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The Generation of Oscillations in Networks of Electrically Coupled Cells

This report follows the development of Loewenstein, Yarom, and Sompolinsky in their paper by the same name.[1] A biologically feasible model of calcium dynamics is used to explain the seemingly paradoxical observation that electrical coupling of non-oscillating cells can lead to synchronous oscillations. The model presented here is also able to produce networks of oscillating cells with multiple stable states and interesting dynamics.

Electrical coupling between cells is mediated by gap junctions. These are essentially a direct connection between the cytoplasm of the two coupled cells. Do due this, the connections are fast compared to chemical synapses, which allows for quick inter-cellular signaling. This is important for vital bodily functions that require quick synchronized action, such as in the smooth aortic muscle cells. Electrical coupling exists between most types of cells that have direct contact with their neighbors.

There are three main characteristics of the model:

1. Individual cells are completely described by their membrane potentials and additional internal variables describing calcium concentrations in the cell.
2. When considered independently of the membrane, the internal variables have a natural tendency to oscillate.
3. The interaction between the membrane potential and the internal variables is to provide negative feedback that prevents these internal oscillations and stabilizes the cell.

Therefore, any factor that disrupts the negative feedback between the membrane and the internal variables will cause the cell to oscillate. One possible way to do this is to increase the membrane conductance so that it is unable to suppress the perturbations caused by the internal variables. Electrical coupling between cells mimics an increase in conductance and hence a large electrical coupling between two cells causes the rest state to become unstable and leads to oscillations.

Internal Model

In the present model, the internal dynamics of a single isolated cell are described in terms of the intracellular calcium concentration. The proposed mechanism is that calcium release from internal stores in the cell is induced by changes in the concentration of calcium in the cytoplasm. This creates a feedback loop that causes oscillations. This interaction is is modeled by the following equations:

$$\frac{dX}{dt} = J(X,Y) - K \cdot X - \phi \cdot U \qquad \text{(Model 1)}$$
$$\frac{dY}{dt} = -J(X,Y)$$

In the equations for model 1, X and Y denote the cytosolic and storage calcium concentrations respectively. $J(X,Y)$ describes the interaction term between the two concentrations, $K \cdot X$ is the efflux

1 Loewenstein, Y., Yarom, Y., & Sompolinsky, H. (2001). The generation of oscillations in networks of electrically coupled cells. *Proceedings of the National Academy of Sciences*, *98*(14), 8095-8100.

of calcium from the cell, and $\phi \cdot U$ describes the change in calcium concentration due to a constant electrical current mediated by calcium ions. For the values of the constants used in the simulation, see the appendix.

The internal dynamics of a single isolated call using the equations above equations is shown in Fig. 1. The cell starts from its equilibrium state and then is given a perturbation that causes it to begin oscillating steadily.

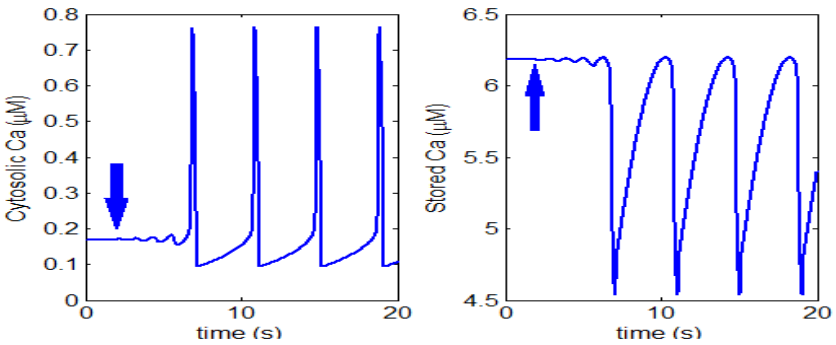


Fig 1: Internal Dynamics

Internal calcium oscillations in an isolated cell. An increase in cytosolic Ca by 0.001 μM at time t = 2 sec drives the cell away from the equilibrium into stable oscillations

Hence the internal variables will oscillate if left unchecked.

