Behavior of a Model Network with Simulated Light Activated Channels.

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Abstract

I implement a Hodkin-Huxley neuron that can be stimulated with a voltage clamp of a timecourse of a neuron stimulated by Channelrodopsin-2. I test this on a model network of four neurons that includes a recurrent loop and inhibitory feedback to explore how the dynamics vary with stimulation type.

1 Background

Neural stimulation via light activated channels has been increasingly used to probe the connections in neural circuits. Behavioral experiments suggest that changing the channel types changes the behavior depending on the details of the stimulation kinetics. [3] For this project , I investigated the sensitivity of a network of neurons to the details of the channel kinetics. Specifically, I asked how in a model analogous to an experiment using optogenetic stimulation the dynamics will differ compared with stimulating with a current injection to a set of the cells.

The optically activated channel that is currently most typically used in experiments is Channelrhodopsin-2 (ChR2). It has been used in several types of cells, and has a well reproducible and precisely timed response to light activation. The photocycle of the channels has been well characterized by Nikolic et. al. [1] and a model has been proposed based on known properties about the kinetics.

ChR2 is a cation channel that is strongly permeable to protons as well as sodium, potassium and somewhat to calcium. For each of these cations, the reversal potential is around 0mV and it is not permeable to anions. The ratios of permeability to the three key ions is: Na:K:H = 1:0.5:10^6. The response of the channel to stimulation suggests that there are two open states – initially the current passed is high, but then falls to a plateau at longer stimulation times. Additionally, the channel does not get excited to the higher state if it is stimulated soon after decay from an activated state. Based on these properties of the kinetics a four state model has been proposed, that includes two open and two closed states. The channel can go from the "dark" closed state to the higher conductance open state but only to the lower conductance from the "light" closed state. This accounts for the two conductance states of the channels. A simpler model that accurately accounts for the main properties is a three state model that has just two open states and one closed state.

Nikolic et. al. [1] provide an experimental charachterization of the kinetics of the channel in response to a light pulse. The initial time constant for activation is 1.2 ms, then the decay to the lower conductance open state occurs at a time constant of 3.8ms, and the decay to a closed state occurs at a time constant of 13.5 ms.

2 Methods

A model of four Hodgkin-Huxley neurons was implemented in MATLAB.
The simulated network contains an excitatory loop (recurrent excitation) and an inhibitory input. The connections are based on a central pattern generator studied in the tritonia swim network. [4] The biological network contains four types of cells (DRI, DSI, C2, VSI) and is connected as follows:

1.Sensory input activates DRI.

2.DRI excites DSI

3.DSI excites C2

4.C2 feeds back and excites DRI, further exciting DSI via a positive feedback loop.

5.C2 excites VSI, which inhibits DSI and C2.

The connectivity Matrices are thus:

Inhibition	*DRI*	*DSI*	*C2*	*VSI*
DRI	0	0	0	0
DSI	0	0	0	0
C21	0	0	0	0
VSI	0	i_{42}	i_{43}	0

Excitation	*DRI*	*DSI*	*C2*	*VSI*
DRI	0	e_{12}	0	0
DSI	0	0	e_{23}	0
C21	e_{31}	0	0	e_{34}
VSI	0	0	0	0

I model a simplified version of the network, with four identical neurons and varying connectivity weights, values shown below. First, I simulate the effects of this stimulation in two neurons coupled via excitatory connection. I plot the membrane voltage as a function of time for an injected current stimulation protocol (Figure 1) and at baseline (Figure 2).

Inhibition	*DRI*	*DSI*	*C2*	*VSI*
DRI	0	0	0	0
DSI	0	0	0	0
C21	0	0	0	0
VSI	0	3.0	1.8	0

Excitation	*DRI*	*DSI*	*C2*	*VSI*
DRI	0	0.8	0	0
DSI	0	0	0.8	0
C21	1.0	0	0	1.0
VSI	0	0	0	0

