ICM Report IV Joe Hakim, Chris Le, Steven Chen, Richard Liu

Introduction

Neural activity during epileptic episodes consists of synchronous activation that is modeled as a recurrent neural circuit (Segal,M.M). External stimuli deliver external currents to the circuit, and these currents can trigger or deactivate ictal activity. The objective of this paper was to propose a MATLAB script model of a two neuron recurrent circuit with external currents delivered in a physiologically relevant distribution, as well as to explore underlying mechanisms of recursive neural activity to gain insight on epilepsy. Similarly, our objectives were to study the oscillatory behavior of the two-neuron model of epilepsy, as well as to find under what forms of externally injected current ictal activity would occur, and what specific characteristics of the current, in terms of timing and other parameters, lead to the termination of the active period of synchronous firing.

Hypothesis

For the synchronous period to end, an ion current must be injected that shortens the depolarization period or extends the repolarization period in order to sufficiently synchronize the synaptic current injected into the cell and that cell's refractory period.

Methods

First, in order to characterize the synchronous neuronal activity, a simulation of a single external impulse was input to the Project 4 AvRon script (Fig. 4) and the average of the time to go from peak to peak was found.

In order to determine how the activation/cessation of synchronous neuronal activity was affected by the randomly generated external current, the delay between two pulses was varied (delay was calculated with respect to the beginning the period) and the effect on the voltages of the recurrent neuronal circuit was observed.

After determining the criteria with which the synchronous neuronal activity would begin/arrest, the model for the distribution of external current firings was found to follow a Poisson distribution. This was also reinforced by literature, which stated that the stimulation pattern resulted in a physiologically accurate, Poisson-distributed recurrent neuronal activation (Wyckhuys, 2010). While testing the randomly distributed impulses, the probability of firing was increased from 0.05 to 0.1 so that the Poisson distribution would have an expected value of 10 rather than 20. This was thought to have more accurately depicted the Poisson distribution characteristics. Other researchers have also used a Poisson distribution to model external current, and so emphasizing these characteristics would theoretically lead to a more accurate model for replicating spontaneous neuronal activity.

Results/Discussion

The average period of the synchronized action potentials was found to be 4.8 ms. Thus, the delay time of the second 1 ms external current injection was varied from 0.1 to 5 ms and an effect on the voltage was observed within a 30 ms window. The synchronous activity stopped when the second current was injected 2.4 - 4.1 ms and 4.2 - 4.7 ms after the start of the period. These intervals aligned with the expectations and it was hypothesized that they were the repolarization and depolarization intervals, respectively (Fig. 6).

We found that because the model does not incorporate any sort of memory (i.e. calcium accumulation in an actual neuron), the effect of the external pulse could be predicted based on its time within the period of a single action potential. We can break this down into three cases based on its effect on the period (shortening and stopping activity, extending and stopping activity, or not enough of an effect to stop activity). The stopping behaviors of extreme shortening and extreme lengthening are demonstrated in figures 3 and 4. Nonstopping behaviour is essentially a more moderate form of either extreme in terms of the effect on the period. However, the magnitude of the change is not extreme enough that one neuron's synaptic current would occur during the refractory period of the others. Given that our selection of the times is randomly distributed with respect to a period, increasing the intervals between external pulses should increase the duration of synchronous neuronal activity as well as the duration of quiescent periods.

Our model supports our hypothesis and demonstrates that, within this two neuron system, the first external stimuli delivered generates an action potential in the first neuron which then propagates to the second neuron to generate an action potential in that cell. These neurons pass the synaptic currents back and forth to each other indefinitely if no other stimulus is delivered (Fig. 4). The action potentials fire consistently with a roughly constant period that converges.

When external current pulses are delivered, they affect the action potential's period depending on the point within the period that the pulse is delivered. If Iext is delivered during depolarization, the depolarization speeds up and the period (the amount of time from peak to peak of action potential) is shortened, which can cause the synaptic current of the first neuron to be delivered prematurely during the second neuron's refractory period, ending the synchronous

activity (Fig. 3). This results in the second neuron failing to reach threshold potential and halting the recurrent firing.