Isolated Cell Model

The model of a single isolated cell is completed by also including the response of the membrane potential.

$$\begin{aligned} C\frac{dV}{dt} &= -(I_{Ca}(V) + I_{K\_Ca}(X,V) + I_{leak}(V)) \\ \frac{dX}{dt} &= J(X,Y) - K \cdot X - \phi \cdot I_{Ca}(V) \\ \frac{dY}{dt} &= -J(X,Y) \end{aligned} \qquad \text{(Model 2)}$$

Note that now the passive current U from the equation for X has now been replaced by the voltage dependent calcium current. With this complete model, the oscillations of the internal variables are suppressed by the membrane potential as seen in Fig 2. below.

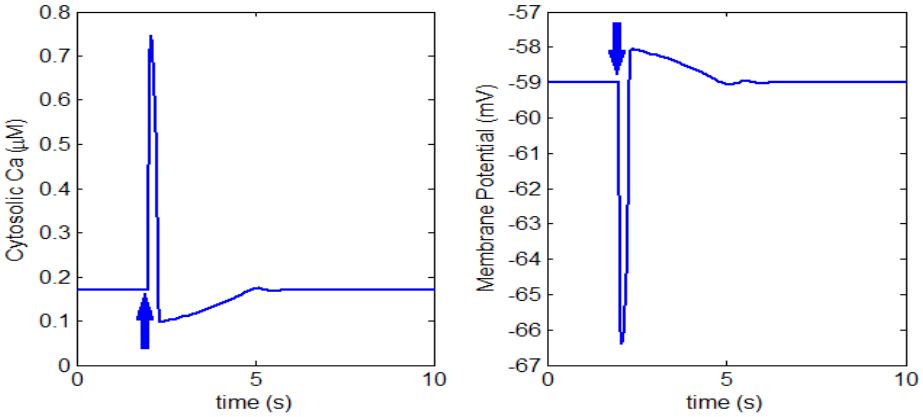


Fig 2: Isolated Cell

An increase in cytosolic Ca by 0.1 μM at time t = 2 sec causes only transient behavior; the cell soon returns to equilibrium. The membrane potential is able to suppress the tendency of the internal variables to oscillate.

Shunted Isolated Cell

The claim that the negative feedback of the membrane potential on the internal oscillations can be tested in the single cell model by adding a shunt current. This shunt current will have a high conductance and a reversal potential that is equal to the resting potential of the cell. This can be included into the model above simply by modifying the dynamical equation for the membrane potential. The relevant equations now become:

$$C\frac{dV}{dt} = -(I_{Ca} + I_{K\_Ca} + I_{leak} + I_{shunt}) \qquad \text{(Model 1)}$$

$$I_{shunt} = g_{shunt}\,(V - V_{equilibrium})$$

A simulation of this new model with a shunt conductance of 2e4 μS/cm^2 is shown in the figure below. This conductance is an order of magnitude larger than any other in the system, and, as expected, the membrane potential is no longer able to suppress the oscillations.

