Teaching Modules in Computational Neuroscience 7 (2015)
The German Neuroinformatics Node – www.g-node.org

Course Module

Data Analysis of Short-Term Synaptic Plasticity

Alex Loebel, PhD

Bernstein Zentrum München
Department Biologie II
Großhaderner Straße 2
D-82152, Planegg-Martinsried
Deutschland
Email: alex.loebel@gmail.com

Synopsis

Synaptic responses to a series of pre-synaptic action-potentials are complex and non-linear. Importantly, they can not be inferred from the responses to single spikes. This phenomenon, termed short-term synaptic plasticity, is observed at all stages of the nervous system, from synaptic connections at the spinal cord to neocortical connections. Some connection types exhibit short-term depression, in which the responses diminish with the stimulus series; while other types exhibit short-term facilitation, in which the responses facilitates. In this module we will learn how to model such responses; and how to extract the model's parameters from experimental data. Specifically, realistic simulations of synaptic responses from layer-5 cortical neurons will be considered. The traces will be fitted to a set of ordinary differential equations that capture the temporal evolution of the responses. Using the Jackknife statistical method we will evaluate the accuracy of our fits. We would then examine a simple case, in which short-term depression helps to differentiate between two forms of long-term synaptic plasticity.

Supplemental Material

With this course module we provide an Introductory Lecture: 'Data Analysis of Short-Term Synaptic Plasticity'. Intra-cellular measurements from cortical slice experiments is courtesy of *Gilad Silberberg*, from the *Nobel Institute for Neurophysiology, Department of Neuroscience, Karolinska Institute, Stockholm, Sweden*.

The supplemental material for this teaching module is available online at the following URL: www.g-node.org/teaching/xxx

Requirements

Practical work on this course module requires Matlab (Version 7 or higher). The supplemental data files are required for the data analysis. Knowledge of ordinary differential equations, basic algebra and calculus is beneficial.

Practical work

(1) Simulating the model for short-term synaptic depression.

Goals:

- *Presenting an example of a dynamical system that captures the temporal dynamics of a neurological process. Here, we discuss the synaptic process of short-term plasticity. Notably, such sets of Ordinary Differential Equations (ODE) are used to model, among other things, action-potentials (e.g., the Hodgkin-Huxeley model), the dynamics of neural networks, and intra-cellular chemical reactions.*
- *Present a numerical method for solving such equations, that is, the Euler method. More sophisticated solvers, such as the Runga-Kutta method, exist and should be considered when designing a numerical solution of a dynamical system.*
- *FYI: although you are asked to solve the system in hand by writing an algorithm that will implement the Euler method explicitly, Matlab offers built-in functions for solving ODEs, such as the ODE23, ODE45, etc (where each function implement a different solver).*

Consider the following model for short-term depression: when an action potential arrives to the pre-synaptic terminal, a fraction of the resources is utilized to evoke a post-synaptic response. If a subsequent action potential arrives before all the utilized resources have recovered, the following post-synaptic response will be smaller. In mathematical terms, the model is represented by the following set of equations:

$$\frac{dx}{dt} = \frac{1-x}{\tau_{rec}} - u \cdot x \cdot \delta(t - t_{sp}), \quad x(0) = 1 \tag{1a}$$

$$\frac{dy}{dt} = -\frac{y}{\tau_{in}} + u \cdot x \cdot \delta(t - t_{sp}), \quad y(0) = 0 \tag{1b}$$

where *x(t)* denotes the fraction of available synaptic resources; *u* determines the fraction of the resources utilized at each spike; and τ_{rec} is the time constant that underlie the recovery process of the utilized resources back to the available state. *y(t)* denotes the amount of utilized resources, and is proportional to the post-synaptic current. It decays with a time constant τ_{in}. $\delta(t)$ is in the Dirac notation, and the product $\Delta(t)\cdot\delta(t)$ is used here in equivalency to $x(t_{sp}^{+}) \rightarrow x(t_{sp}^{-}) + \Delta(t_{sp}^{-})$ whenever a spike occurs (t_{sp} represents the timing of a spike, and t_{sp}^{-} and t_{sp}^{+} are the times just prior and after a spike).

Completing the model is the equation for the membrane potential of the post-synaptic neuron:

$$\tau_{mem} \frac{dV}{dt} = -V + Ay, \quad V(0) = 0 \tag{2}$$

where τ_{mem} is the membrane filter constant, and *A* is the proportionality factor, which represents the absolute synaptic efficacy of the connection.