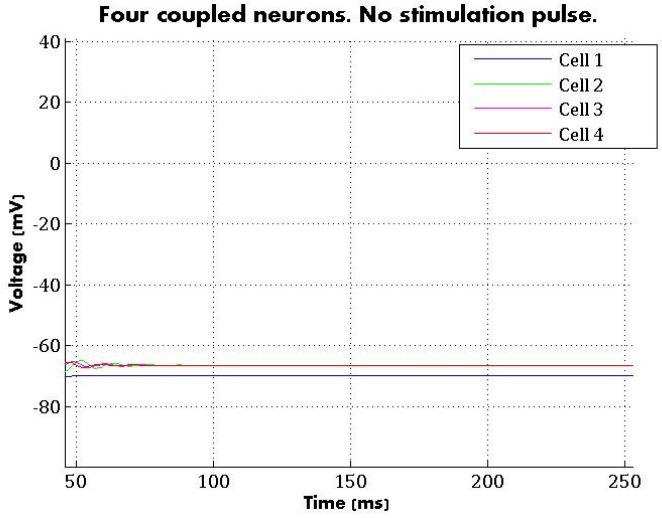

Figure 1: Four coupled neurons simulated with no stimulation

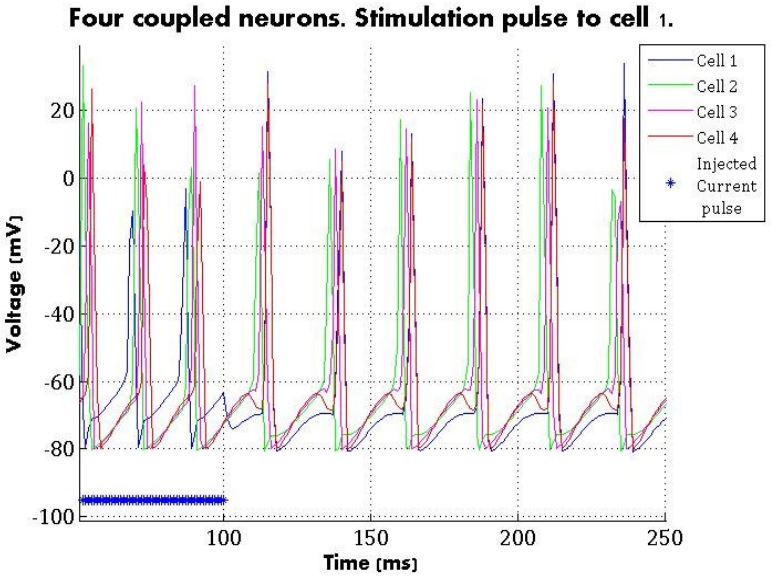

Figure 2: Four coupled neurons with the same parameters at in figure one when an injected current stimulation is applied to cell 1.

A simulated voltage clamp was used to implement the dynamics of a ChR2 channel. Specifically, the neurons are implemented as a set of differential equations solved by a numerical solver. I construct a model time course of the cell membrane voltage based on data about the kinetics of channel opening and closing. I incorporated these values into the differential equations by adjusting the rate of change of the membrane voltage potential at the target points so that the next point approaches the target value for the membrane voltage. Thus, the membrane behaves normally when it is unstimulated.
The equation used for membrane current is:

$$Cm\frac{dV_{neuronn}}{dt}=(-I_K-I_{Na}-I_{leak}-I_{syn}^{(i)}-I_{syn}^{(e)})*\begin{pmatrix}1, light\ stimulus\ off\\ 0, light\ stimulus\ on\end{pmatrix}+(V_{ChR2}(t)-V(t))*dt \quad (1)$$

Where the ionic currents have Hodgkin Huxley dynamics, and the excitatory and inhibitory synaptic currents $I_{syn}^{(e)}, I_{syn}^{(i)}$ are implemented via modelling glutamatergic and GABAergic channels, respectively.
The equations for these are:

$$I_{syn}^{(e)}=g_{glutamate}*r_{post}^{(e)}*(V_{pre}-E_{glutamate}) \quad (2)$$

$$I_{syn}^{(i)}=g_{GABA}*r_{post}^{(i)}*(V_{pre}-E_{GABA}) \quad (3)$$

Where $r_{post}^{(e,i)}$ are gating variables that evolve according to the voltage in the post-synaptic cell.
The ChR2 current is a current clamp according to the following dynamics:

$$I_{ChR2}=-70+A*(1-e^{-t_r/1.205}-\frac{0.8}{(1+e^{-(t_r-t_{del})/3.8})}-\frac{0.2}{1+e^{-(t_r-t_{del}-t_{on})/13.5}}) \quad (4)$$

Where tr is the time since the start of the last stimulation pulse, t_{del} is a time constant and

A is the amplitude of the pulse. The time constants (denominators in the exponentials) are in milliseconds and are taken from the characterization done by [ref].

I show two examples of a simulated pulse in a network of two neurons coupled with an excitatory connection. The stimulated neuron spikes normally until the light pulse is applied. At the time of the stimulation, the gating kinetics vary with but do not affect the membrane voltage.