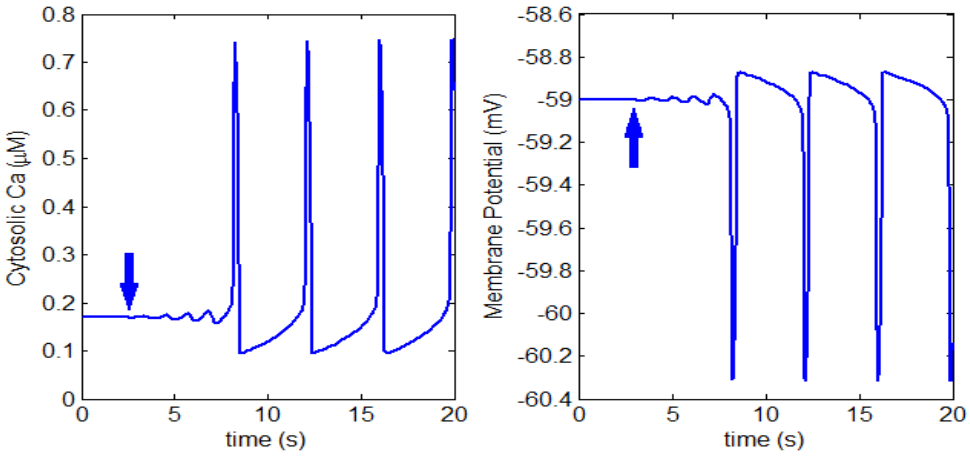


Fig 3: Shunted Cell
An increase in cytosolic Ca by 0.001 μM at time t = 2 sec is enough to trigger the oscillations when there is a large conductance present.

Networks of Electrically Coupled Cells

Model 2 above for a single isolated is easily extendable to networks of such cells only requiring the addition of a coupling current term in the capacitive membrane equation. Hence, the model for a network of such cells is:

$$\begin{aligned} C\frac{dV^i}{dt} &= -(I^i_{Ca} + I^i_{K\_Ca} + I^i_{leak} + I^i_{coupling}) \\ \frac{dX^i}{dt} &= J^i - K\cdot X^i - \phi\cdot I^i_{Ca} \\ \frac{dY^i}{dt} &= -J^i \end{aligned} \qquad \text{(Model 2)}$$

$$I^i_{coupling} = \sum_j g_{ij}(V^i - V^j)$$

Two Coupled Cells

Consider first a network of two coupled cells starting from equilibrium. If a perturbation is applied to the cytosolic calcium concentration of one cell, then charge will begin to flow from that cell to the

other due to the coupling current. Since the potential of this second cell is initially at rest, the reversal potential of this current will be equal to the resting potential as in the shunted cell model. Therefore, we expect a similar oscillatory behavior. A simulation of the above model for a network of two cells is shown below. Notice that the membrane potential oscillates synchronously at twice the frequency of the individual cells and that the oscillations of the internal variables are asynchronous.

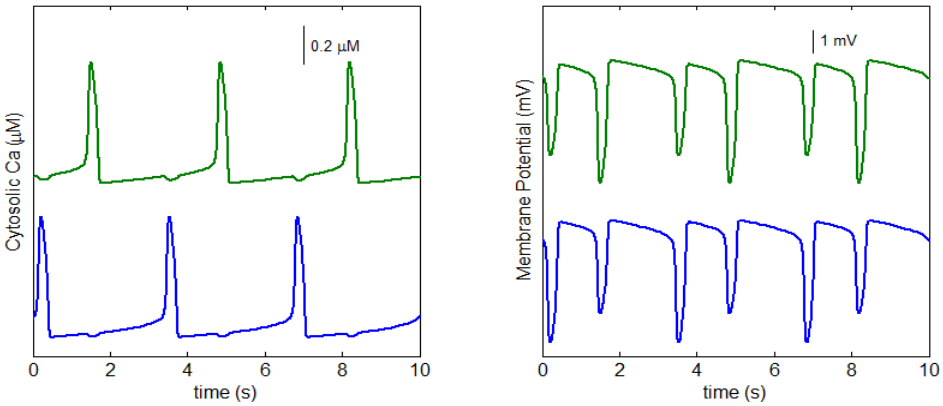
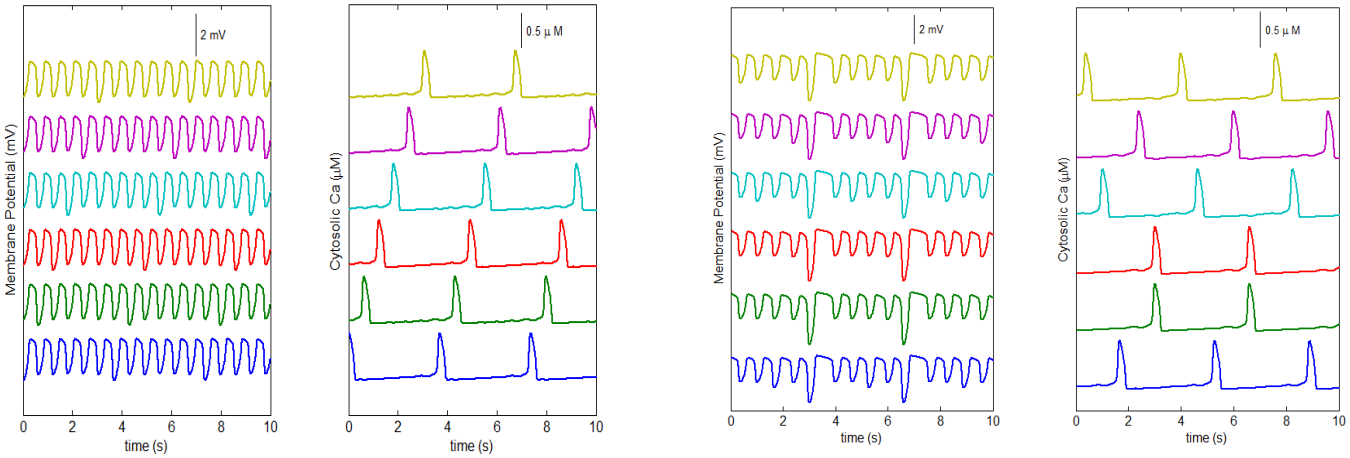