(**1i**) A simple example for how to implement the Euler method is given in the file *Solving_a_simple_dynamical_system.m*, in which the system dx/dt = bx, x(t = 0) = a, is solved numerically. In particular, *a* and *b* are free parameters, and *t* represents time. Explore the effect of choosing different values of the time step *dt* on the accuracy of your numerical solution by comparing it to the graph of the analytical solution of this system, that is, the exponential function x(t) = a•exp(b•t). What are your conclusions? What determines the size of *dt* that you should take? Is it depends on the *a* parameter, the *b* parameter, or both?

(**1ii**) Write an algorithm that simulates the above set of equations (Eqs. 1-2) for a spike train of eight spikes at 20Hz, followed by a single spike at 550ms after the last spike of the train (so all together there are nine spikes in the stimulus). Use the following parameters: τ_{mem} = 32ms, τ_{in} = 1.8ms, A = 144, u = 0.26, τ_{rec} = 1000ms.

(**1iii**) Have your algorithm produce the plots of *x(t)*, *y(t)* and *V(t)* as a function of time (use the Matlab function *plot* to produce your figures. Don't forget to edit and annotate the figures using the various relevant commands in Matlab, e.g., *Title*, *Legend*, *Ylabel*, *Xlabel*, etc.).

(**1iv**) Open the file *Data_depressing.mat*. The first variable is *Sampling_rate*, which is the rate by which the data was sampled during the experiment. Here it is 4Khz, i.e. the temporal difference between each data point is 0.25ms. It is important for converting the data set into real time values (as time appears in the equations). The second variable is the matrix *V_depressing*. Each row is a single trace (there are 30 of those). Create the average trace with the function *mean*, and observe the trace by using the function *plot*. In particular, your plot of *V(t)* from (1iii) should be similar to the mean of the experimental trace.

(**1v**) Use your algorithm to better understand the functional role of the different parameters (*u*, *A* and τ_{rec}) in shaping the synaptic responses. That is, run simulations in which the parameters have different values. What do you find? explain.

(2) Fitting the parameters of the model for short-term depression.

Goals:

- *Discuss the topic of Parameter Fitting.*
- *Present two approaches: in the first, the search for the best set of parameters is done by writing your own code.*
- *The second approach is done by using a Matlab built-in function, fminsearch.*

In this section we will fit the model above to a data measured from a synapse. The idea here is to find the set of parameters that produces a model-trace that fits best the data. In our case, it is more efficient to actually fit the amplitudes that are induced by the different spikes along the spike train (instead of fitting the whole trace point-by-point).

For that, you will need to consider the following iterative equation of *x(t)*, which represents the value of *x(t)* at the times just before the spikes arrives:

$$x_n = x_{n-1} \cdot (1-u) \cdot e^{-\frac{\Delta t}{\tau_{rec}}} + 1 - e^{-\frac{\Delta t}{\tau_{rec}}}, \quad \text{with } x_1 = 1 \tag{3}$$

where Δt is the inter-spike-interval.

You will subsequently need to combine eq. (3) with the iterative solutions of the equations for the active resources, *y(t)*, and the voltage membrane, *V(t)* (given below). This will provide with the equations for the EPSP amplitudes as measured from their initial point to the maximum value of the EPSPs (in the following, the sub-scripts represent the number of the spike along the spike train; α is a variable that is used to make the following equations more readable; *V0* is the value of the voltage at the initial point of an EPSP; and *VMax* is the value of the voltage at the maximum point of an EPSP):

$$\begin{aligned} \alpha_n &= A \cdot u \cdot x_n \\ V0_1 &= 0 \end{aligned} \tag{4}$$

For n=2:8

$$VMax_{n-1} = \alpha_{n-1} \cdot \left(\frac{\alpha_{n-1} \cdot \tau_{mem}}{\alpha_{n-1} \cdot \tau_{in} - V0_{n-1} \cdot (\tau_{in} - \tau_{mem})}\right)^{\frac{\tau_{mem}}{\tau_{in} - \tau_{mem}}} \tag{5}$$

$$V0_n = V0_{n-1} \cdot e^{-\frac{\Delta T_1}{\tau_{mem}}} + \frac{\alpha_{n-1} \cdot \tau_{in}}{(\tau_{in} - \tau_{mem})} \cdot \left(e^{-\frac{\Delta T_1}{\tau_{in}}} - e^{-\frac{\Delta T_1}{\tau_{mem}}}\right) \tag{6}$$