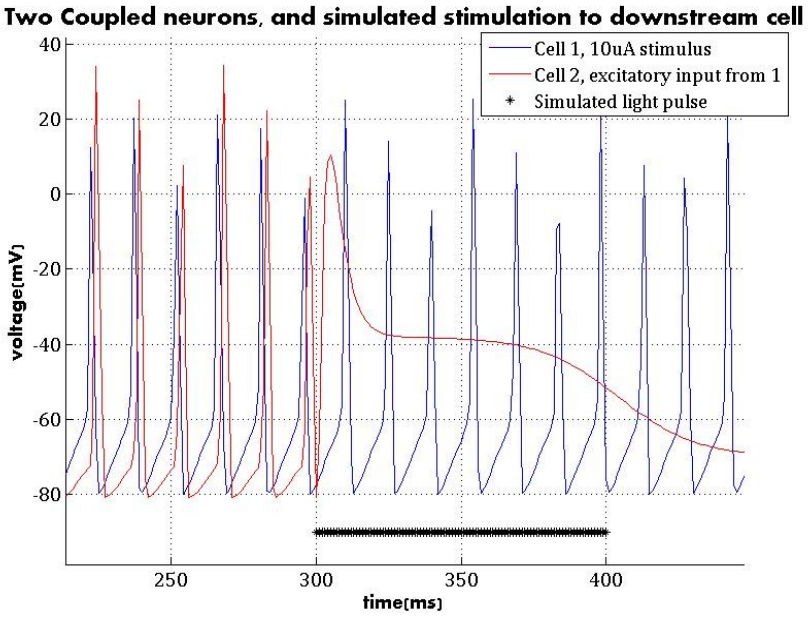

Figure 3: Simulation of two coupled neurons with electrical and light stimulation

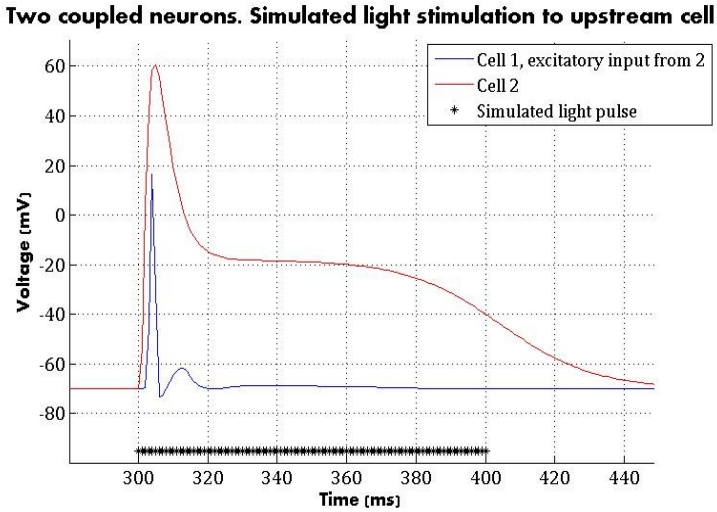

Figure 4: Simulation of two coupled neurons with light stimulation

Finally, I apply the same duration of light stimulation as shown in Figure (4), but pulsed (Figure 5). In this condition, the downstream neuron spikes more than with the constant stimulation protocol.

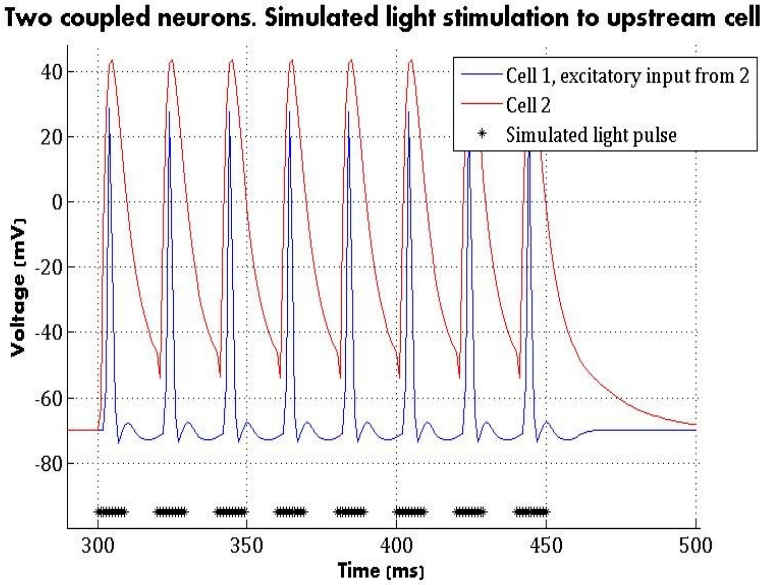

Figure 5: Simulation of two coupled neurons with pulsed light stimulation

These manipulations demonstrate that the spiking of the second cell will be affected by type of stimulation in the first.