Additionally, for external current delivered during repolarization, the period is lengthened and the refractory period will occur at a later time, such that the second neuron's synaptic current occurs during the first neuron's refractory period. This potential would normally activate the first neuron after its refractory period, but instead does not stimulate the first neuron to reach activation threshold (Fig. 4). This results in the first neuron failing to reach threshold potential and halting the recurrent firing.

When the period of a neuron is adjusted such that it either tries to activate its partner during its partner's refractory period OR its refractory period aligns with its partners synaptic current, then an action potential threshold isn't reached and synchronous activity stops. This silent behavior continues until another external stimuli is delivered and starts the process again.

Conclusion:

Stopping recurrent neural activity is based on offsetting some neurons' action potential in some way such that synaptic currents are delivered during the refractory period. As such for a random distribution of firings we can find a probability of a constant external stimuli halting the signal as ((interval of stopping during depolarization) + (interval of stopping during repolarization))/(period of a neuron's firing). We found that this could be approximated to 0.35 from testing cases throughout a period and looking at its effects on the next action potential of itself and the other neuron. Having a stopping probability of 0.35 when stimulated during recurrent neural activity and a starting probability of 1 when stimulated during quiescent periods

supports the notion that the durations should follow Poisson-based distribution that is dependent on the probability of firing and the probability of stopping. We confirmed that these intervals followed a Poisson like distribution by running a simulation for extended periods of time and recording intervals from this period.

We believe that the active periods are terminated when an impulse is delivered that shifts the action potential of one neuron such that the firing of the other neuron stimulates the first neuron during its refractory period. This can be seen in figures 2 and 3, where the specific timing of injection that leads to termination is identified. Qualitatively, we can see that when impulses are delivered in a period where they make the second action potential "earlier", the active period is maintained, but after a threshold, the injected current would delay the first action potential until its activation coincides with a refractory period of the second neuron, thus preventing the first from continuing the synchronous period.

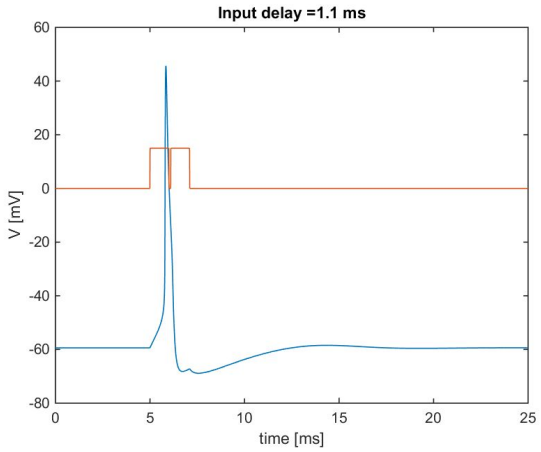
The termination is related to all of the synaptic and ionic currents, as well as the refractory period of the neurons. For the synchronous period to end, an ion current must be injected to shorten the depolarization period or extend the repolarization period in order to sufficiently synchronize the synaptic current being injected into a cell and that cell's refractory period.

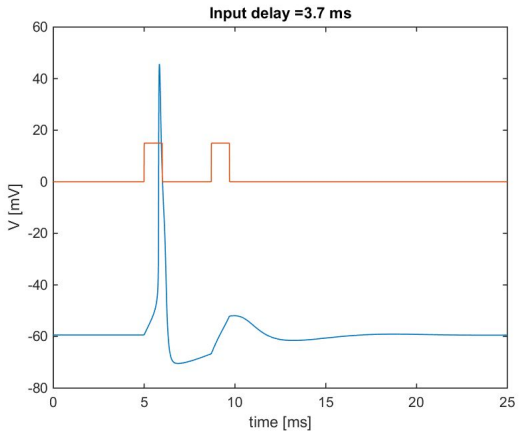
Contributions to report: Joe Hakim and Steven Chen helped simulate and collect data to support our hypothesis. Chris Le and Richard Liu analyzed and interpreted data. All group members contributed to the report.

Citations

Segal MM (1991) Epileptiform activity in microcultures containing one excitatory hippocampal neuron. *J Neurophysiol* 65:761–770.

