Pyramid" button to load the neuron.



Once the neuron is loaded you can see a shape plot with the neuron created as showed in below screen shot.



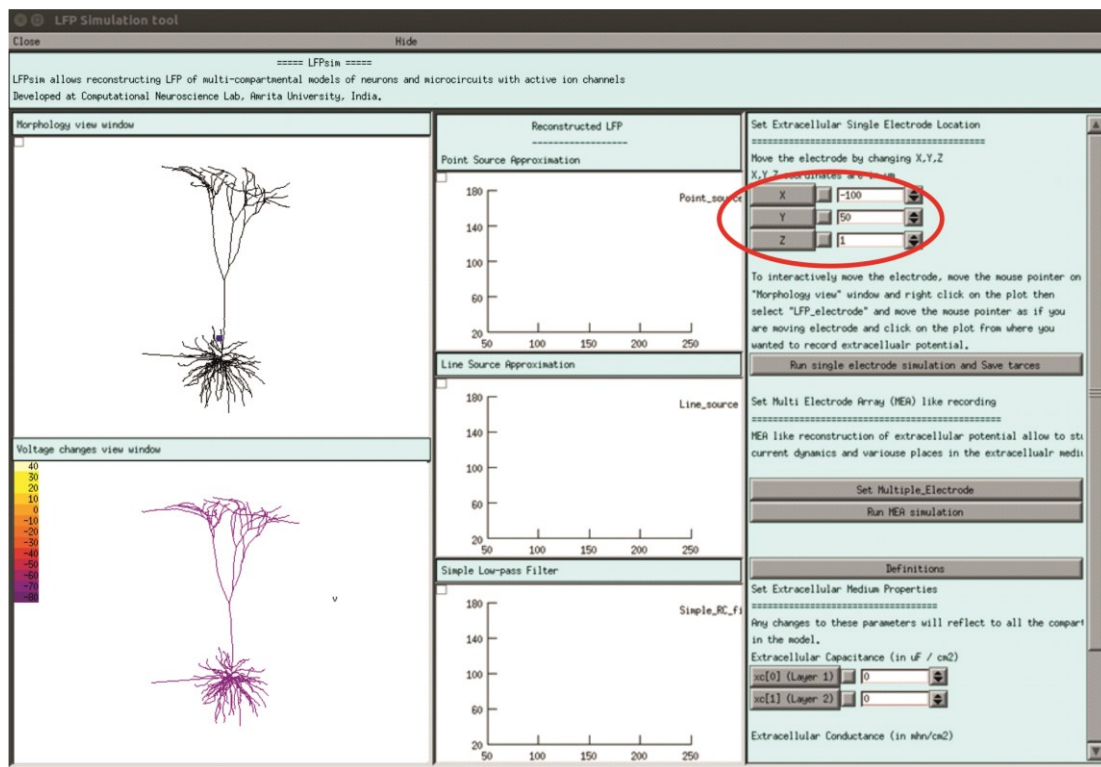
8. After loading the model into NEURON, call “extracellular\_electrode.hoc” from NEURON’s “oc>” terminal by typing `xopen(“extracellular_electrode.hoc”)` to load the LFP simulation tool in NEURON.

```
cluster@lfp:~/Desktop/LFP_release/develop/test/examples/patdemo$ nrngui mosinit.
hoc
NEURON -- Release 7.2 (562:42a47463b504) 2011-12-21
Duke, Yale, and the BlueBrain Project -- Copyright 1984-2008
See http://www.neuron.yale.edu/credits.html

loading membrane mechanisms from /home/cluster/Desktop/LFP_release/develop/test/
examples/patdemo/x86_64/.libs/libnrnmech.so
Additional mechanisms from files
  ca.mod cad.mod kca.mod km.mod kv.mod lfp.mod mea.mod na.mod
nrniv: unable to open font "helvetica-medium-r-normal*-14*", using "fixed"
1
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oc> 1
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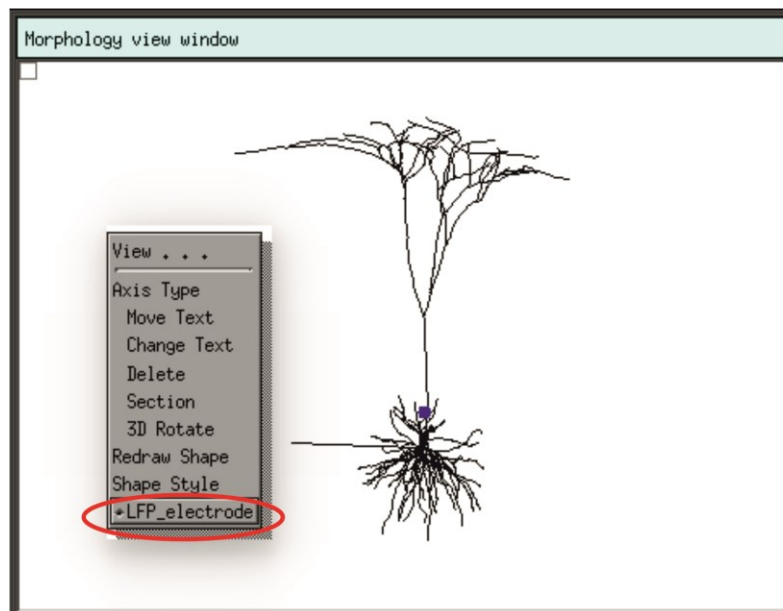
oc>xopen("extracellular_electrode.hoc")
```

9. If everything went well you can see LFP tool interface on your screen as shown below.



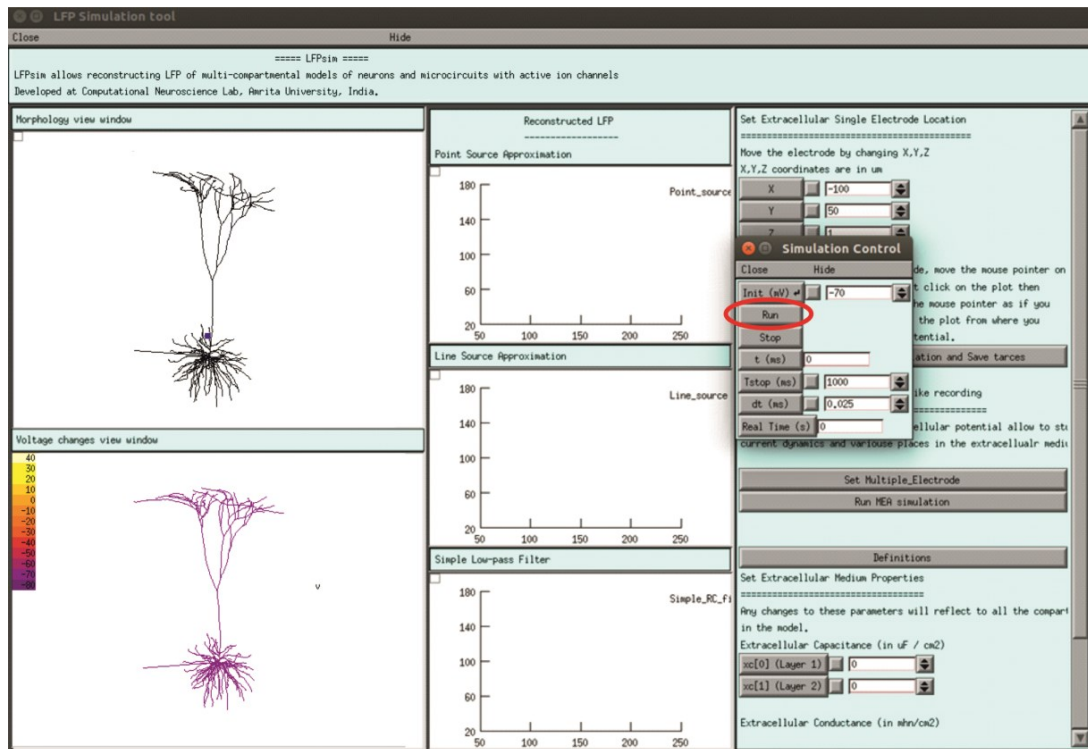
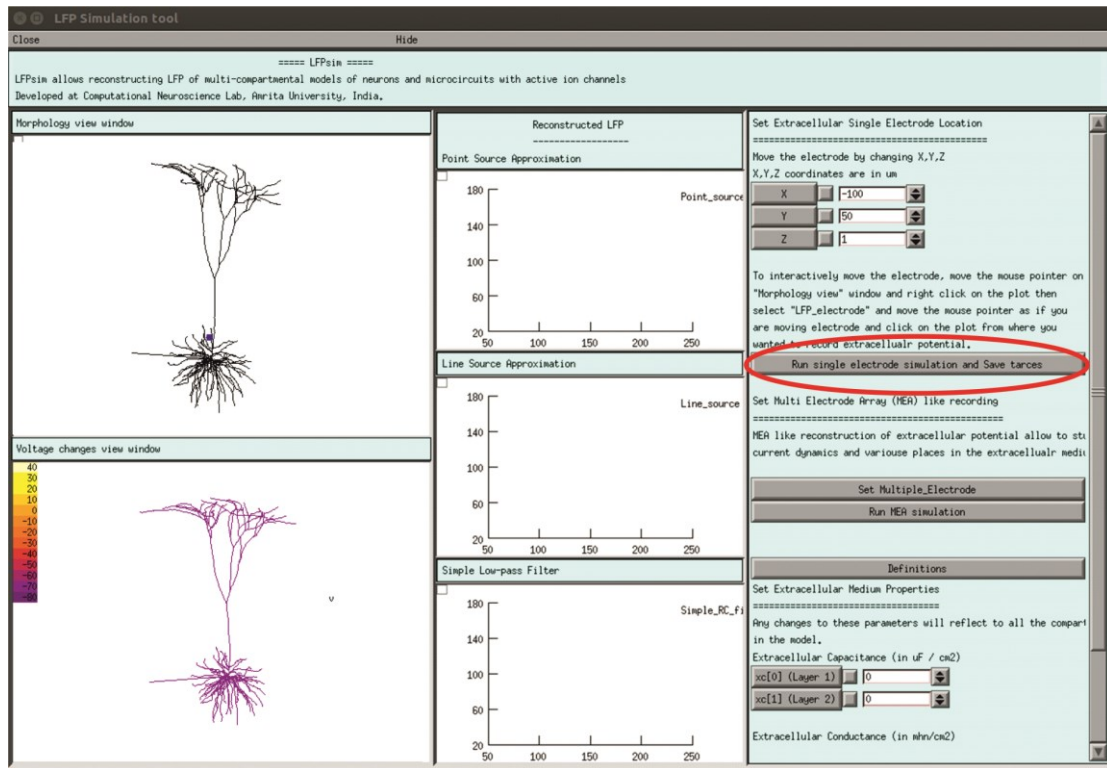
10. Set the stimuli to neuron as per the model.

11. The user can set single electrode location both manually and interactively (see figure 1D of the article). To set manually, the user need to give values for x,y,z of electrode location in panel D (see figure 1 of the article). To interactively change the electrode position, move the mouse pointer on "Morphology view" window and right click on the plot, then select "LFP\_electrode" and move mouse pointer as if you are moving electrode and click on the plot from where you wanted to record the extracellular potential.