Fig 4: Coupled Cells
Steady state oscillations of a pair of coupled cells show a 2:1 ratio between the frequencies of the potential and Ca oscillations. The coupling conductance is 1e4 μS/cm^2.

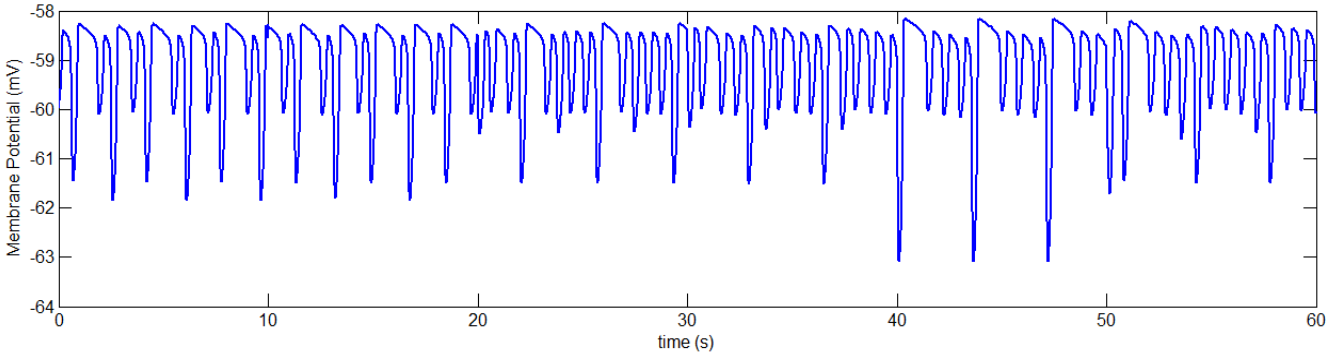
Small Network of Six Cells

Even more interesting behavior can be seen in a network of six of these identical cells. In these larger networks, the coupling conductance is chosen to be a symmetric function of the (arbitrary) cell index given by $g_{ij} = (4 + 2 \cdot i + 2 \cdot j) \cdot 10^3 \mu S/cm$. In networks with more than two cells, there are multiple stable states of oscillations with different spiking trails. Two such states are given below.