Wyckhuys, T., Boon, P., Raedt, R., Van Nieuwenhuyse, B., Vonck, K. and Wadman, W. (2010), Suppression of hippocampal epileptic seizures in the kainate rat by Poisson distributed stimulation. Epilepsia, 51: 2297–2304. doi: 10.1111/j.1528-1167.2010.02750.x





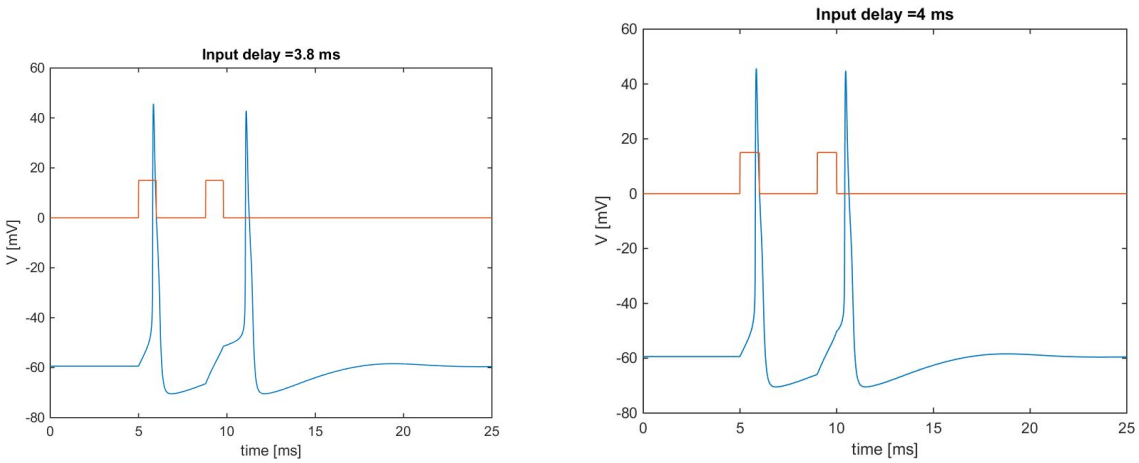


Figure 1. Finding the Refractory period of a Single Cell. A trial-and-error method was used to determine that the input delay necessary for an impulse to exceed the refractory period of a single neuron was approximately 3.8 ms. This was identified by trying shorter delays and observing that the refractory state prevented a second action potential. Note that other refractory periods are observed for different lengths of applied current, however in the two-cell portion of our experiment we kept the length of the impulse (1 ms) consistent so as to remain quantitatively consistent.

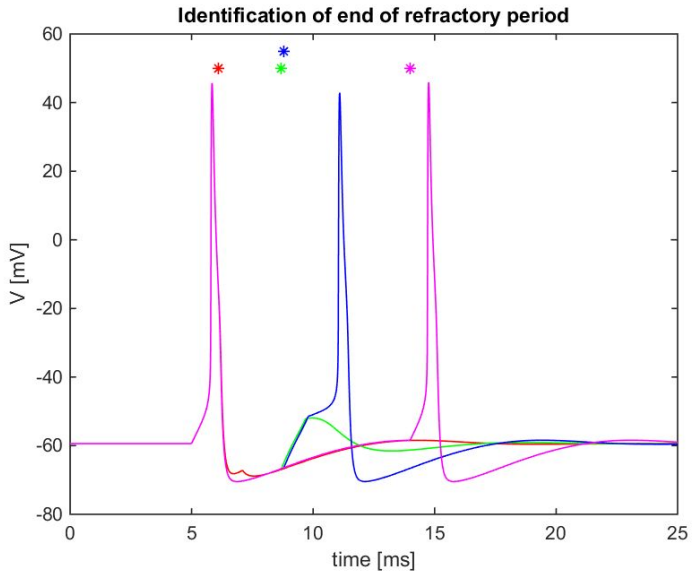


Figure 2: Superimposed plots demonstrating the threshold behaviour of the refractory period. Same data as previous figure. Red line: second impulse at t=1.1 ms. Green line: t=3.7 ms. Blue line: t=3.8 ms. Magenta: t=9 ms. We observe here that only the blue and magenta lines exhibit second action potentials, since the impulse occurred after the refractory period.