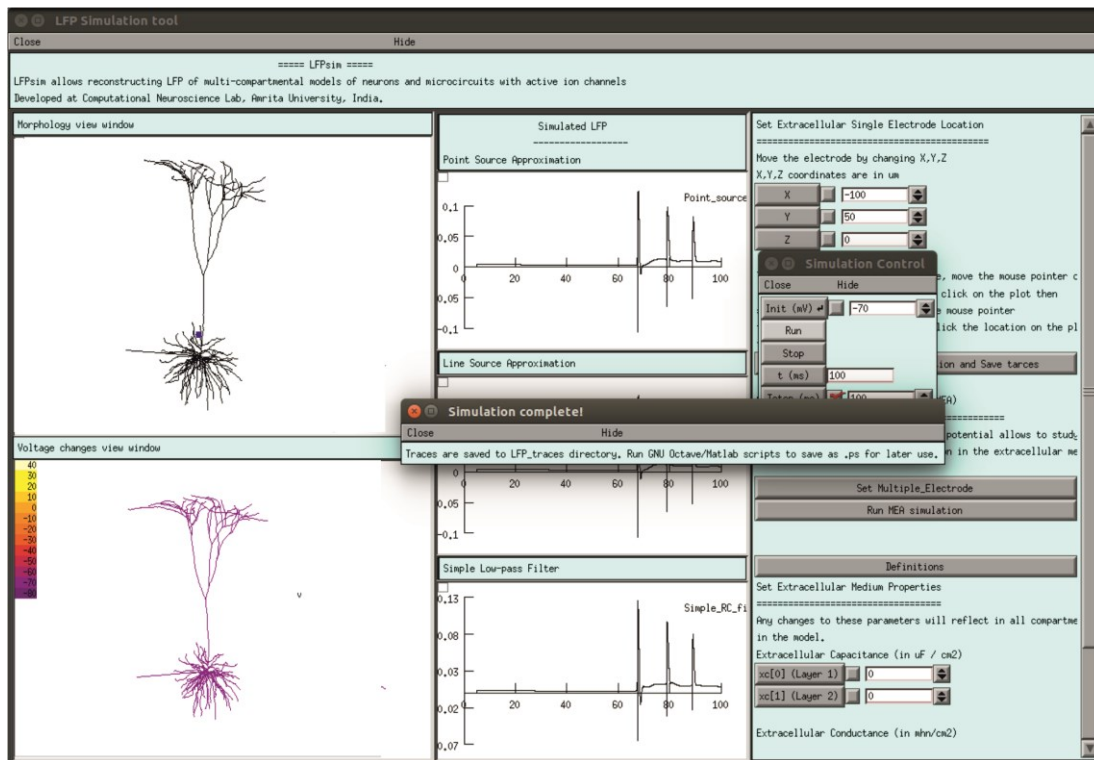




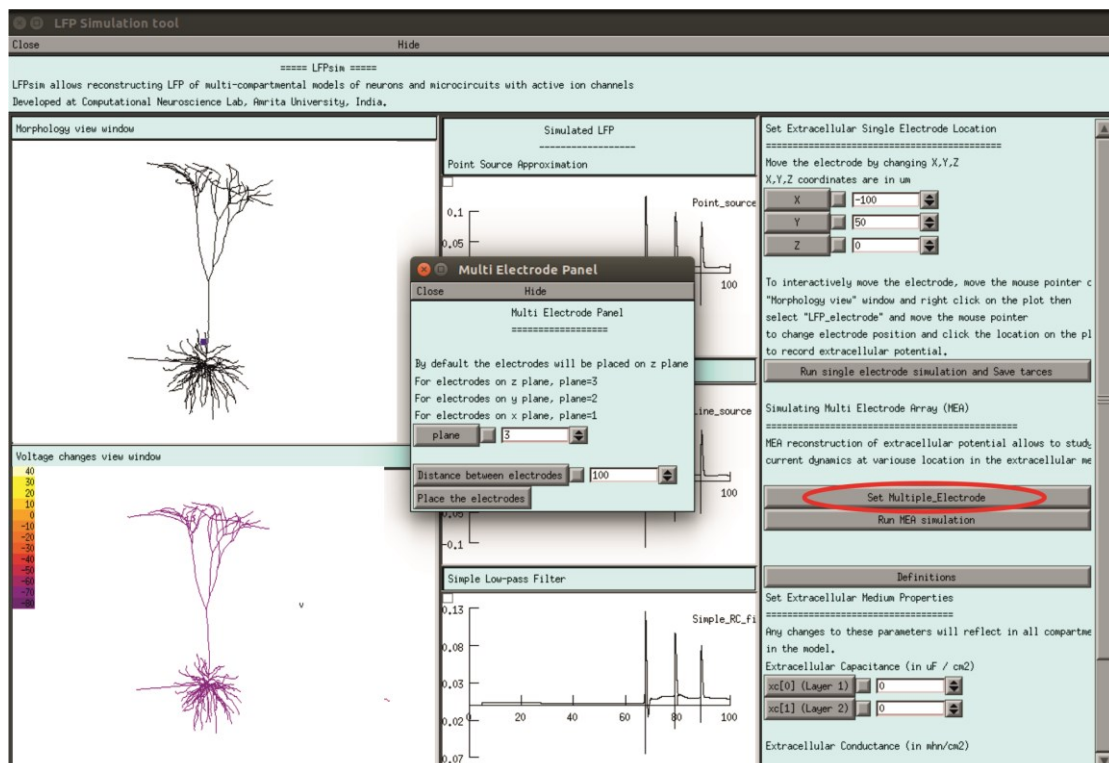
12. Now run single LFP electrode simulation by clicking on “Run single electrode simulation and save traces” button.



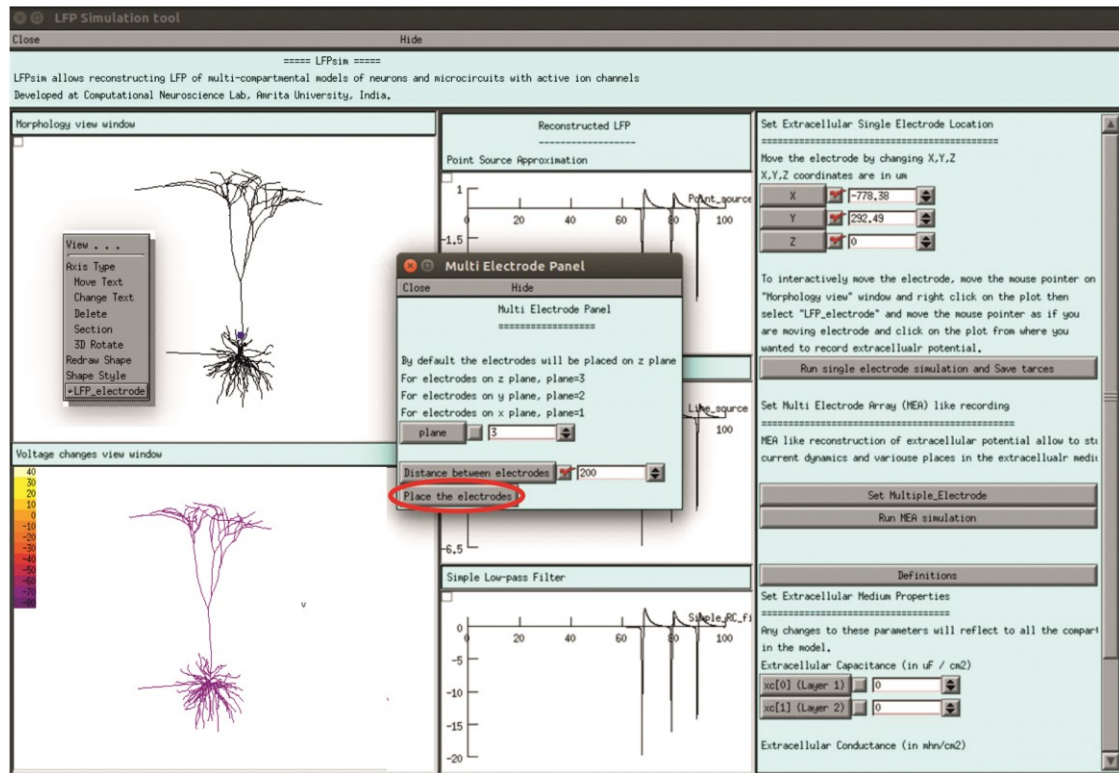
13. Once the simulation is finished, a panel will pop up with a text saying the simulation completed and the traces are saved to “LFP\_traces”. A sample screenshot is given below.



14. Saved traces can be latter used to make plots of your choice in Matlab or Python, sample scripts were given in the “LFP\_traces” folder.
15. **For Multiple electrode simulation, Please follow steps upto 10, then Click on “Set Multiple\_Electrode” button in simulation control window (see figure1D of the article), which popup a panel for setting multi electrode locations as shown in the below screenshot.**



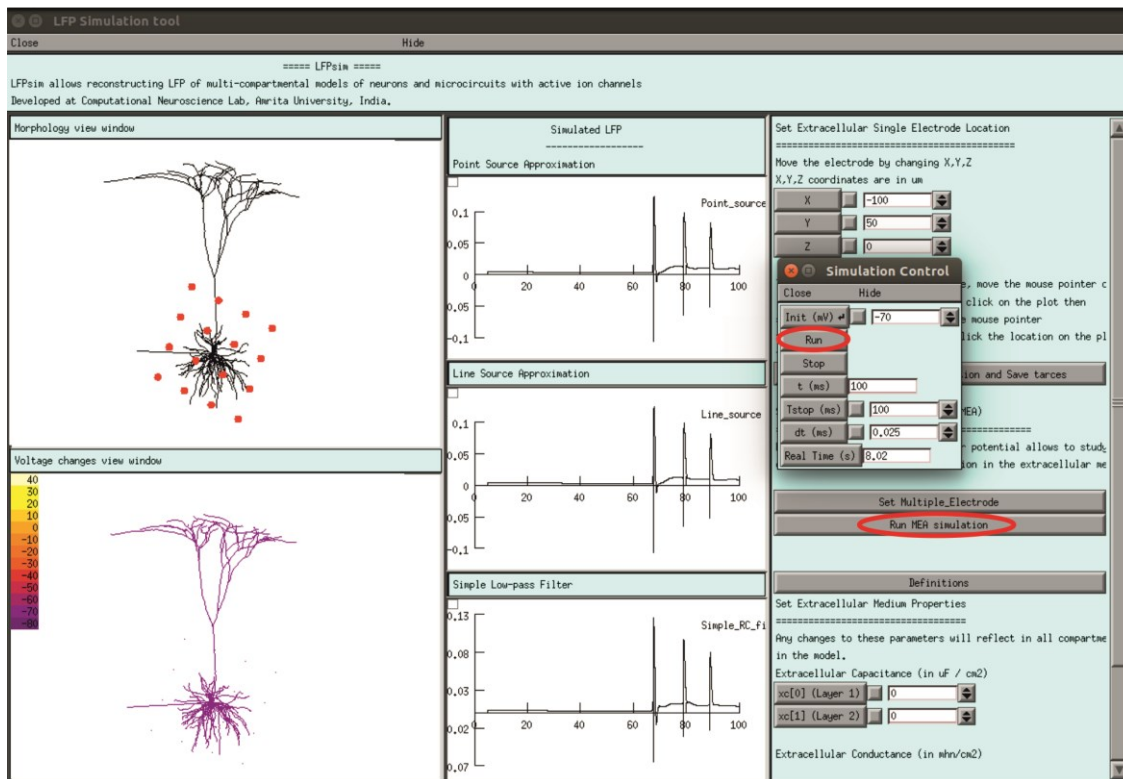
User can change distance between the virtual electrodes (here as an example we set it to 200 $\mu$ m). To place the electrode, please click on “Place the electrode” button. User can see multiple virtual electrodes as red dots in Morphology view window as shown in below screenshot.



