Dynamic Model of Glial Signaling

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Abstract

Over the last decade, the presumed role of glial cells in the nervous system has diversified. Glial cells have long been known to provide support, nutrition, and form the myelin sheath that protects nerve cells. More recently, it has been found that glia experience calcium transients and can send signals between themselves and other glia as well as neural cells. The model presented here attempts to replicate some of the experimental dynamics observed for in vitro glial-glial signaling using a model consisting of a diffusive signal along with a stochastic element to represent thermal fluctuations in the diffused signal. The model was then simulated and compared against the experimental data. The results of modeling the experimental data for an astrocyte culture indicate that, as opposed to active signal propagation between cells, the glial signal originates at the point of stimulation, and then decays over time as it diffuses over space.

1. Experimental data

Experimental data was taken in video form. A confocal microscope was used to image a cell culture of astrocytes. Cells were labeled with fluo-4, which fluoresces in the presence of calcium. Thus, when a calcium transient is in effect at the site of the cell, it can be seen by the increase in fluorescence at the cell site. Cells in culture were stimulated mechanically by a micropipette at a site near the center of the image, and a movie was recorded. An image taken from the recorded movie is shown in figure 1 below[1].

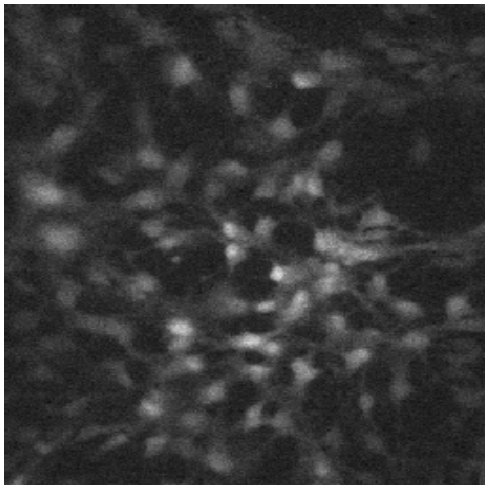

Figure 1: Microscope image of astrocyte signaling - The brighter the cell, the stronger the calcium transient

From here, one can process the images and locate the center of each cell in each frame[2] as well as the intensity of the calcium transient versus time.

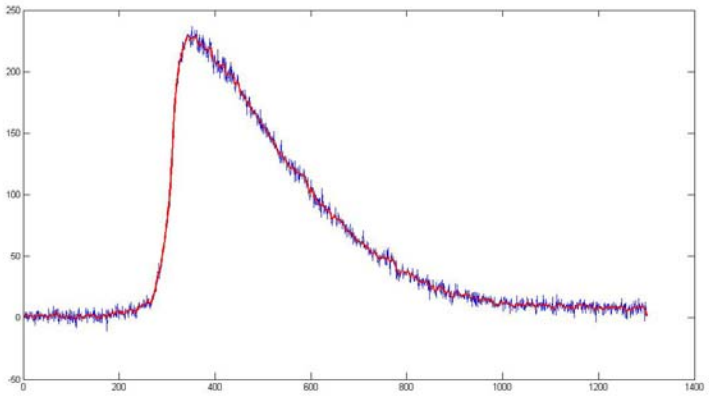

Figure 2: Intensity of a cell over time

Each cell in the movie has a graph of intensity over time which corresponds nonlinearly but monotonically to the calcium transient in that cell. One can define the threshold for a cell 'activating' at which the change intensity over time exceeds some threshold, or

$$\frac{dI}{dt} \geq I_{threshold}$$

Equation 1: Threshold for cell activation

As shown below in figure 3, the intensity profiles over time are not always as simple as the one in figure 2, so the choice of threshold has a large effect on the determination of which cells 'activate'. A state of 'active' for the purposes of this paper will be when the cell experiences a quick rise in the calcium fluorescence signal, and at this point sends out a signal.