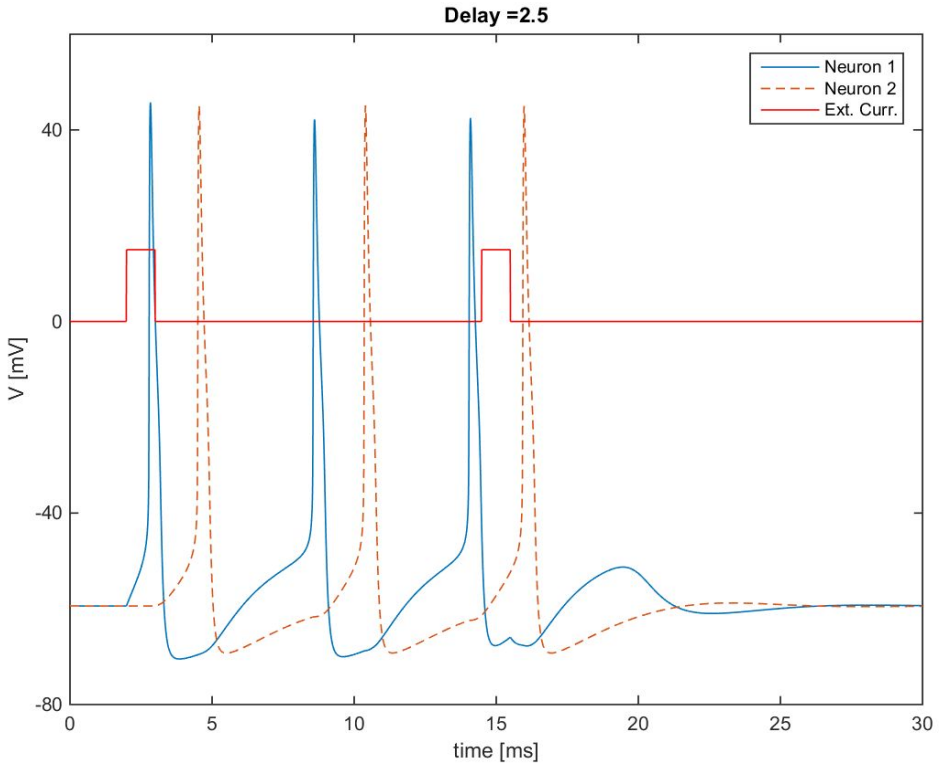


Figure 3: Voltage of a two neuron recurrent network with the second external current generated 2.5 ms after the start of the period.