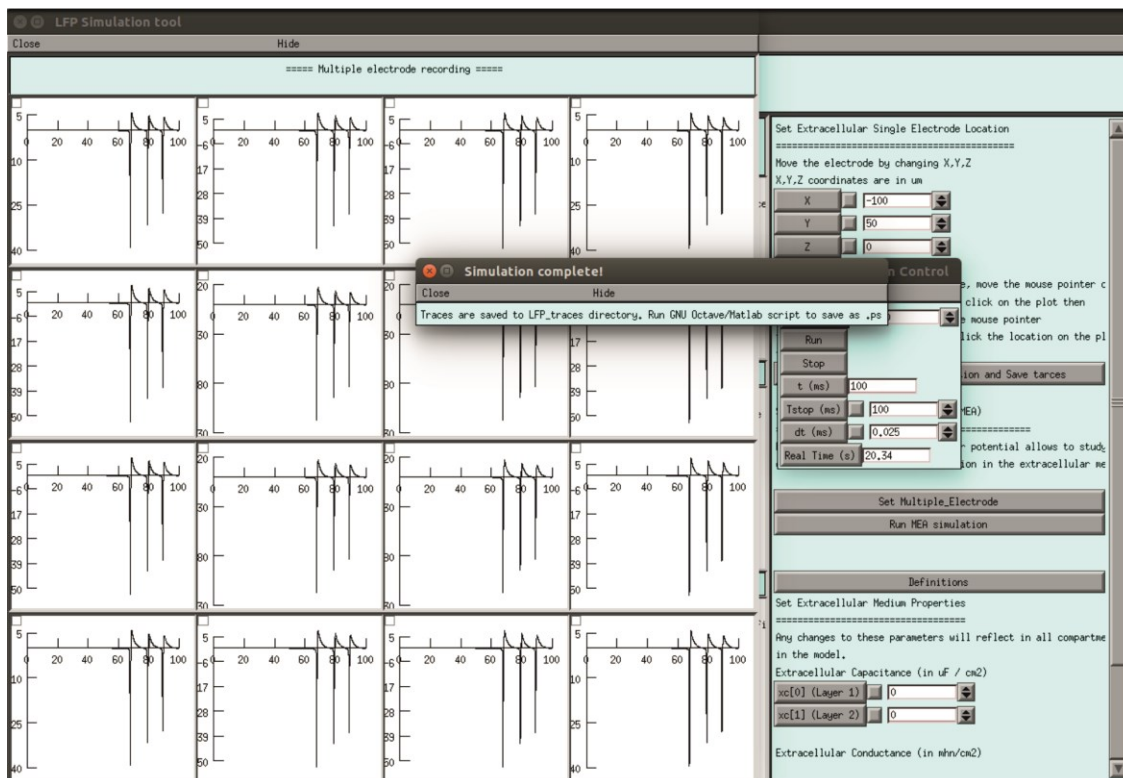
User also can shift the electrodes to different plane by changing the values for plane variable in the panel according to the need.

16. After placing the MEA electrodes user can run the MEA simulation by clicking on “Run MEA simulation” button. Sample screen short given below.



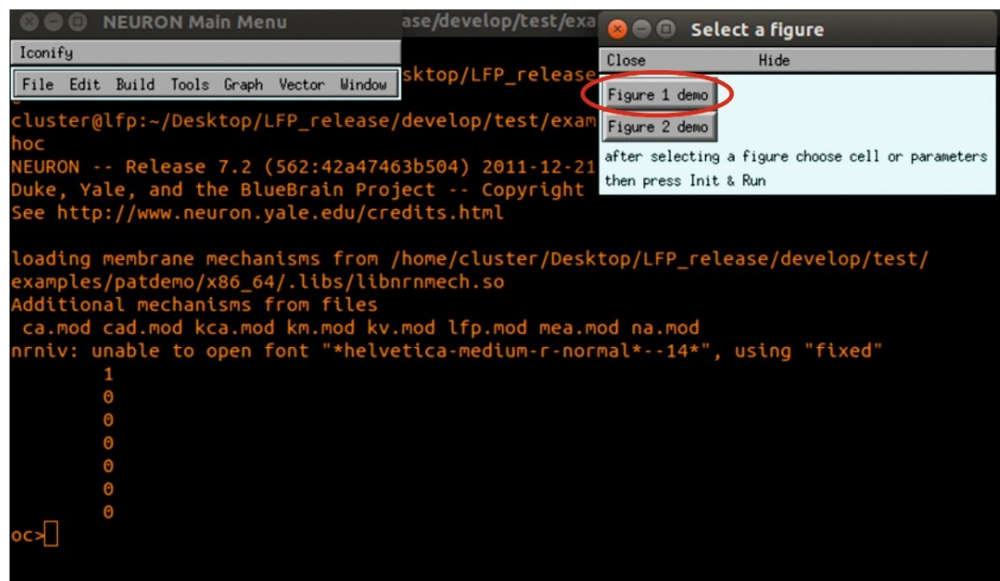


17. Once the simulation is finished, a panel will pop up with a text saying the “simulation completed” and the mea traces are saved to LFP\_traces folder as shown below. Saved traces can be used to make plots of choice in Matlab or Python.



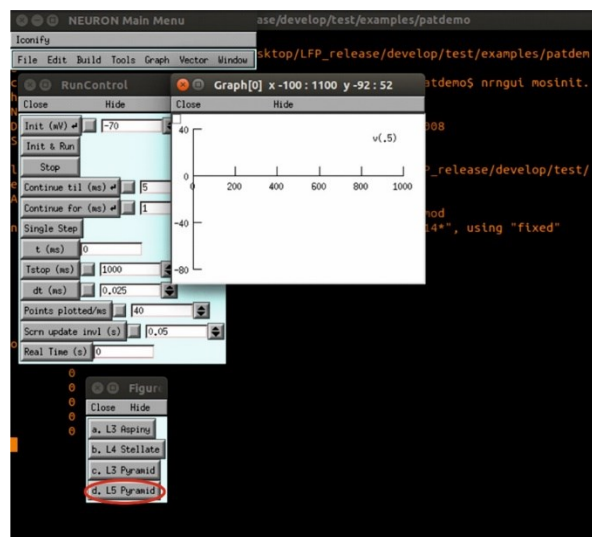
## Readme for reconstructing figure 2

1. Download the LFPsim source code and biophysical model of neuron/network from ModelDB.  
LFP tool can be downloaded from:  
<https://senselab.med.yale.edu/ModelDB/showmodel.cshtml?model=190140>  
In this example, mathematical models of pyramidal neuron (deep, superficial, aspiny, stellate) by (Mainen and Sejnowski 1996) was used (ModelDB Accession ID: 2488).
2. Unzip or extract LFPsim files and model neuron/network.
3. Copy and paste all files and folder in the LFP tool folder to neuron/network model folder. Do note "lfp.mod" and "mea.mod" must be copied and placed along with model's mechanism (mod) files.
4. It is recommended to follow the model's "README" file for any specific procedures regarding compiling the model in NEURON.
5. For Linux/Unix users, opening a terminal and changing the present working directory to the neuron model folder, executing *nrnivmodl* will compile the model. If code was pre-compiled before copying "lfp.mod" and "mea.mod" files to the model directory, it is recommended to recompile after including the mod files along with other channels and receptor mod files.
6. For Windows users, double clicking on "mknrndll" and setting the path to location of the ".mod" files and clicking on "nrnmech.dll" button, compiles the mechanism files (including the mea.mod and lfp.mod files in the same directory).
7. It is recommended to follow the model's "README" file to load the neuron model in NEURON. In this example, mosinit.hoc file was used to load neuron models. On the Linux terminal, type "nrngui mosinit.hoc" to load the model in Linux. For Windows users, double clicking on mosinit.hoc file in the model directory, loads the model. Two NEURON windows popping up indicates the model was loaded. Follow the model's README, and click on "Figure 1 demo" button to load the neuron model.



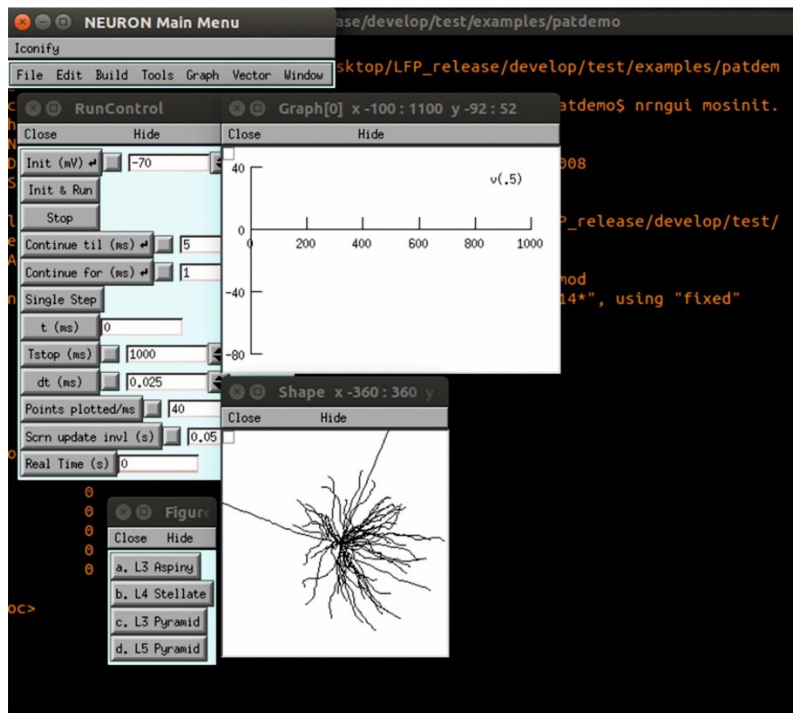
**Supplementary Figure A. Executing pyramidal neuron model.**

Click on “L5 Pyramid” button to load the neuron model.



**Supplementary Figure B. Executing L5 pyramidal neuron model.**

Once loaded, a shape plot will be generated as shown in the Figure.



Supplementary Figure C. L5 pyramidal neuron space plot.

- 8 After loading the model into NEURON, call “extracellular\_electrode.hoc” from NEURON’s terminal by typing `xopen(“extracellular_electrode.hoc”)` to load LFPsim in NEURON.

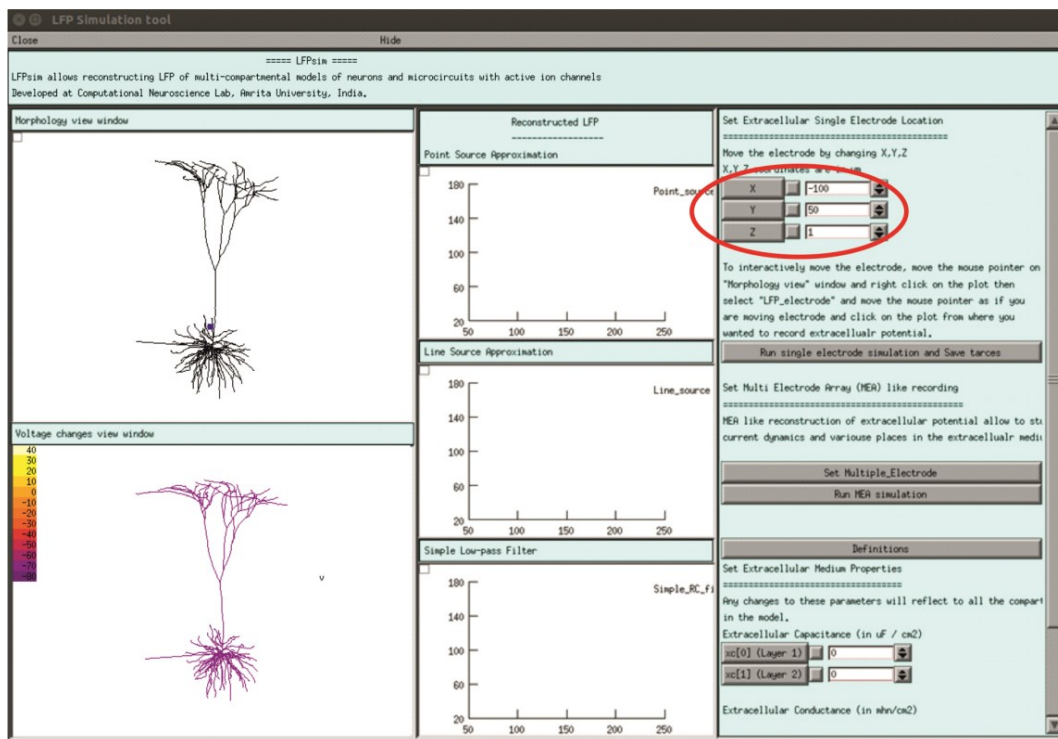
```
cluster@lfp:~/Desktop/LFP_release/develop/test/examples/patdemo$ nrngui mosinit.
hoc
NEURON -- Release 7.2 (562:42a47463b504) 2011-12-21
Duke, Yale, and the BlueBrain Project -- Copyright 1984-2008
See http://www.neuron.yale.edu/credits.html

loading membrane mechanisms from /home/cluster/Desktop/LFP_release/develop/test/
examples/patdemo/x86_64/.libs/libnrnmech.so
Additional mechanisms from files
  ca.mod cad.mod kca.mod km.mod kv.mod lfp.mod mea.mod na.mod
nrniv: unable to open font "helvetica-medium-r-normal*-14", using "fixed"
1
0
0
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oc> 1
0
0
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0

oc>xopen("extracellular_electrode.hoc")
```