3 Results

I simulate the dynamics of the network with stimulation to two cells at once – which mimics the result of a current injection extracellular. While the dynamics of the network change it is difficult to determine which cells have been stimulated.

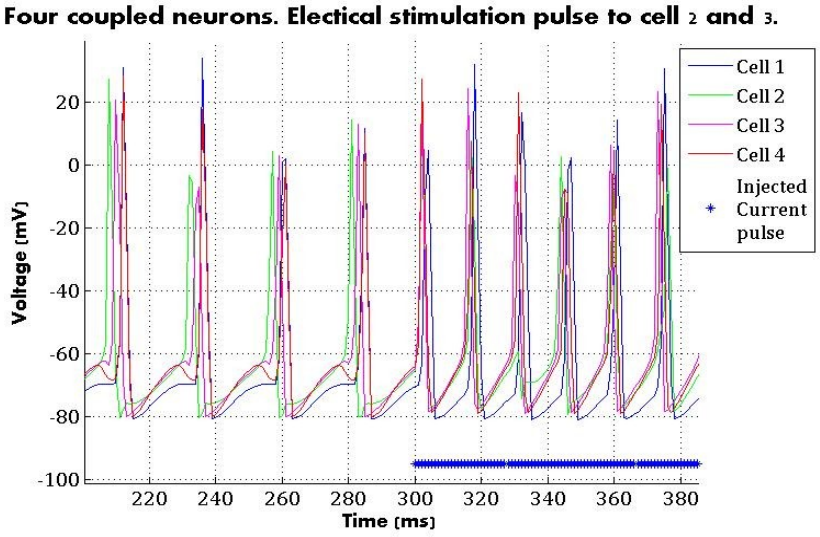

Figure 6: Simulated electrical stimulation of a set of coupled neurons

Next, I replace this with stimulation of cell 2 with a light pulse:

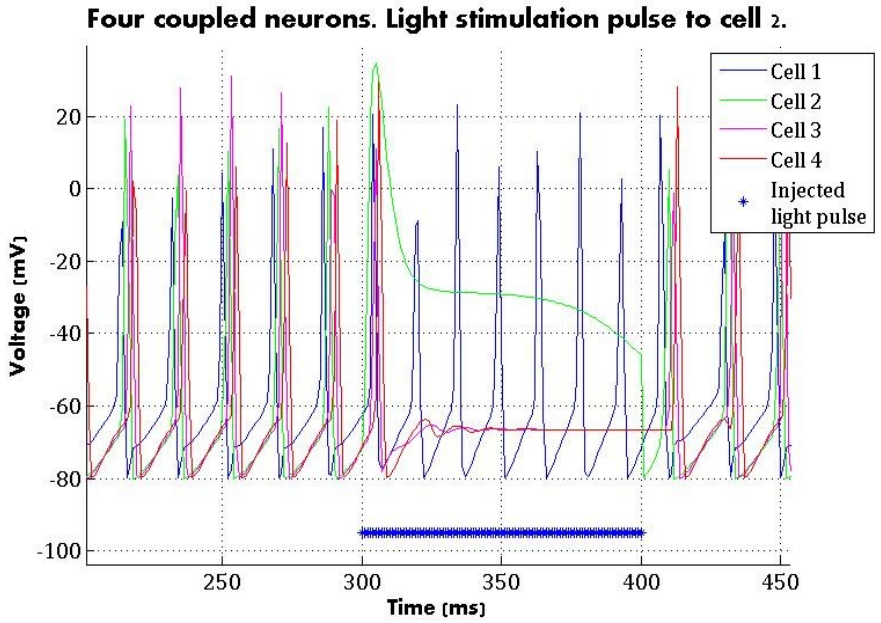

Figure 7: Light stimulation of a cell in a network of four neurons

Next, I show a plot of pulsed stimulation to cell 2. In this case, the stimulation stops the rhythmic spiking that happened before the pulses.