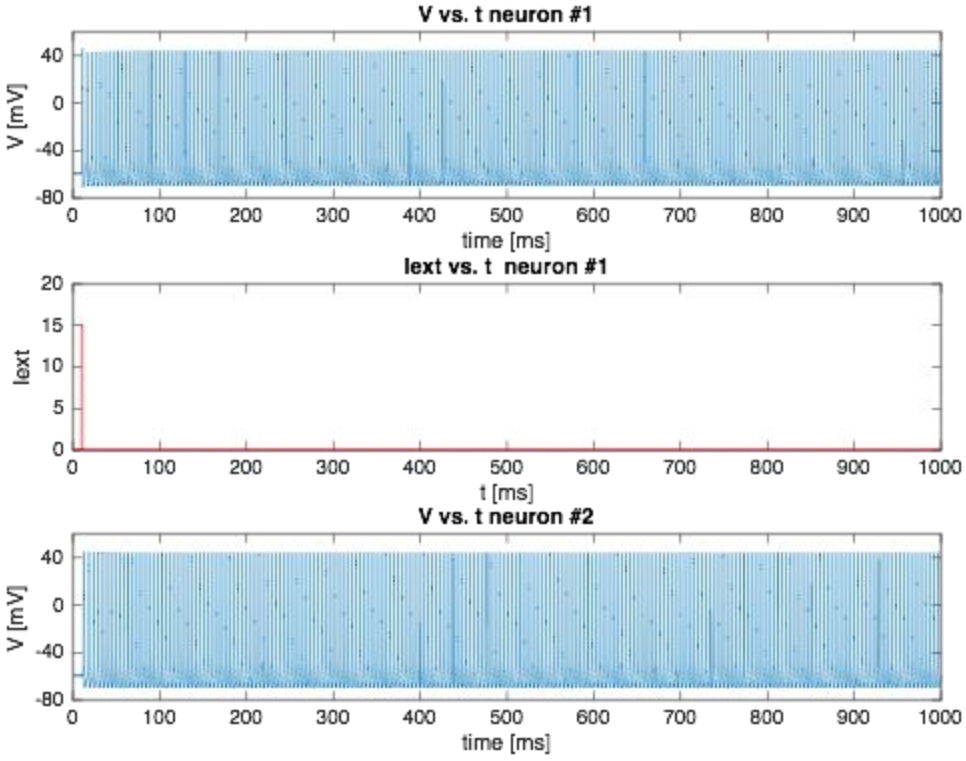


Figure 4:Demonstration of a single pulse on the two neuron model. This is a supplement demonstrating that oscillations due to the positive feedback loop are completely stable in time, reach a single steady state, and the oscillatory behavior is persistent if there is no external impulse. Thus the only way that the system can exit active periods is by applying an external stimulus.

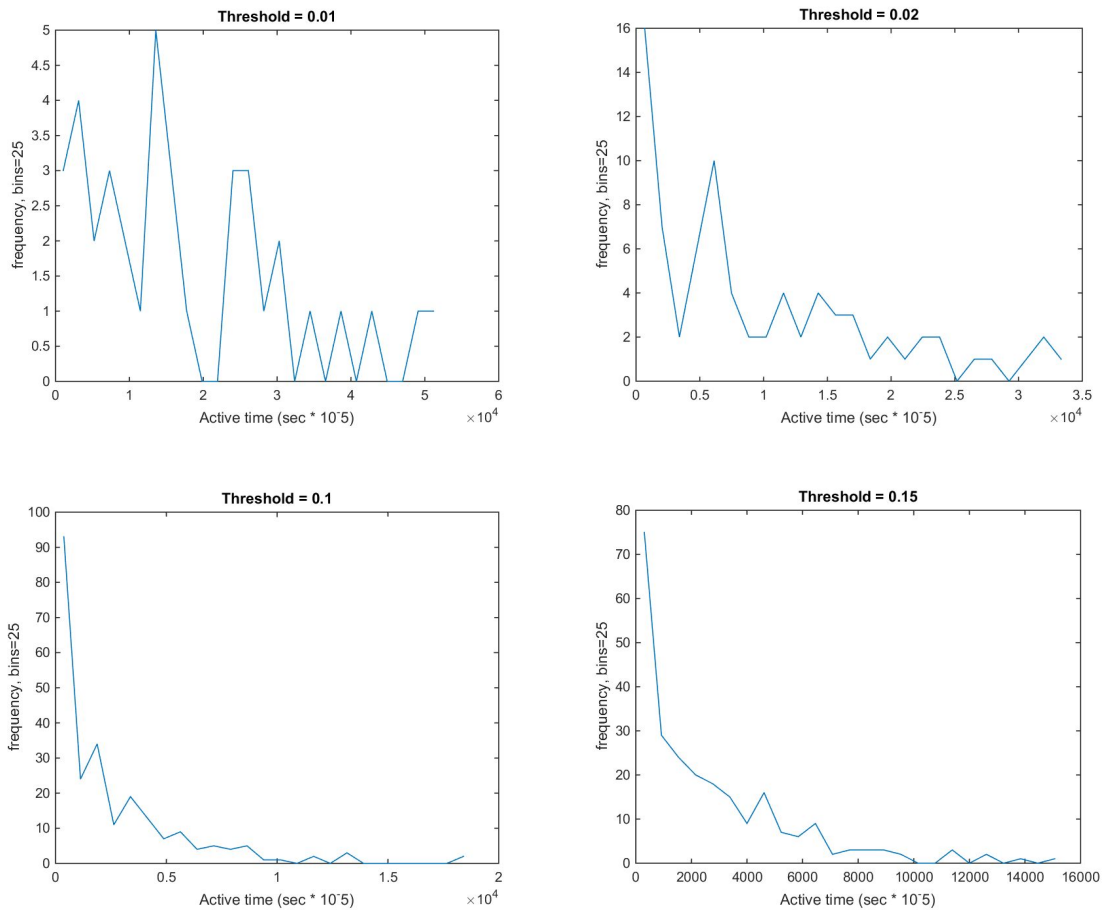
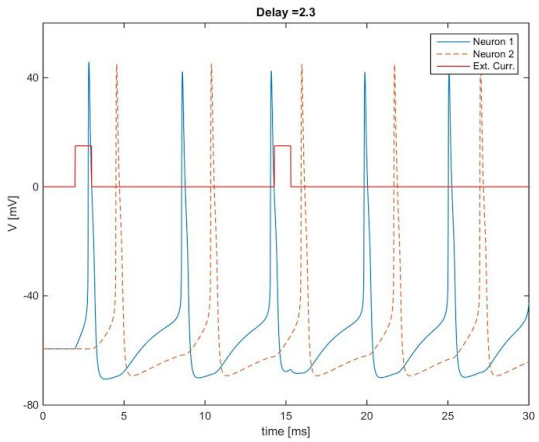
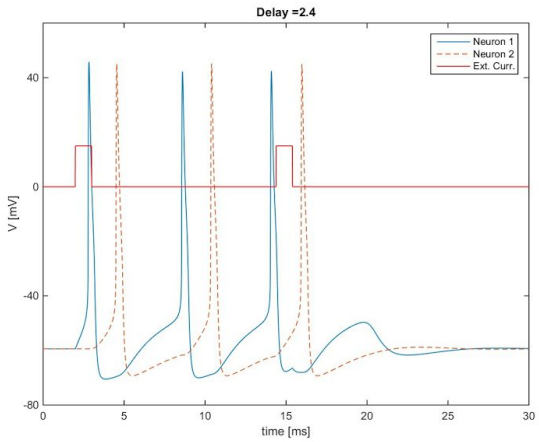
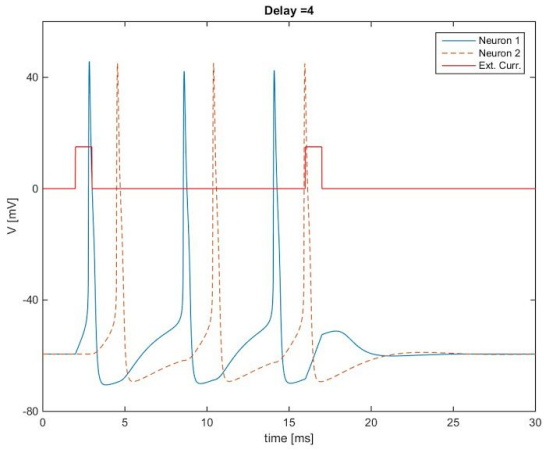