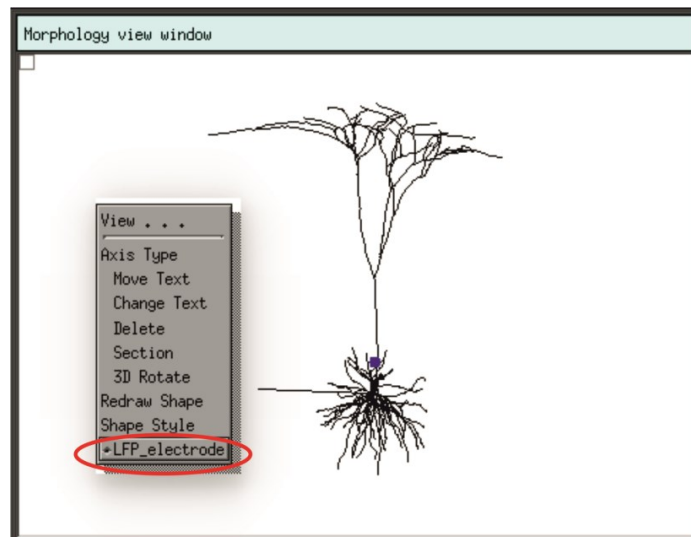
Supplementary Figure D. Loading LFPsim with the NEURON model.

- 9 This invokes the LFPsim GUI on successful execution.



**Supplementary Figure E. LFPsim and pyramidal neuron model.**

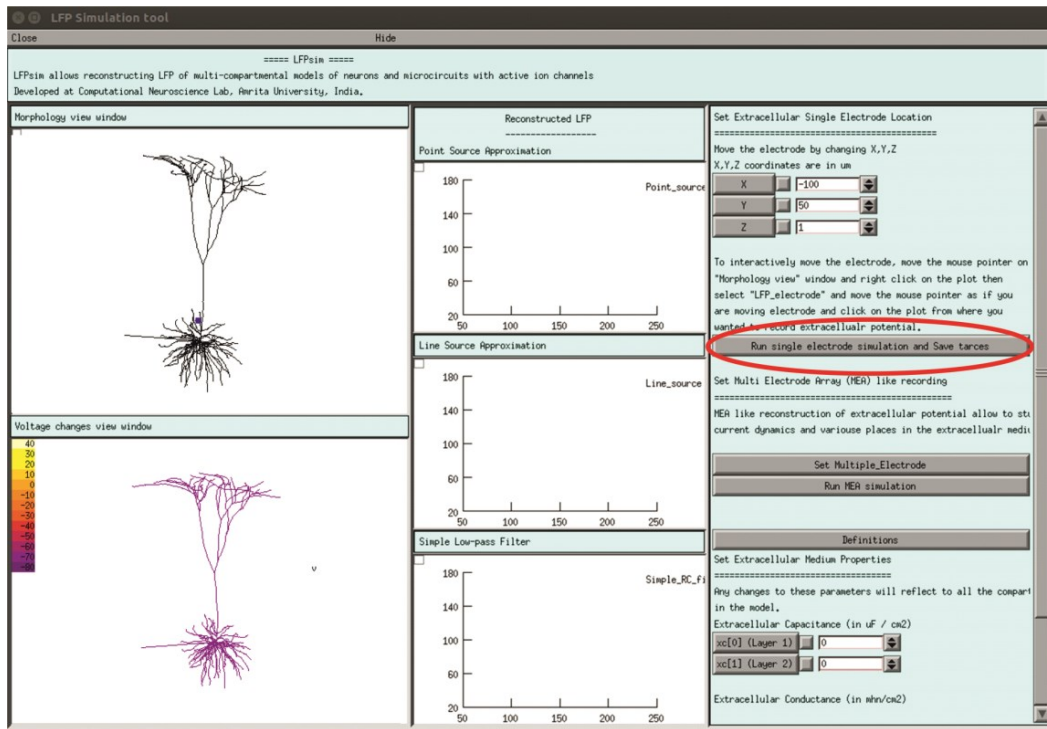
- 10 Set input stimuli to neuron model.
- 11 Users can set single electrode location both manually and interactively (see Figure 1D). To set manually, the user needs to provide values for x,y,z of electrode location in panel D (see Figure 1). To interactively change the electrode position, the mouse pointer on "Morphology view" window may be moved and by right clicking on the plot, then select "LFP\_electrode". Moving electrode is performed by moving the mouse pointer and clicking on the plot at the point of interest to record the extracellular potential.



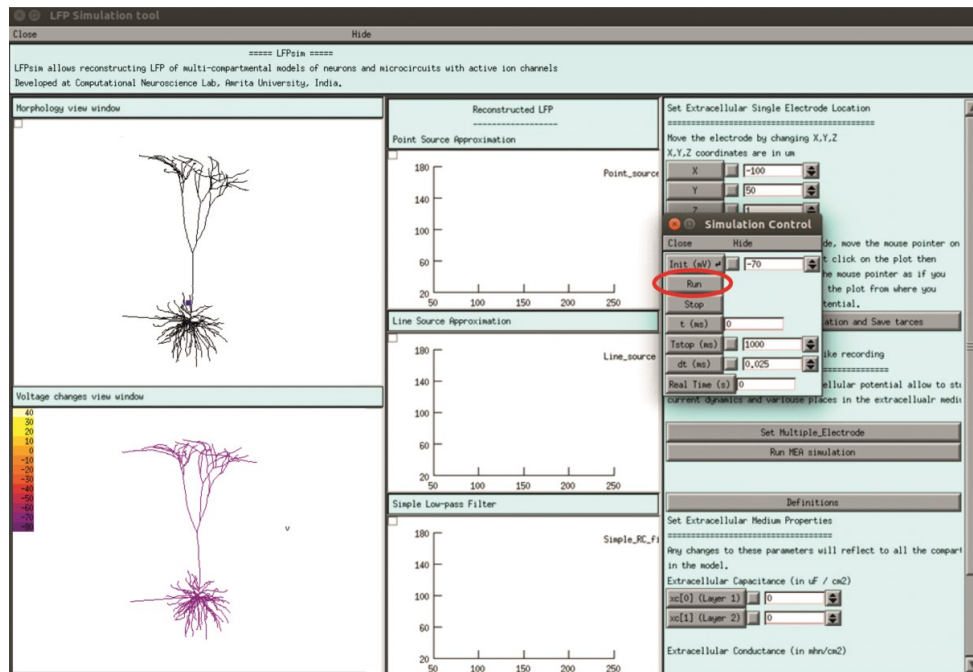
**Supplementary Figure F. Modifying LFP electrode settings.**



- 12 Execute single LFP electrode simulation by clicking on “Run single electrode simulation and save trace” button.

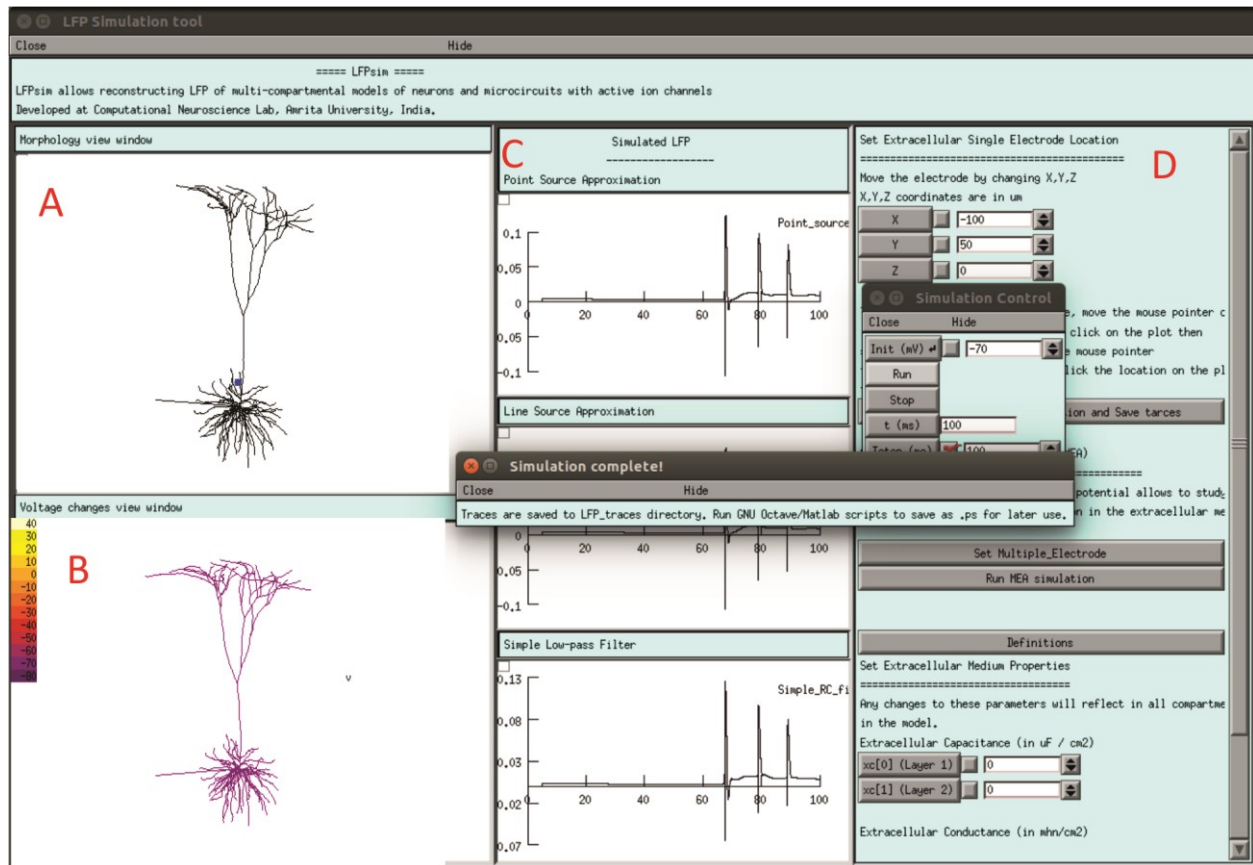


**Supplementary Figure G. Executing LFP simulation on L5 neuron model.**



**Supplementary Figure H. Running LFP simulations.**

- 13 When run is completed, a pop up will indicate “Simulations complete” and traces will be saved to “LFP\_traces” directory within the model’s directory.



## Readme for reconstructing figure 3

1. Download the LFPsim source code and biophysical model of neuron/network from ModelDB. LFP tool can be downloaded from: <https://senselab.med.yale.edu/ModelDB/showmodel.cshtml?model=190140>  
In this example, cerebellar granular layer network model (Parasuram 2011, 2015) was used to reconstruct the LFP.
2. Unzip or extract LFPsim files and model neuron/network.
3. Copy and paste all files and folder in the LFP tool folder to neuron/network model folder. Do note “lfp.mod” and “mea.mod” must be copied and placed along with model’s mechanism (mod) files.
4. It is recommended to follow the model’s “README” file for any specific procedures regarding compiling the model in NEURON.
5. For Linux/Unix users, opening a terminal and changing the present working directory to the neuron model folder, executing `nrnivmodl` will compile the model. If code was pre-compiled before copying “lfp.mod” and “mea.mod” files to the model directory, it is recommended to recompile after including the mod files along with other channels and receptor mod files.