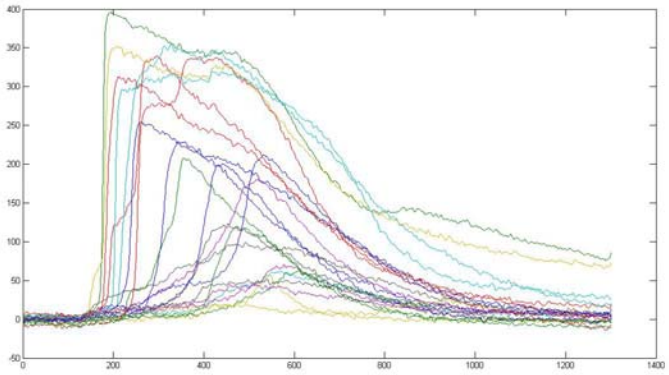

Figure 3: Intensity of multiple cells over time

Combining the threshold function with the cell positions, one can reconstruct which cells in the data 'activate' and which ones do not, and display them graphically as

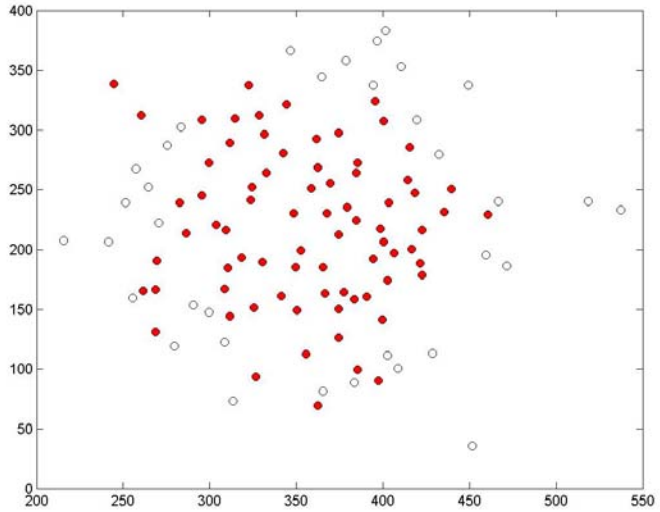

Figure 4: Cell map, $I_{threshold}$ = 2, experimental data
Red - cells which activated, Black - cells which did not exceed the threshold for activation

Figure 4 shows the map of cells which are considered ‘activated’ at a threshold

$I_{threshold} = 2$

Whereas figure 5 shows a map of cells which ‘activate’ at a threshold of

$I_{threshold} = 6$

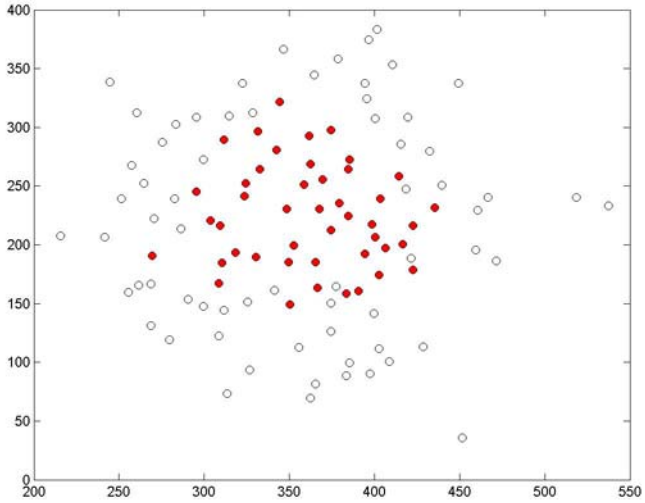

Figure 5: Cell map, $I_{threshold} = 6$, experimental data
Red - cells which activated, Black - cells which did not exceed the threshold for activation

Already, there is a problem. The amount of cells and the shape of the wave is different depending on choice of spike behavior. For the purposes of this project, the model is made to show the qualitative behavior of the signal wave. The cell at (350,225) is activated and sends out a signal, and the observed wavefront from the signal has a few main characteristics.

1) The wave is transient – it dies out before activating all cells in the cell map
2) The wave exhibits a rough wave front
3) The wave of activated cells can skip some cells to activate other which are farther away

The goal of the project is to come up with a model which can qualitatively account for these phenomena. It will be expandable to a quantitative model, but this requires a monte-carlo simulation of the parameter space of the model, which is beyond the time constraints of the project.