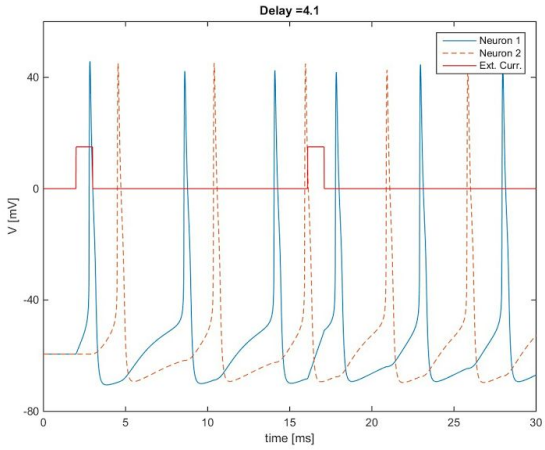
Figure 5. Distributions of times in active state, as functions of the probability of applying external current. For each of these, we can approximately state that the distribution follows a poisson-like profile, although perhaps an exponential or simpler fit would work as well. The reasoning is that these times are generated by having a pulse occur at random intervals, essentially comprising a bernoulli random variable, which sampled at various times yields an idealized poisson distribution. In addition, as shown with the timed injected currents, approximately a range of 2.5 to 4.5 msec in a total period of approximately 5 msec stops the active phase, therefore about 40% of injected currents cause arrestation. Since a fixed ratio of a bernoulli-trial current yields in arrestation, the times until arrestation, ideally, are poisson. Here,

if a uniformly sampled random variable is under the threshold in each case, with time discretized into hundredths of milliseconds, a current is injected.