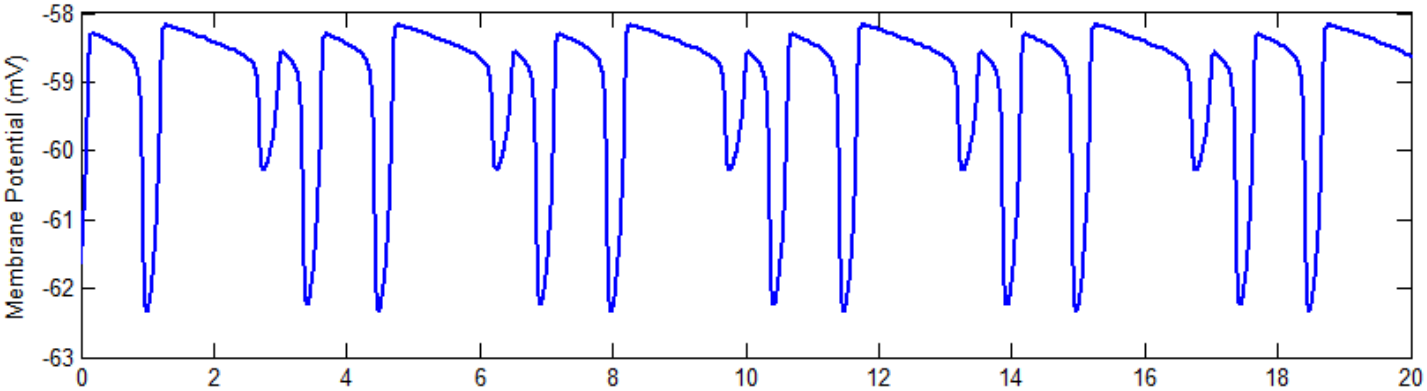
In the first case on the left, each cell spikes at a different time and so there are 6 peaks in the membrane potential per cycle. In the second case, two of the cells (red and green) spike synchronously; because of this, there are now 5 spikes in the potential with one of them being nearly twice the magnitude of the others. In general, the cells form up to 6 clusters that spike synchronously within the cluster but not between different clusters. Then the number of cells in the cluster determines the magnitude of the dip in the (nearly) synchronized membrane potential. The symmetric nature of the coupling conductance is not required for these results, but the magnitude of the conductance does matter. Changing the coefficients of *i* and *j* changes the steady state spiking pattern, but the general behavior still holds. However, when the magnitude of the conductance is decreased, the coupling current is no longer strong enough to synchronize all of the membrane potentials. The dip in the membrane potential of each cell when another one spikes is dependent on the coupling conductance and this becomes more evident when the conductance is decreased.

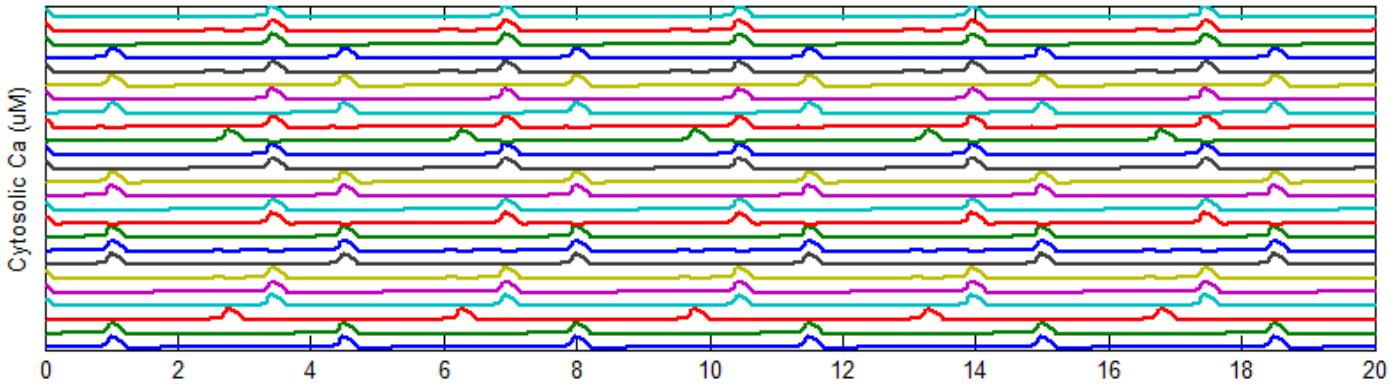
It is also interesting to see how the network responds to perturbations after it has settled into one of the stable oscillation states. The figure below shows a simulation of this experiment. The membrane potential of one of the cells is displayed over a period of one minute while the cell is receiving a perturbative increase of its cytosolic calcium every 10 s. It is evident that this perturbation may cause the network to change stable states. The effect of the perturbation and the new steady state reached depends on when the perturbation occurs relative to the natural spiking of the cell. The first kick at 10s occurs right after the cell has spiked on its own and is in its refractory period; therefore, this perturbation does not effect the dynamics of the system.