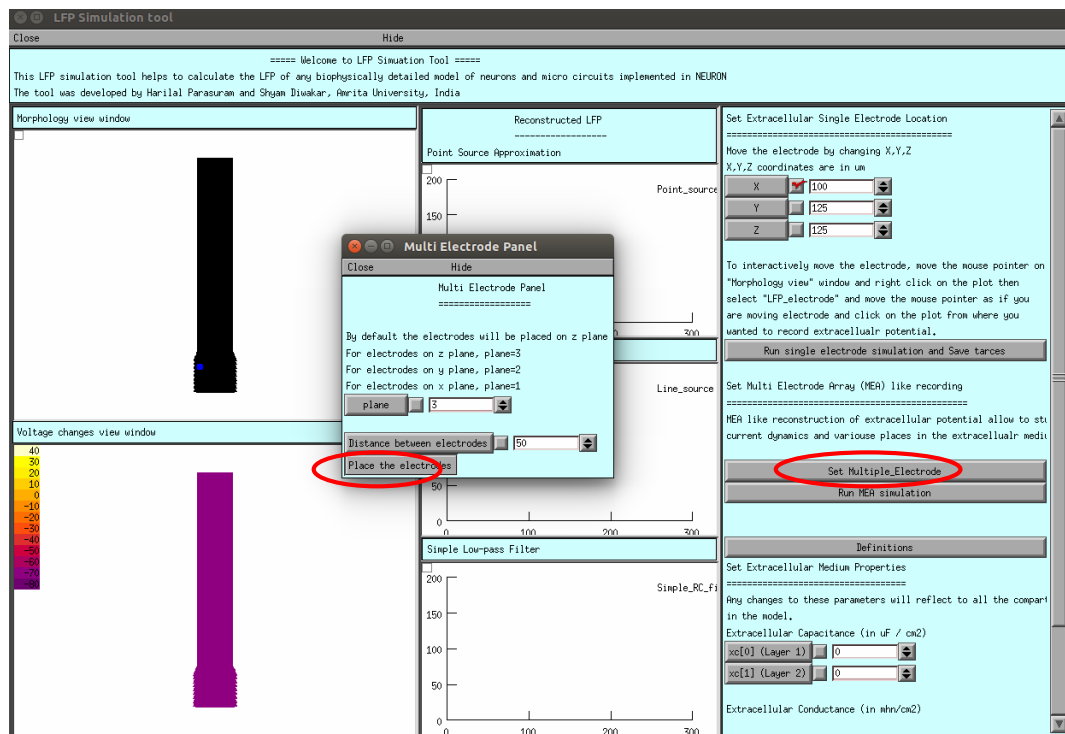
6. For Windows users, double clicking on “mknrndll” and setting the path to location of the “.mod” files and clicking on “nrnmech.dll” button, compiles the mechanism files (including the mea.mod and lfp.mod files in the same directory).
7. It is recommended to follow the model’s “README” file to load the neuron model in NEURON. In this example, mosinit.hoc file was used to load neuron models. On the Linux terminal, type “nrngui mosinit.hoc” to load the model in Linux. For Windows users, double clicking on mosinit.hoc file in the model directory, loads the model.
8. After loading the model into NEURON, call “extracellular\_electrode.hoc” from NEURON’s terminal by typing `xopen(“extracellular_electrode.hoc”)` to load LFPsim in NEURON.

```
cluster@lfp:~/Desktop/LFP_release/develop/test/examples/patdemo$ nrngui mosinit.hoc
NEURON -- Release 7.2 (562:42a47463b504) 2011-12-21
Duke, Yale, and the BlueBrain Project -- Copyright 1984-2008
See http://www.neuron.yale.edu/credits.html

loading membrane mechanisms from /home/cluster/Desktop/LFP_release/develop/test/
examples/patdemo/x86_64/.libs/libnrnmech.so
Additional mechanisms from files
  ca.mod cad.mod kca.mod km.mod kv.mod lfp.mod mea.mod na.mod
nrniv: unable to open font "*helvetica-medium-r-normal*--14*", using "fixed"
      1
      0
      0
      0
      0
      0
      0
oc>      1
      0
      0
      0
      0
      0
      0
oc>xopen("extracellular_electrode.hoc")
```

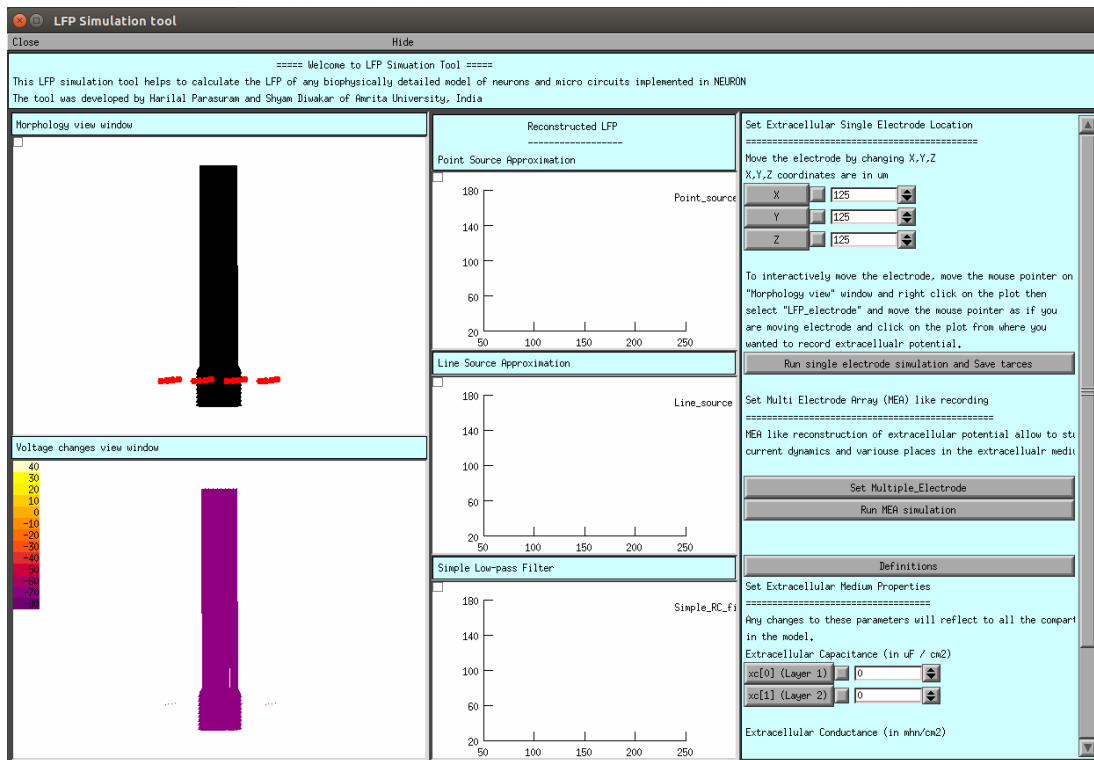
### Supplementary Figure A. Loading LFPsim with the NEURON model.

9. This invokes the LFPsim GUI on successful execution.
10. Set input stimuli to neuron model.
11. **For multiple electrode “MEA” simulation**, Click on “Set Multiple\_Electrode” button in simulation control window.



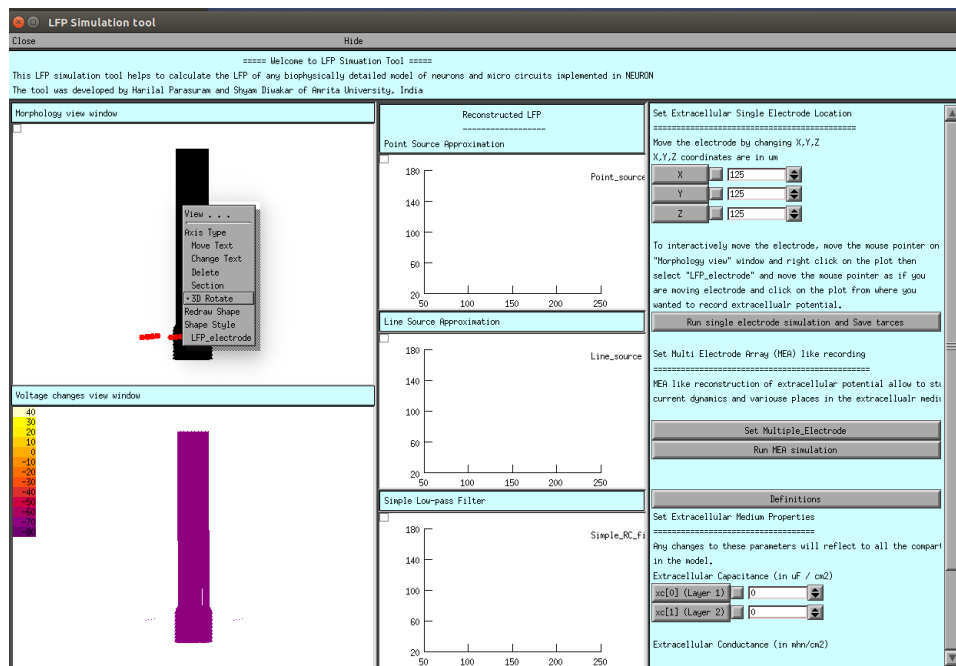
**Supplementary Figure B. “Placing” the MEA electrode.**

12. Users can change distance between the virtual electrodes (as an example, 200 $\mu$ m was set). To “set” the electrode location, click on “Place the electrode” button. Users can see multiple virtual electrodes as red dots in Morphology view window. Electrodes can also be relocated on to a different plane by changing plane variable in the panel.



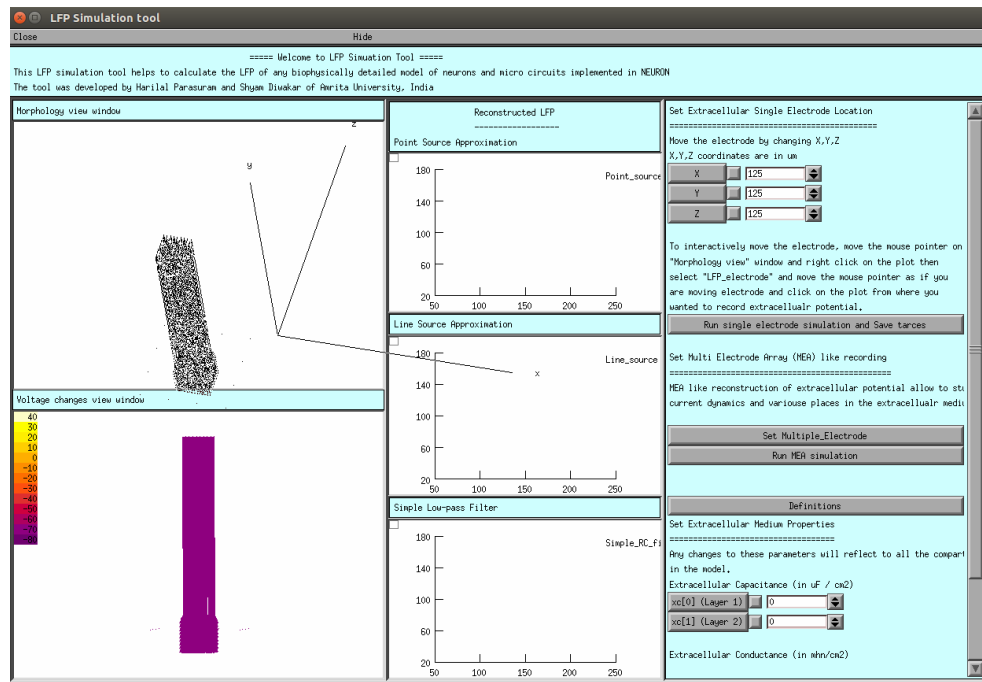
**Supplementary Figure C. “Placing” the MEA electrode.**

13. User can rotate the view of the model by right click on the morphology view window and select “3D rotate”, as shown below. [Read more.](#)