$$VMax_8 = \alpha_8 \cdot \left(\frac{\alpha_8 \cdot \tau_{mem}}{\alpha_8 \cdot \tau_{in} - V0_8 \cdot (\tau_{in} - \tau_{mem})}\right)^{\frac{\tau_{mem}}{\tau_{in} - \tau_{mem}}} \tag{7}$$

and for the last response (n=9):

$$V0_9 = V0_8 \cdot e^{-\frac{\Delta T_2}{\tau_{mem}}} + \frac{\alpha_8 \cdot \tau_{in}}{(\tau_{in} - \tau_{mem})} \cdot \left(e^{-\frac{\Delta T_2}{\tau_{in}}} - e^{-\frac{\Delta T_2}{\tau_{mem}}}\right) \tag{8}$$

$$VMax_9 = \alpha_9 \cdot \left(\frac{\alpha_9 \cdot \tau_{mem}}{\alpha_9 \cdot \tau_{in} - V0_9 \cdot (\tau_{in} - \tau_{mem})}\right)^{\frac{\tau_{mem}}{\tau_{in} - \tau_{mem}}} \tag{9}$$

Finally, the set of model amplitudes to compare to those measured from the experiment is:

$$Amp\_fit = VMax - V0 \tag{10}$$

(**2i**) Open the file *Data_depressing.mat* again. The variable *Sampling_rate* is the rate by which the data was sampled during the experiment. Here it is 4Khz, that is, the temporal difference between each data point is 0.25ms. It is important for converting the data set into real time values (as time appears in the equations). Plot again the average synaptic response, as you did in (1iv). Using the '.-' option in the *plot* function detect the initial points of the EPSPs. Create a vector of the amplitudes of the EPSPs, measured from their initial rising points to their peaks.

(**2ii**) Estimate the membrane time constant (τ_{mem}) and the inactivation time constant (τ_{in}) from the last (or the first) EPSP. Use the following equation:

$$V(t) = \frac{B \cdot \tau_{in}}{\tau_{in} - \tau_{mem}} \cdot (e^{-\frac{t}{\tau_{in}}} - e^{-\frac{t}{\tau_{mem}}}) \qquad (11)$$

where *t* is time, and *B* is a dummy parameter that you will need to consider in the fitting for capturing the amplitude of the EPSP (although we don't use it again after this step, hence its name). The values you should receive are: τ_{mem} ~ 32ms, τ_{in} ~ 1.8ms.

Note: for examples on how to approach the solution for this section, in case you are 'stuck', have a look at the files *Fit_Epsp_own_solution.m* and *Fit_Epsp_Matlab_function.m*. The first shows an example of how to solve (2ii) using a self-made code, while the second used the built-in Matlab function *fminsearch*.

(**2iii**) Knowing τ_{mem} and τ_{in}; that the stimulus train frequency is 20Hz (so ΔT_1 = 50ms); and that ΔT_2 = 550ms, you are now ready to fit the other parameters of the model. This is achieved by fitting Eq. (10) above to the set of amplitudes you calculated in (2i). The parameters you should receive are: *A* ~ 144, *u* ~ 0.26, τ_{rec} ~1000ms. Plot a figure that shows the best set of nine amplitudes in comparison to those from the data.

Note: to save time, the file *Iterative_equations.m* provides you with the code for Eqs. (4-9).

(3) Confidence intervals for the parameters: The Jackknife approach.

Goals:

- *Introducing the Jackknife statistical method, with which the accuracy of fitted parameters could be estimated when the acquisition of data is expensive (time or money wise), or when the repetition of a given experiment is not possible (e.g., the temporal window for collecting data in a patch-clamp experiment is limited by the washing out of the cell milieu).*
- *Note that the Jackknife method is strongly related to the Bootstrap method. The built-in function Bootstrp implement this method in Matlab (you will need to have the Statistical Toolbox component of Matlab to be able to run this function on your computer).*

We will now examine how accurate is our estimation of the parameters. We will do it by using the Jackknife approach. The idea is to fit the parameters of the model to average traces that are calculated from the data, only this time each average includes only 29 of the single traces. We will then have 30 different averages of the data set, albeit similar to one another. Then, the parameters are fitted for each of the averages, so that for each parameter you will have a vector with 30 values. You are now able to calculate the coefficient of variation (CV) of each parameter from the following Jackknife equations:

$$< Par >= \frac{1}{J} \sum_{i=1}^{J} Par_i$$

$$\mathrm{Std} = \sqrt{\frac{J-1}{J}\sum_{i=1}^{J}(\mathrm{Par}_i - <\mathrm{Par}>)^2}$$

$$\mathrm{CV} = \frac{\mathrm{Std}}{<\mathrm{Par}>} \qquad (12)$$

with *J* being the number of averages you considered (30 in our case), and *Par* is any of the estimated parameters (e.g., τ_{rec}, *u*, etc.).