Larger Networks

The dynamics and clustering behavior of the six cell model generalizes fairly well to larger networks of cells. Below is a simulation of at network of strongly coupled (gij is high) of a network of 200 cells. The cytosolic spike trains for 25 of these cells is also shown.



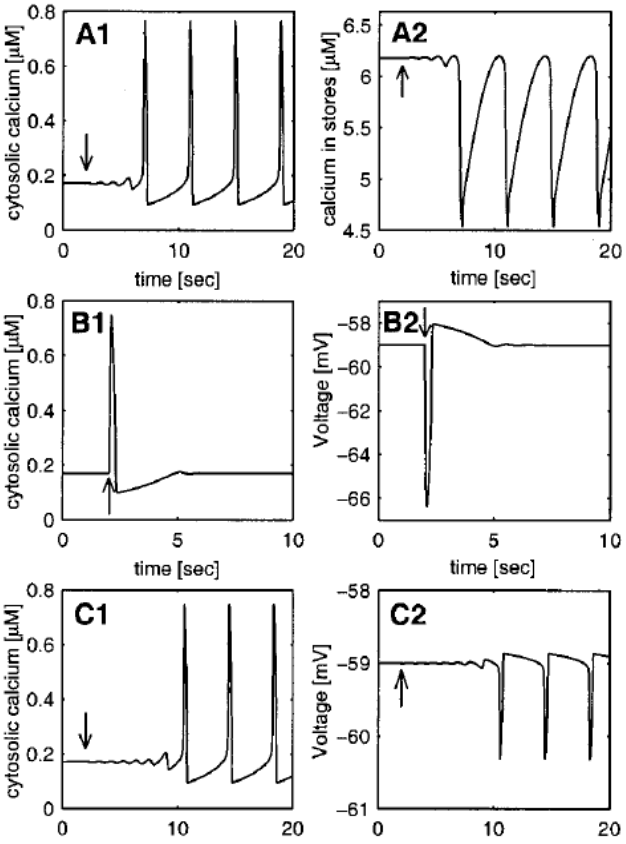


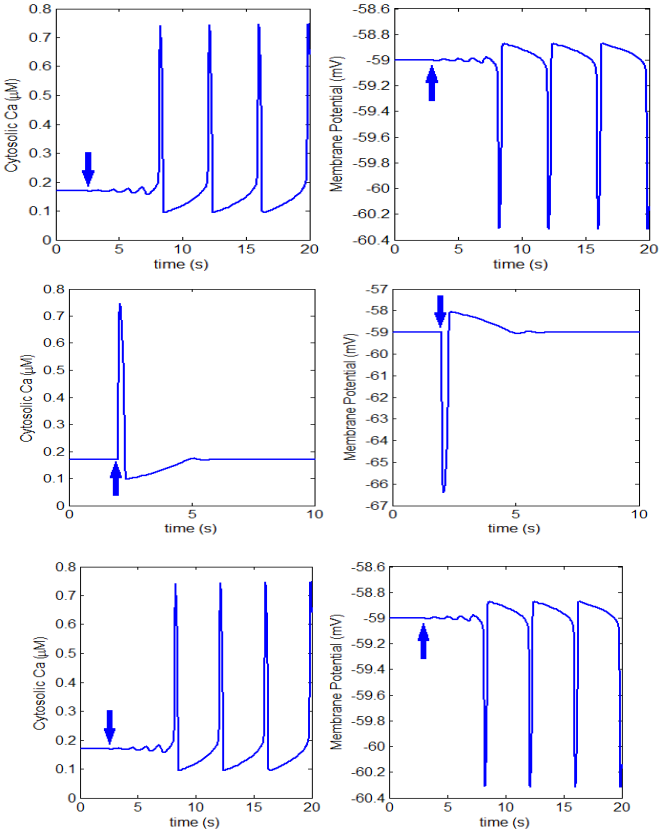
Conclusions

The results shown above give insight into the seemingly paradoxical observation that a network of identical non-oscillating cells that are electrically coupled can generate synchronous membrane potentials. In this model, the membrane potential of an isolated cell provides negative feedback that suppresses the natural tendency of the cell to oscillate. Electrical coupling acts to disrupt this feedback by increasing the membrane conductance. The simple model of presented herein is also able to produce very interesting dynamics with multiple stable states. The flexibilty of the simulated networks shows that there is great potential for biological systems to use electrically coupled networks to perform non-trivial tasks and computations.

Meta-Report

All of the simulations and figures in this report were generated using MATLAB. I found that the ode15s solver was very good at solving the differential equations quite quickly, only taking on the order of seconds for smaller networks integrated over a period of about a minute. The ode45 solver was slower at finding the solutions due to the stiffness of the problem that arises from the Boltzmann factors in the equation for the calcium current. Overall I enjoyed the