2. Model

Assume a state function V exists which governs when a cell goes into the active state and sends out a signal. This change in this state function is dependent on three things:

1) A damping function – the state V will return to a resting state of V = 0 when unperturbed
2) A sum of signals from coming from other cells
3) A gaussian noise term which accounts for fluctuations in the local area

Mathematically, this can be represented as

$$\dot{V}_i = -\gamma V_i + \sqrt{\sigma^2 \gamma} * N(x, y, t) + \sum_j f_{i,j}$$

Equation 2: State function V
γ = damping term
σ = standard deviation of Gaussian noise term

Where $f_{i,j}$ is the term for the signals from other cells,

$$f_{i,j} = \frac{k}{4\pi D\tau} e^{at - \frac{R_{i,j}^2}{4D\tau}}$$

Equation 3: Signal from other cells
D = diffusion constant for molecular signal
τ = time since cell j fired
k = coupling constant
a = 1st order reaction rate in diffusion equation
$R_{i,j}$ = distance between cells i and j

$f_{i,j}$ is obtained from the solution to the diffusion equation in two dimensions with a first order reaction term,

$$\frac{\partial C}{\partial t} = D\nabla^2 C + aC$$

Equation 4: Diffusion equation with a first order reaction term

$$C(t, x, y) = \frac{k}{4\pi Dt} e^{at - \frac{x^2 + y^2}{4Dt}}$$

Equation 5: Solution to diffusion equation

From here, a simulation of the state equation was run, with one initial cell being activated to model the pipette stimulation. When the threshold of the state function exceeded a certain value, the cell was labeled as activated and sent out a signal of its own.

For all parameters tried in this model, either all cells in the simulation fired, on none other than the initial activation did. This did not accurately represent the qualitative behavior of the cells in the experimental data. From here, an adjustment was made to the model, and the assumption was made that the strength of the signal a cell sends out is proportional to the derivative of the state function with respect to time, or

$$k_i = k_o \left. \frac{dV_i}{dt} \right|_{t=t_{fire}(i)}$$

Equation 6: Coupling constant dependence on state function

Once again, the model was simulated with a fixed activation event for a cell in the center of the region, and various parameters were run. Results which satisfy the criteria identified in the experimental data section were obtained as k_o became very low, and approached zero. This indicates that the model is best represented by a signaling event which comes out from the initial cell but does not propagate out from other cells when they are activated.

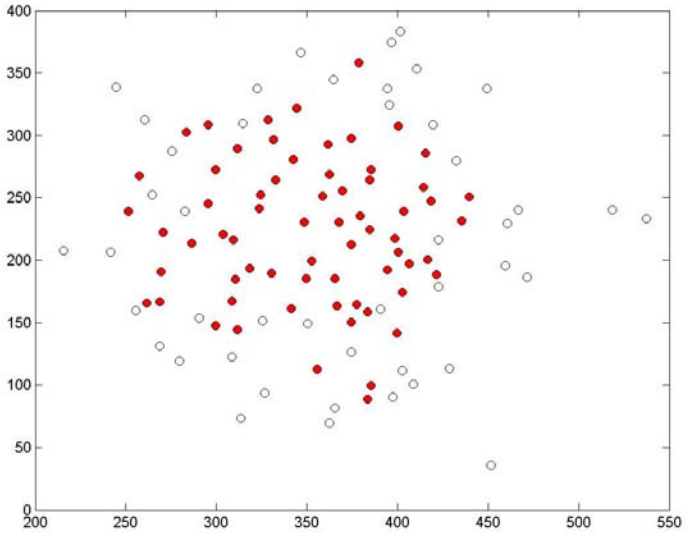

Figure 6: Cell map, model
Red - cells which activated, Black - cells which did not exceed the threshold for activation

Figure 6 shows the results of one run of a simulation of the model. Qualiatatively, the behavior approaches that of the experimental data. The signal is transient, exhibits a rough wave front, and can skip over cells which are nearer to the center than others which were activated.

To further refine the model, a probability distribution of cells activated in the model needs to be determined from many runs, and this needs to be compared to experimental data. The strength of the noise term can also be determined from experimental data in which the same stimulation in the same place is applied and the change in signal pattern is observed. We do not have this data at the present time so this is as far as the model cn go, until further experimental evidence is available.

In this project, a model was developed in a attempt to describe experimental data. It did not succeed at initially, and for the model to fit, the signal has to originate at a center point and either propagate from other cells very weakly or not at all. If further refinement as well as comparison with more experimental data validates the model, it then indicates something about the nature of signal propagation in this system originating from one single point, providing insight into the dynamics of in vitro astrocyte signaling.

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[1] All experimental and imaging work done by Diana Yu, Silva Lab, UCSD Bioengineering
[2] Image processing work to locate cell positions done by Marius Buibas, Silva Lab, UCSD Bioengineering