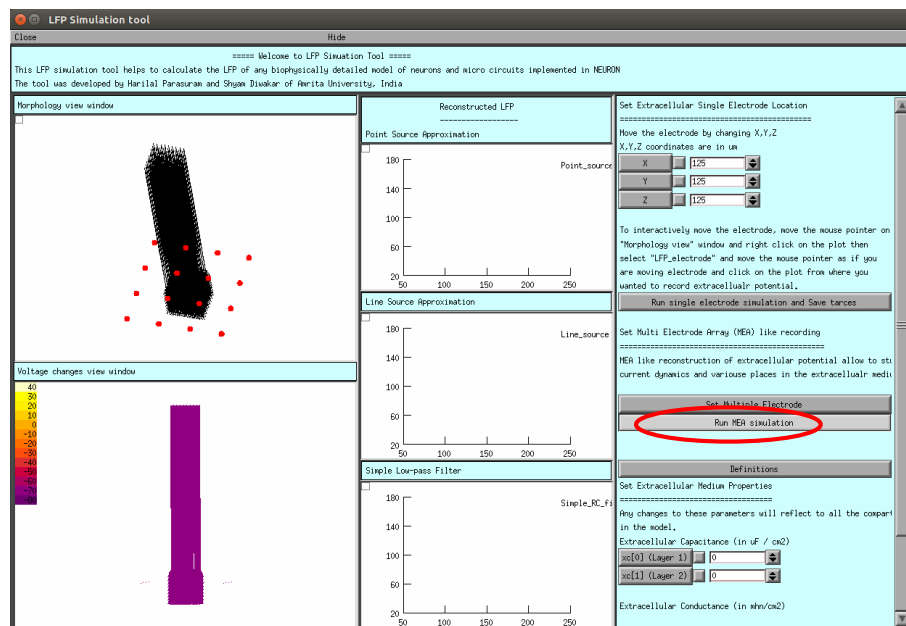
**Supplementary Figure D. Selecting 3D rotate.**



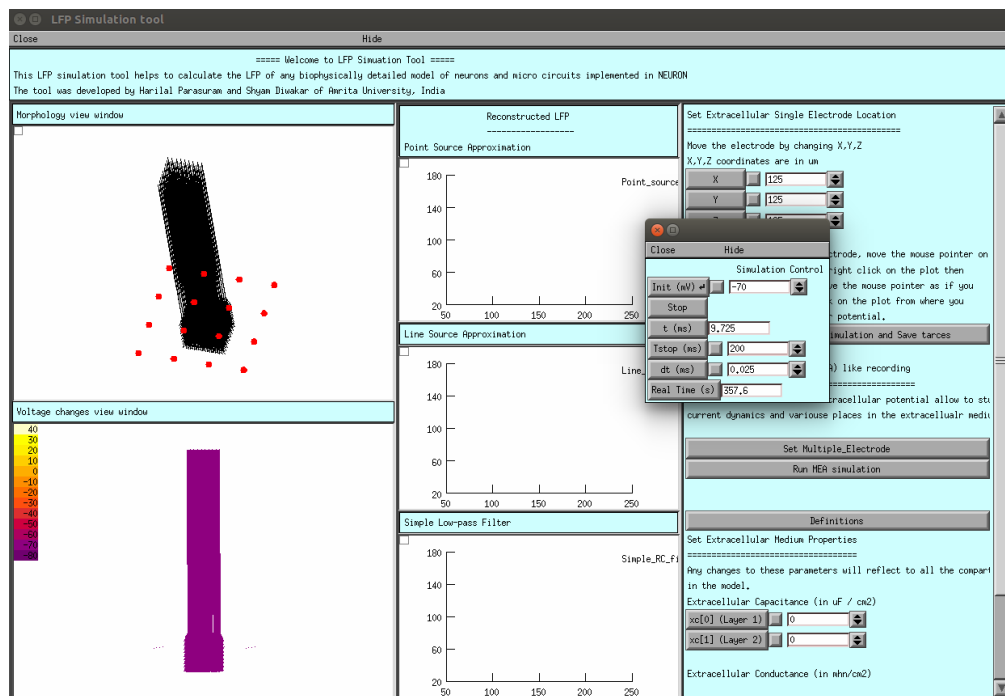


**Supplementary Figure E. Performing 3D rotation of the model**

14. After placing the MEA electrodes, user can execute “MEA” simulation by clicking on “Run MEA simulation” button.

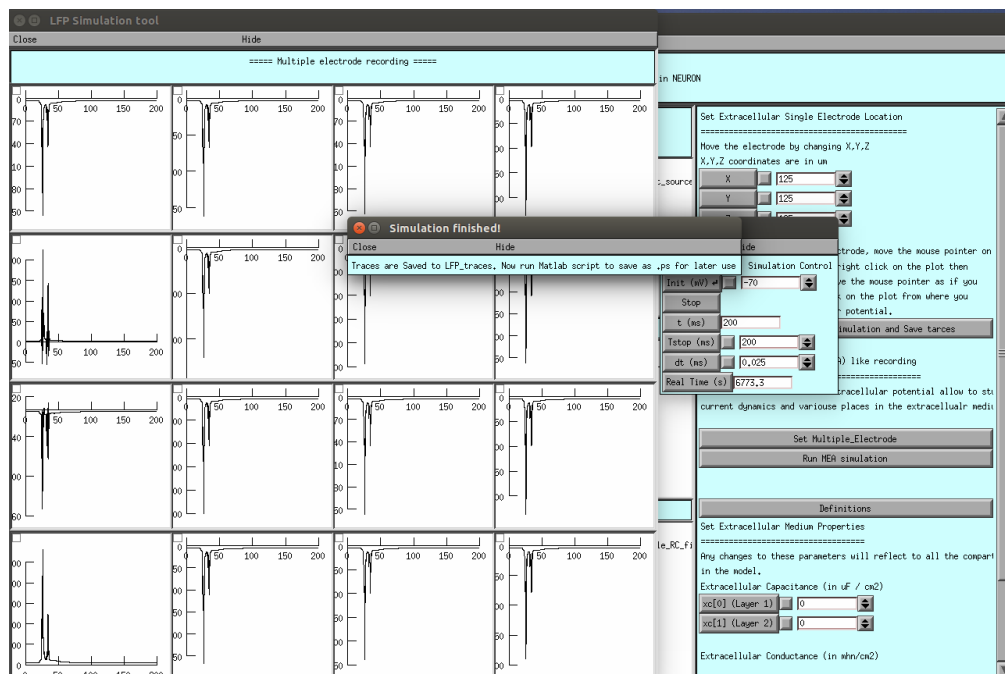


**Supplementary Figure F. Simulating “MEA”.**



**Supplementary Figure G. Simulating “MEA”.**

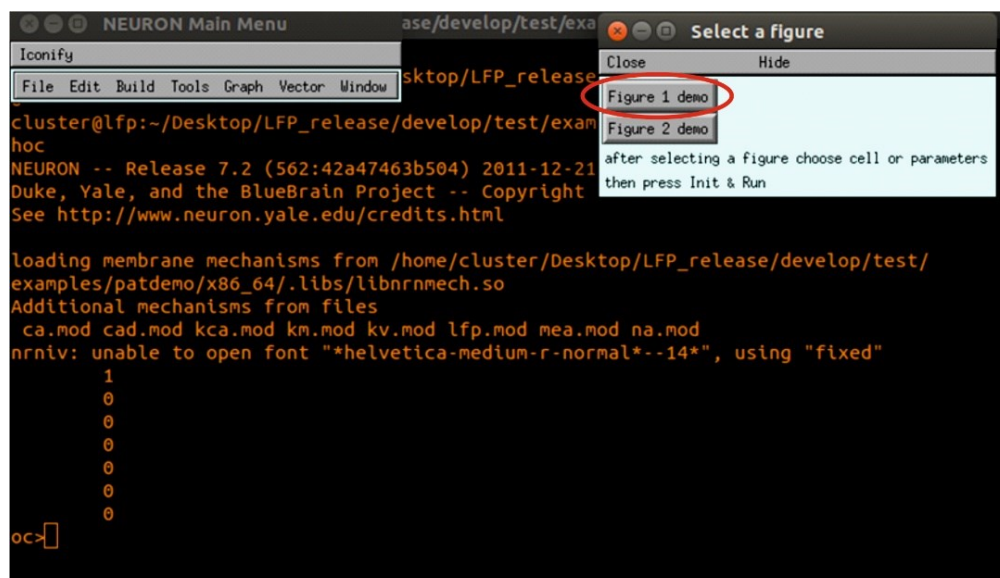
15. A pop up “Simulation complete” will indicate run completed and MEA traces will be saved to “LFP\_traces”.



**Supplementary Figure H. “MEA” GUI in LFPsim.**

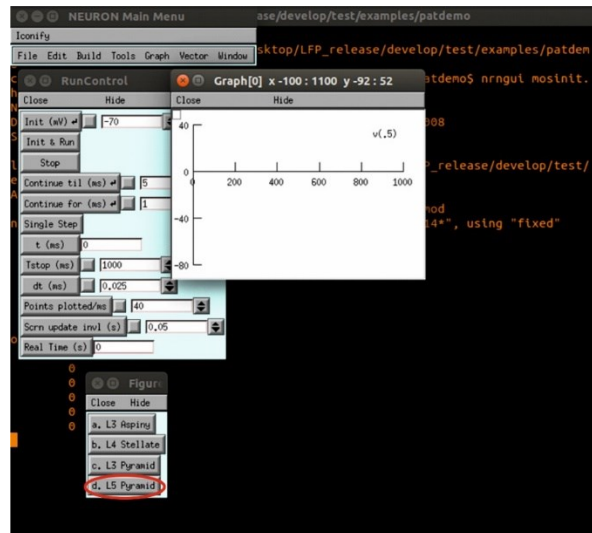
## Readme for reconstructing figure 4

1. Download the LFPsim source code and biophysical model of neuron/network from ModelDB. LFP tool can be downloaded from: <https://senselab.med.yale.edu/ModelDB/showmodel.cshtml?model=190140>  
In this example, mathematical models of pyramidal neuron (deep, superficial, aspiny, stellate) by (Mainen and Sejnowski 1996) was used (ModelDB Accession ID: 2488). Cerebellar granule neuron model can be downloaded from ModelDB with Accession ID: 116835.
2. Unzip or extract LFPsim files and model neuron/network.
3. Copy and paste all files and folder in the LFP tool folder to neuron/network model folder. Do note "lfp.mod" and "mea.mod" must be copied and placed along with model's mechanism (mod) files.
4. It is recommended to follow the model's "README" file for any specific procedures regarding compiling the model in NEURON.
5. For Linux/Unix users, opening a terminal and changing the present working directory to the neuron model folder, executing `nrnivmodl` will compile the model. If code was pre-compiled before copying "lfp.mod" and "mea.mod" files to the model directory, it is recommended to recompile after including the mod files along with other channels and receptor mod files.
6. For Windows users, double clicking on "mknrndll" and setting the path to location of the ".mod" files and clicking on "nrnmech.dll" button, compiles the mechanism files (including the mea.mod and lsp.mod files in the same directory).
7. It is recommended to follow the model's "README" file to load the neuron model in NEURON. In this example, mosinit.hoc file was used to load neuron models. On the Linux terminal, type "nrngui mosinit.hoc" to load the model in Linux. For Windows users, double clicking on mosinit.hoc file in the model directory, loads the model. Two NEURON windows popping up indicates the model was loaded. Follow the model's README, and click on "Figure 1 demo" button to load the neuron model.