(**3i**) What did you find? Can you explain your findings? How can you increase the accuracy in the parameters' estimation?

(4) A prediction (inspired by Fig.1 in Tsodyks and Markram, 1997).

Goals:

- *Discussing the issue of generalization: how good is our fitted model in predicting the responses of the model to novel stimuli? To what extent the parameters' values depend on the stimulus features? With that, the limits of the validity of the model are checked.*

(**4i**) Can the model that its parameters were fitted from a regular spike train input predict the responses of the synaptic connection to a more realistic input? Open the file *Data_irregular_pattern.mat*. It includes two variables: *V_irregular_traces* is a matrix for the voltage traces of the same synaptic connection as in (2), in response to an irregular spike train stimulus. The times of the inputs are given in the vector *Input_spike_time*. You can now use the model with the parameters you found above to simulate it for that specific input pattern, and check if the output of the model fits the data.

(**4ii**) Do you think that you could have estimated the model's parameters from the synaptic responses to the irregular spike train stimulus? If so, how could that been done?

(5) Determining a post- vs. pre-synaptic source of LTP (inspired by Fig.5 in Tsodyks and Markram, 1997).

Goals:

- *Discussing how models can assist in better understanding the biological processes that underlie observed phenomena.*

In this section we will compare two forms of long-term plasticity. One is governed by post-synaptic mechanisms, and will lead to a change in the scaling parameter of the synaptic responses. The other is governed by a pre-synaptic mechanisms, and will lead to changes in the temporal profile of the synaptic responses. Load the file *Data_LTP.mat*, and plot the average traces of the matrices *V_after_1* and *V_after_2*. Compare the mean voltage trace from (2) to the mean traces of the new voltage responses. Which parameter do you think changed in *V_after_1*? Which in *V_after_2*? Fit the parameters and show that your guesses are correct.

(6) Fitting the parameters of the model for short-term synaptic facilitation.

Goals:

- *Extending the model for short-term synaptic depression such that it captures the properties of short-term facilitation.*

In this section we will consider the responses from a synapse that exhibits short-term facilitation. This type of responses is similar to those found at synaptic connections between pyramidal cells in the pre-frontal cortex and between pyramidal and inhibitory cells at the somato-sensory cortex. As mentioned during the lecture, the model that captures short-term facilitation is quite similar to that of short-term depression. The main difference is that here, the utilization parameter changes in time, and we have one more parameter to fit, τ_{facil}. That is, the following equation describes the temporal dynamics of *u* from Eqs. (1a-b, 3 and 4):

$$\frac{du}{dt} = -\frac{u}{\tau_{facil}} + U \cdot (1-u) \cdot \delta(t - t_{sp}), \quad u(0) = 0 \qquad (1c)$$

and the subsequent iterative equation:

$$u_{n+1} = u_n \cdot (1-U) \cdot e^{-\frac{\Delta t}{\tau_{facil}}} + U, \qquad \text{with } u_1 = 0. \qquad (3a)$$

(**6i**) Open the file *Data_facilitating.mat*. The variables *Sampling_rate* and *V_facilitating* are as in (2i). Find the values of the membrane time constant and the inactivation time constant, and then find *Amp_exp* (the amplitudes of the synaptic responses). Finally, estimate the parameters of the model by fitting these amplitudes to *Amp_fit* derived from the iterative solution of the model. Here, ΔT_1 = 33.3ms and ΔT_2 = 500ms (notice the difference in value of ΔT_1 and ΔT_2 to that in (2) above). The number of stimuli during the stimulus spike train here is 12 (and not 8). The values of the parameters you should receive are: *A* ~ 60, *U* ~ 0.05, τ_{rec} ~90ms, τ_{facil} ~1100.

Reading material:

1. Tsodyks M, Markram H (1997). The neural code between neocortical pyramidal neurons depends on neurotransmitter release probability. PNAS 94(2):719-23.
2. Markram H, Wang Y, Tsodyks M (1998). Differential signaling via the same axon of neocortical pyramidal neurons. PNAS 95(9):5323-8.

Acknowledgements

We thank Gilad Silberberg for providing the data that supports this module.