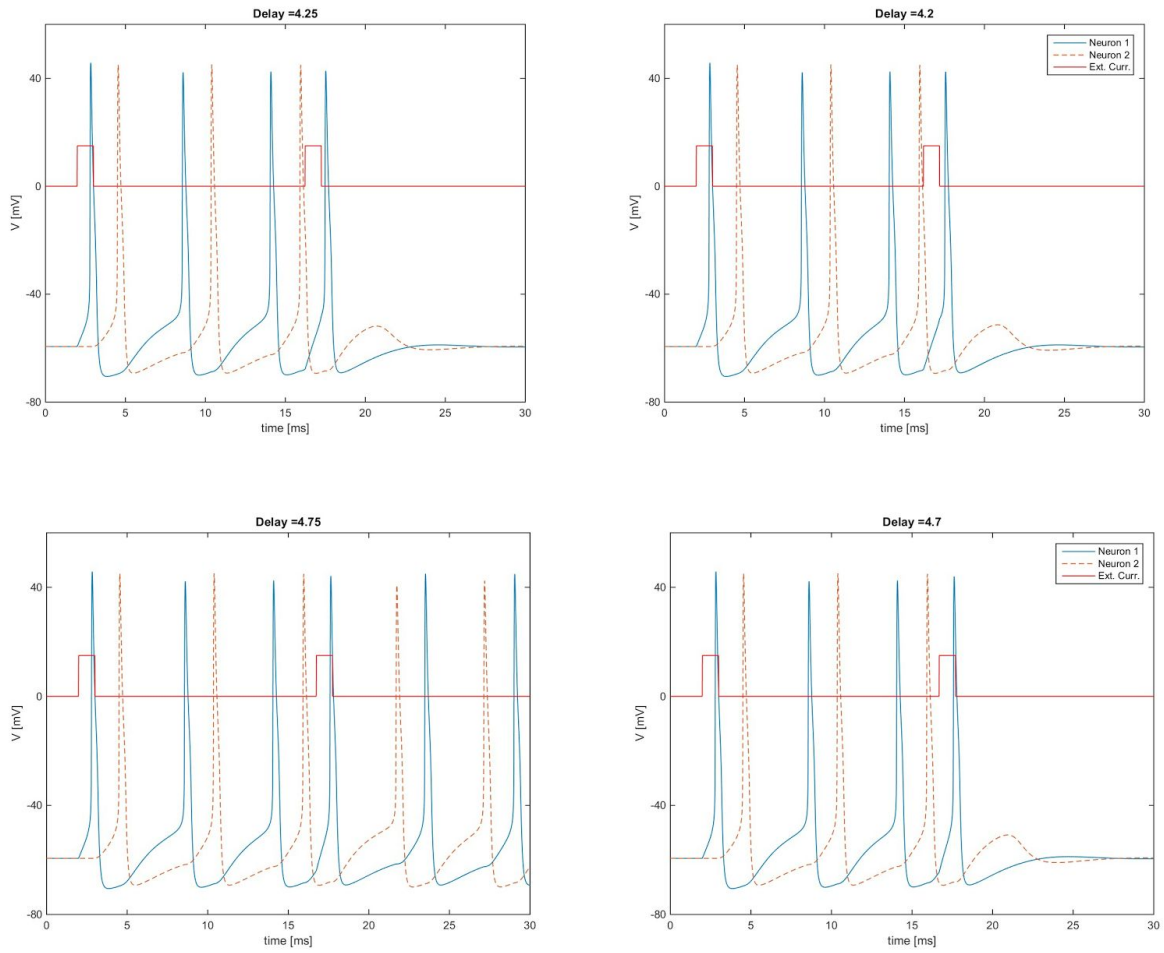


Fig. 6 Voltage of a two neuron recurrent network with the second 1ms external current generated after the start of the period with varying times. Here we demonstrate the exact timing window necessary in order to align the injected current with the period after refractory for the first neuron, so it can overlap and cause the first neuron's action potential to be delayed into the refractory period of the second. Note for long enough delays, the cessation caused by the injected current no longer occurs.