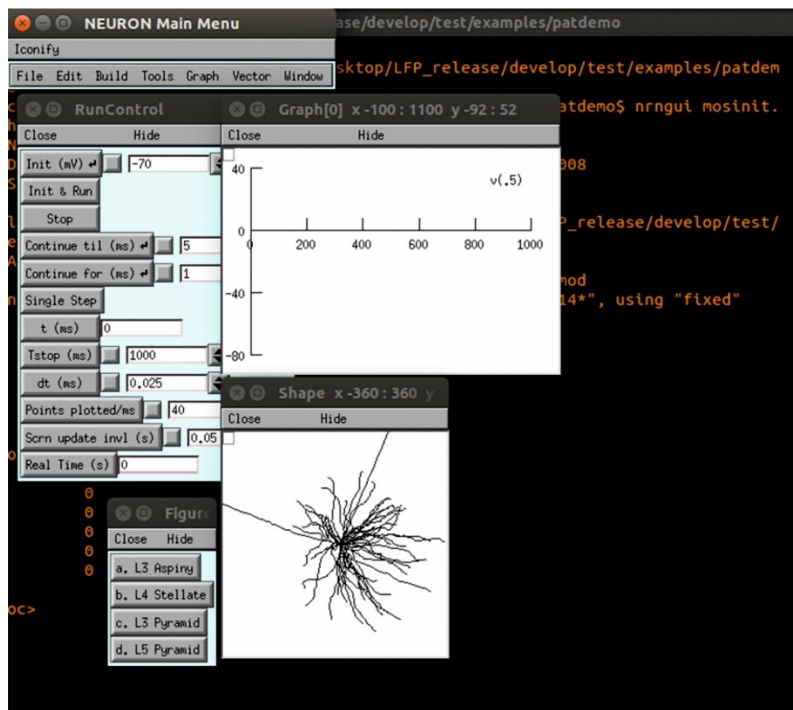
### Supplementary Figure A. Executing pyramidal neuron model.

Click on “L3 pyramidal or L3 stellate or L5pyramidal or L5 stellate” button to load the respective model neuron model.



### Supplementary Figure B. Executing L5 pyramidal neuron model.

Once loaded, a shape plot will be generated as shown in Supplementary Figure 4.



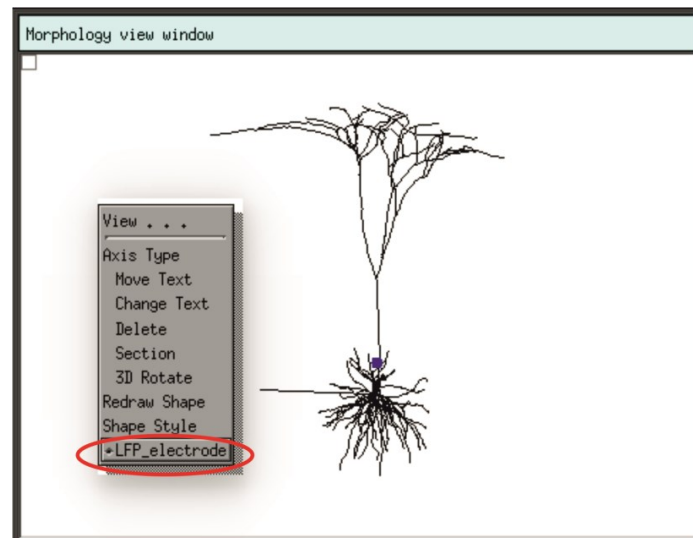
### Supplementary Figure C. L5 pyramidal neuron space plot.

8. After loading the model into NEURON, call “extracellular\_electrode.hoc” from NEURON’s terminal by typing `xopen(“extracellular_electrode.hoc”)` to load LFPsim in NEURON.



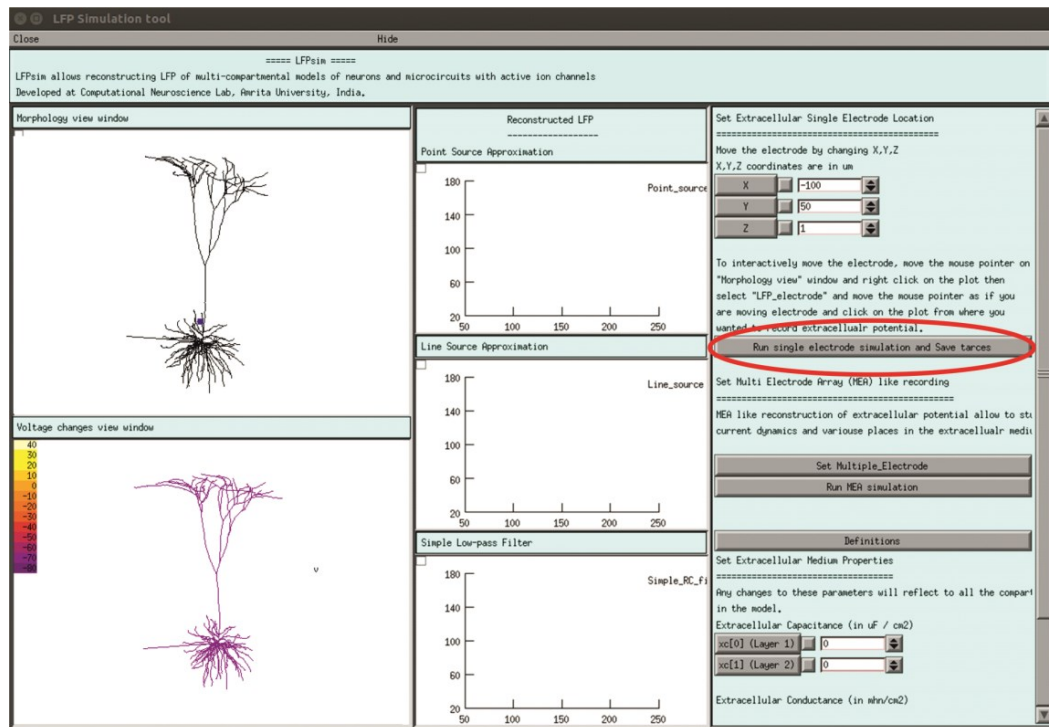


1). To interactively change the electrode position, the mouse pointer on "Morphology view" window may be moved and by right clicking on the plot, then select "LFP\_electrode". Moving electrode is performed by moving the mouse pointer and clicking on the plot at the point of interest to record the extracellular potential.

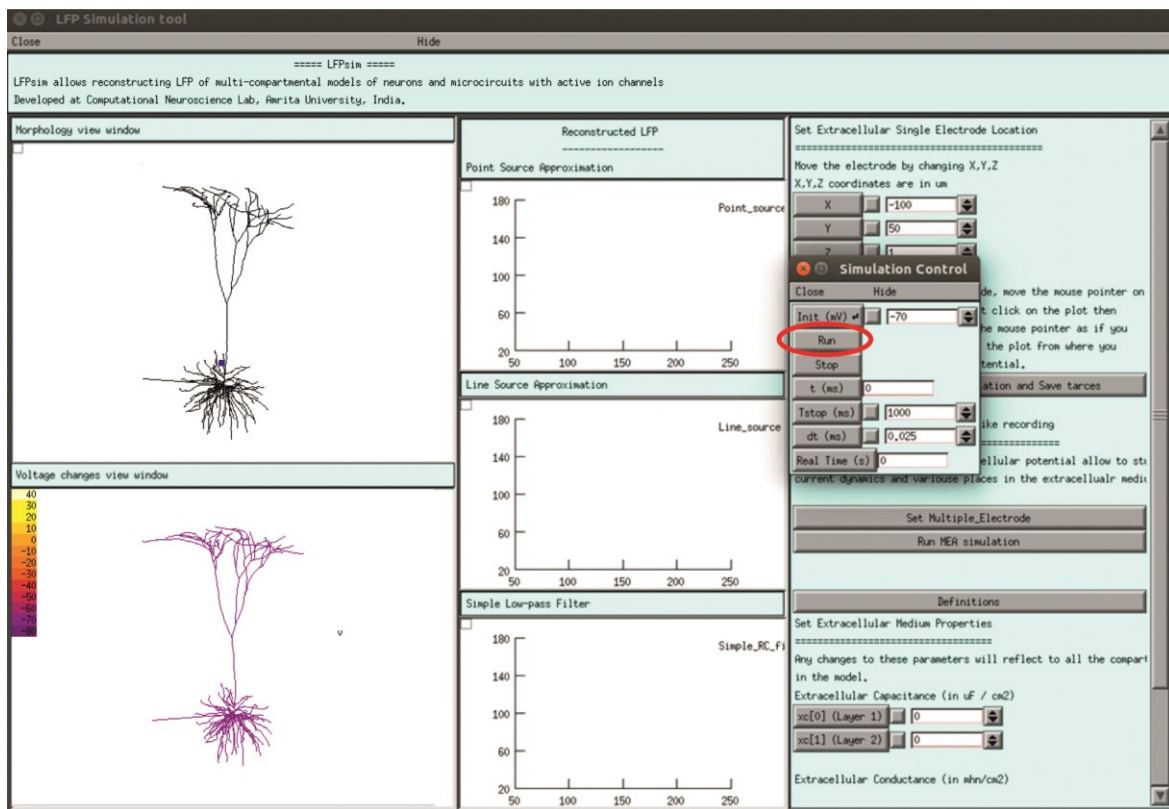


**Supplementary Figure F. Modifying LFP electrode settings.**

12. Execute single LFP electrode simulation by clicking on "Run single electrode simulation and save trace" button.

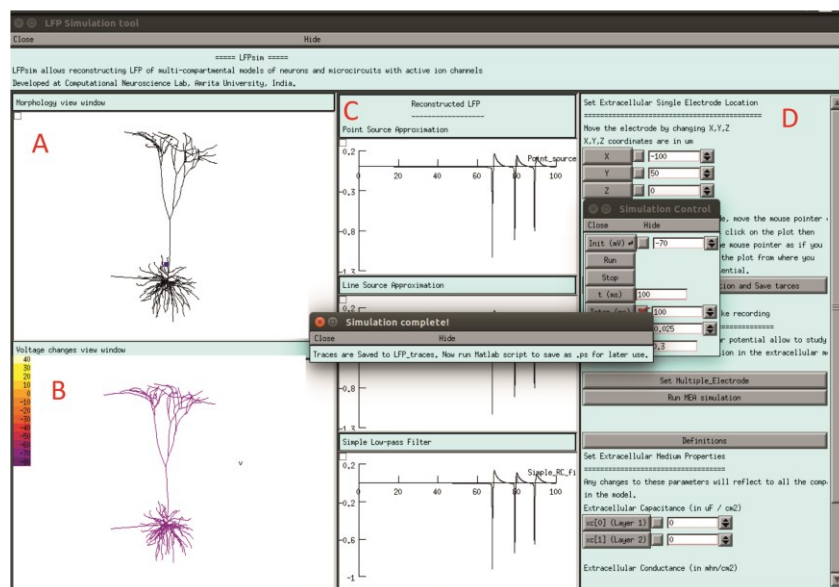


**Supplementary Figure G. Executing LFP simulation on L5 neuron model.**



**Supplementary Figure H. Running LFP simulations.**

- When run is completed, a pop up will indicate "Simulations complete" and traces will be saved to "LFP\_traces" directory within the model's directory.



**Supplementary Figure I. Simulated single neuron LFP simulations.**

14. LFP at various electrode position was calculated to study the individual compartmental contribution to the single neuron LFP.