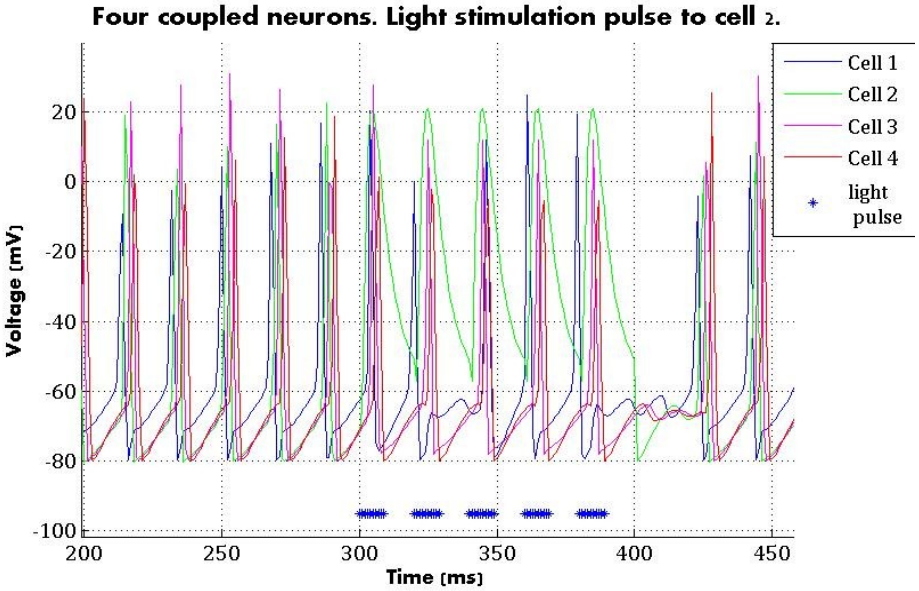

Figure 8: Pulsed light stimulation of a cell in a model network of four neurons

Finally, in figure 9 I overlay the voltage traces of a downstream cell with each different stimulation protocol to cell 2. This demonstrates that the response of a network will differ in accordance to dynamics of stimulation type.

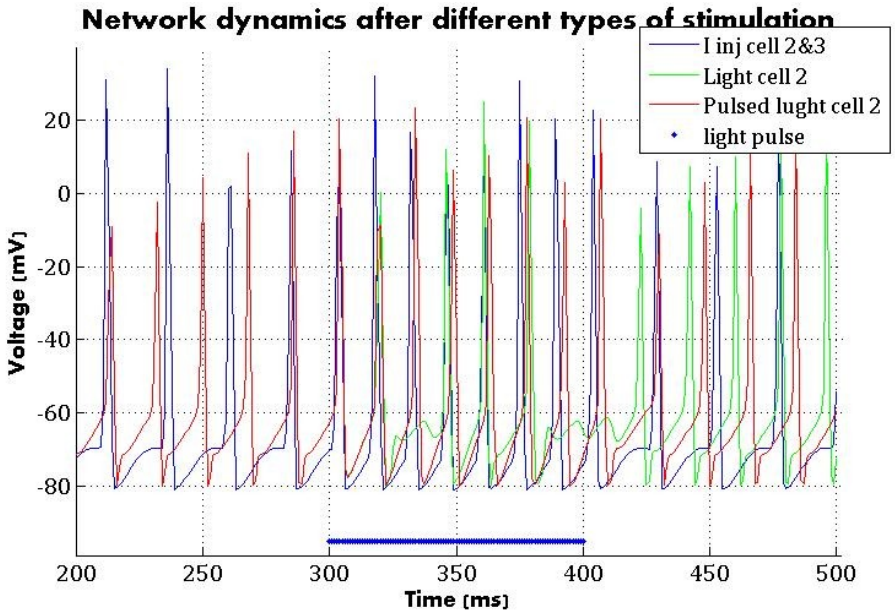

Figure 9: Responses of cell 1 before and after different types of stimulation to cell 2

4 Summary

I have implemented a model of ChR2 voltage dynamics in a network of HH neurons, to simulate the response of a sample network to a stimulation pulse. I show that the responses in the network depend on the kinetics of stimulation.

References

[1] K Nikolic, N Grossman, MS Grubb Juan Burrone2, Chris Toumazou, Patrick Degenaar Photocycles of Channelrhodopsin-2 Photochemistry and Photobiology Volume 85, Issue 1, pages 400–411, 2009

[2] Konstantin Nikolic, Patrick Degenaar and Chris Toumazou Modeling and Engineering aspects of Channelrhodopsin2 System for Neural Photostimulation Engineering in Medicine and Biology Society, 2006. EMBS

[3] Pulver S R et al. J Neurophysiol 2009;101:3075-3088

[4] Getting PA Mechanisms of pattern generation underlying swimming in Tritonia. II. Network reconstruction. Journal of Neurophysiology 1983, 49(4):1017-35