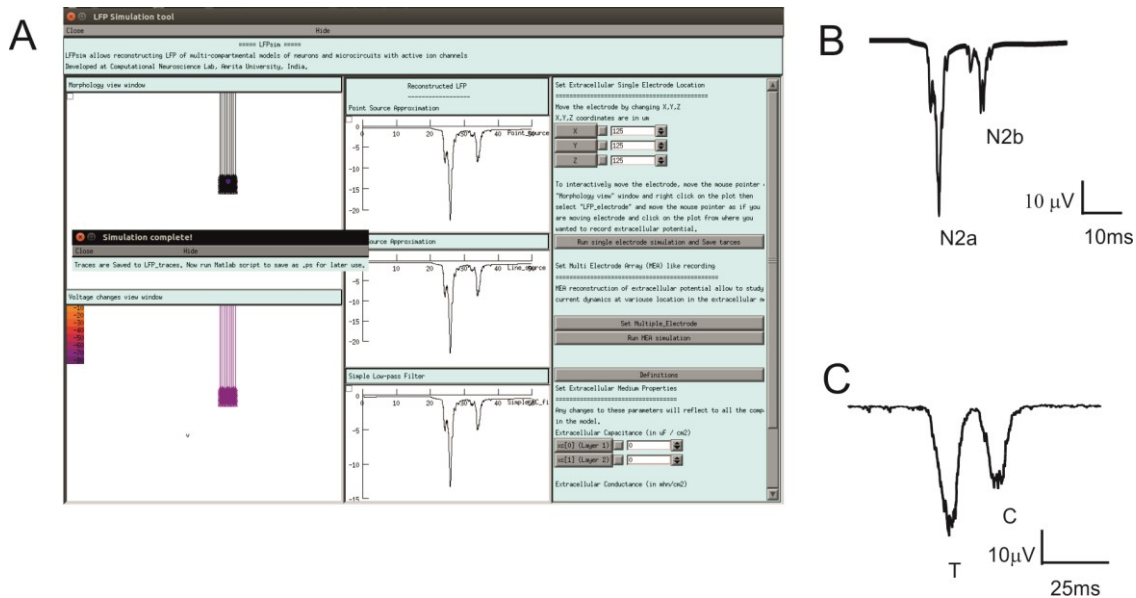
## Readme for reconstructing figure 5

1. Download the LFPsim source code and biophysical model of neuron/network from ModelDB. LFP tool can be downloaded from: <https://senselab.med.yale.edu/ModelDB/showmodel.cshtml?model=190140>. In this example, cerebellar granular layer network model (Parasuram 2011, 2015) was used to reconstruct the LFP.
2. Unzip or extract LFPsim files and model neuron/network.
3. Copy and paste all files and folder in the LFP tool folder to neuron/network model folder. Do note "lfp.mod" and "mea.mod" must be copied and placed along with model's mechanism (mod) files.
4. It is recommended to follow the model's "README" file for any specific procedures regarding compiling the model in NEURON.
5. For Linux/Unix users, opening a terminal and changing the present working directory to the neuron model folder, executing *nrnivmodl* will compile the model. If code was pre-compiled before copying "lfp.mod" and "mea.mod" files to the model directory, it is recommended to recompile after including the mod files along with other channels and receptor mod files.
6. For Windows users, double clicking on "mknrndll" and setting the path to location of the ".mod" files and clicking on "nrnmech.dll" button, compiles the mechanism files (including the mea.mod and lfp.mod files in the same directory).
7. It is recommended to follow the model's "README" file to load the neuron model in NEURON. In this example, mosinit.hoc file was used to load neuron models. On the Linux terminal, type "nrngui mosinit.hoc" to load the model in Linux. For Windows users, double clicking on mosinit.hoc file in the model directory, loads the model. Two NEURON windows popping up indicates the model was loaded.
8. After loading the model into NEURON, call "extracellular\_electrode.hoc" from NEURON's terminal by typing *xopen("extracellular\_electrode.hoc")* to load LFPsim in NEURON.



In the model, the *in vivo* LFP, T-wave was generated by a short burst along the mossy fibers and C-wave by a longer burst. Our assumptions were that two separate clusters of granule cells generated the T and C waves (Roggeri et al., 2008). In the model, Twave was generated by five spikes at 500 Hz along the MF synapses and C-wave by the nine spikes at 500 Hz via the MF synapses.

11. Users can set single electrode location both manually and interactively. To set manually, the user needs to provide values for x,y,z of electrode location.
12. Execute single LFP electrode simulation by clicking on “Run single electrode simulation and save trace” button.
13. When run is completed, a pop up will indicate “Simulations complete” and traces will be saved to “LFP\_traces” directory within the model’s directory.



## Readme for reconstructing figure 6

1. Download the LFPsim source code and biophysical model of neuron/network from ModelDB. LFP tool can be downloaded from: <https://senselab.med.yale.edu/ModelDB/showmodel.cshtml?model=190140>  
In this example, neocortical microcircuit was used, downloaded the model from Model DB (Accession number 141273).
2. Unzip or extract LFPsim files and model neuron/network.
3. Copy and paste all files and folder in the LFP tool folder to neuron/network model folder. Do note “lfp.mod” and “mea.mod” must be copied and placed along with model’s mechanism (mod) files.
4. It is recommended to follow the model’s “README” file for any specific procedures regarding compiling the model in NEURON.



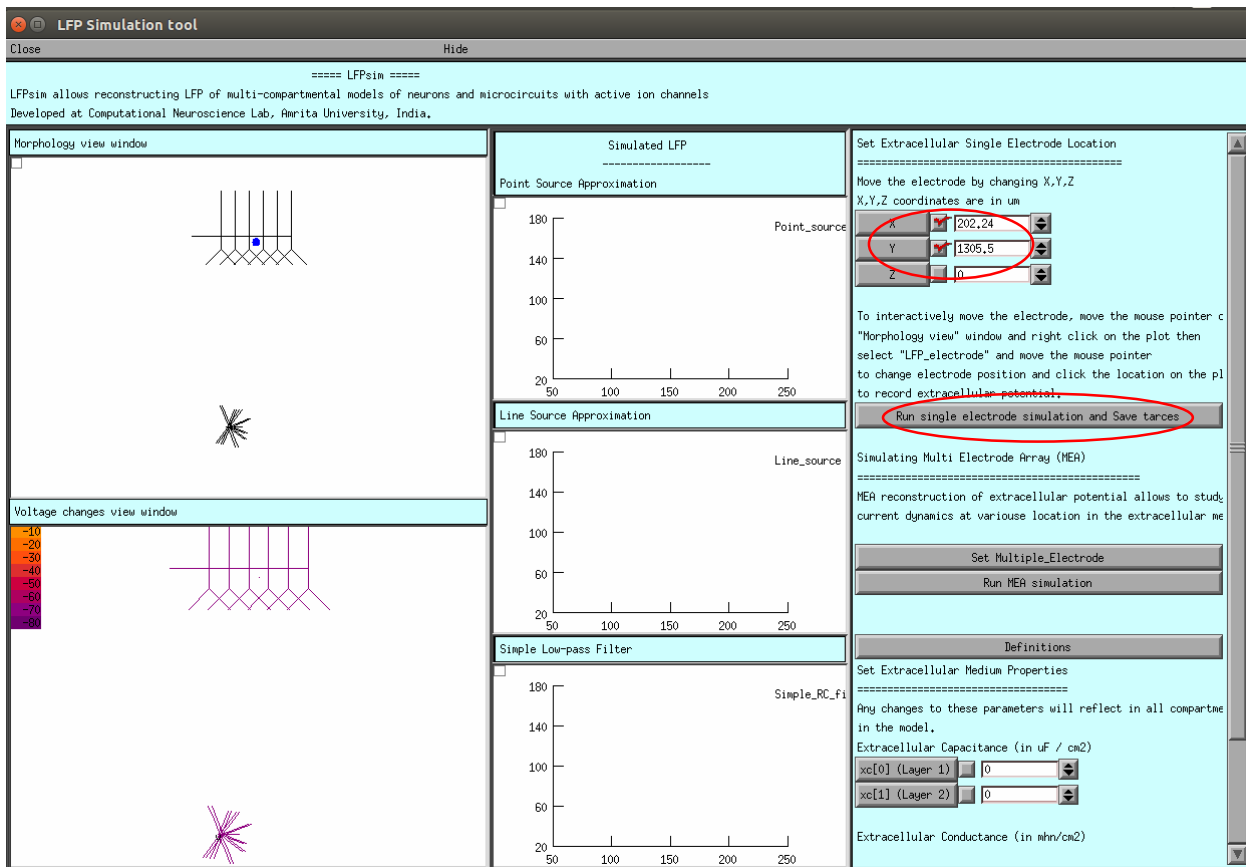
5. For Linux/Unix users, opening a terminal and changing the present working directory to the neuron model folder, executing *nrnivmodl* will compile the model. If code was pre-compiled before copying “lfp.mod” and “mea.mod” files to the model directory, it is recommended to recompile after including the mod files along with other channels and receptor mod files.
6. For Windows users, double clicking on “mknrndll” and setting the path to location of the “.mod” files and clicking on “nrnmech.dll” button, compiles the mechanism files (including the mea.mod and lfp.mod files in the same directory).
7. It is recommended to follow the model’s “README” file to load the neuron model in NEURON. In this example, mosinit.hoc file was used to load neuron models. On the Linux terminal, type “nrngui mosinit.hoc” to load the model in Linux. For Windows users, double clicking on mosinit.hoc file in the model directory, loads the model. Two NEURON windows popping up indicates the model was loaded.
8. After loading the model into NEURON, call “extracellular\_electrode.hoc” from NEURON’s terminal by typing *xopen(“extracellular\_electrode.hoc”)* to load LFPsim in NEURON.

```
cluster@lfp:~/Desktop/LFP_release/develop/test/examples/patdemo$ nrngui mosinit.hoc
NEURON -- Release 7.2 (562:42a47463b504) 2011-12-21
Duke, Yale, and the BlueBrain Project -- Copyright 1984-2008
See http://www.neuron.yale.edu/credits.html

loading membrane mechanisms from /home/cluster/Desktop/LFP_release/develop/test/
examples/patdemo/x86_64/.libs/libnrnmech.so
Additional mechanisms from files
  ca.mod cad.mod kca.mod km.mod kv.mod lfp.mod mea.mod na.mod
nrniv: unable to open font "helvetica-medium-r-normal*--14*", using "fixed"
1
0
0
0
0
0
0
0
oc> 1
0
0
0
0
0
0
0
oc>xopen("extracellular_electrode.hoc")
```

**Supplementary Figure A. Loading LFPsim with the NEURON model.**

9. This invokes the LFPsim GUI on successful execution.



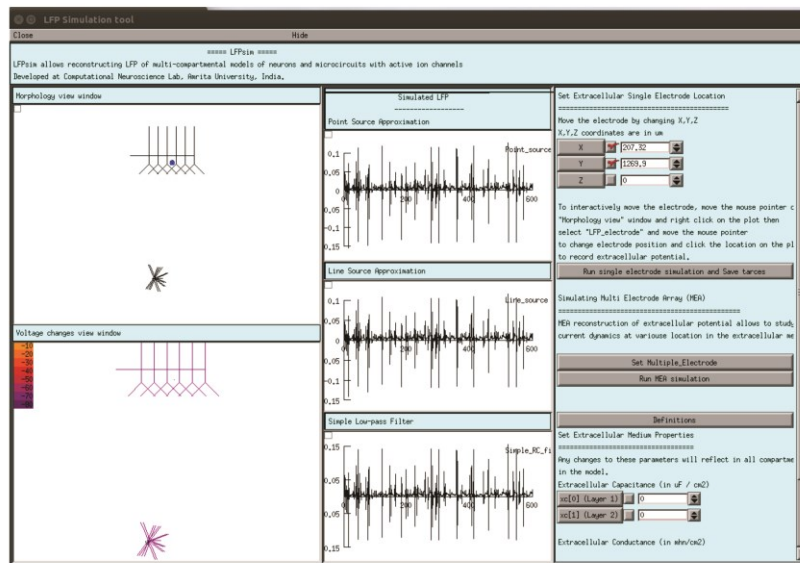
**Supplementary Figure B. LFPsim and neocortex model.**

10. Set input stimuli to neuron model as per the model README.

On the neocortical microcircuit simulations with LFPsim, gamma resonance during FS drive was reproduced (see Figure 6B) as reported in the study (Vierling-Claassen et al., 2010). Light drive input frequency in the model was varied at frequencies (8Hz, 32Hz and 56 Hz) to generate corresponding LFP wave responses.

11. Users can set single electrode location both manually and interactively. To set manually, the user needs to provide values for x,y,z of electrode location.
12. Execute single LFP electrode simulation by clicking on “Run single electrode simulation and save trace” button.
13. When run is completed, a pop up will indicate “Simulations complete” and traces will be saved to “LFP\_traces” directory within the model’s directory.

A



B