project and doing the simulations; it was definitely a good fit for my abilities and interests. In the end, I was able to produce figures nearly identical to those in the paper, as can be seen in the figures below, which felt very rewarding. Thank you for suggesting this project to me.





Appendix

Internal Variable Dynamics

The dynamical equations for the internal variables inside are:

$$\frac{dX}{dt} = J(X,Y) - K \cdot X - \phi \cdot U$$
$$\frac{dY}{dt} = -J(X,Y)$$

The calcium efflux constant in is; the conversion factor between calcium current and a change in the concentration of cytosolic calcium is. For the simulation of the internal variables, the constant calcium current is taken to be $U = -184 nAmp/cm^2$. The interaction term in the above equations is given by:

$J(X,Y) = -V_2 + (V_3 + K_s) \cdot Y$ with

$$V_2 = V_{M2} \frac{X^2}{{K_2}^2 + X^2} \qquad V_{M2} = 50\,\mu M/sec \qquad K_s = 1\,sec^{-1}$$
$$V_{M3} = 600\,sec^{-1} \qquad K_2 = 0.2\,\mu M$$
$$V_4 = V_{M3} \frac{(K_4 X)^3}{(X + K_4)^6} \qquad K_4 = 0.69\,\mu M$$

See the paper for the details and references on where these numbers came from.

Membrane Potential Dynamics

The dynamical equation for the membrane potential is as follows

$$C\frac{dV}{dt} = -(I_{Ca}(V) + I_{K\_Ca}(X,V) + I_{leak}(V))$$

where the expressions for the currents are given by

$$I_{Ca} = g_{Ca} m_\infty^3 h_\infty (V - V_{Ca}) \qquad m_\infty = \frac{1}{1 + e^{-(V - V_m)/T_m}}$$
$$I_{K\_Ca} = g_{K\_Ca} \sigma (V - V_K) \qquad h_\infty = \frac{1}{1 + e^{-(V - V_h)/T_h}}$$
$$I_{leak} = g_{leak}(V - V_{leak}) \qquad \sigma = \frac{1}{2}\left(1 + \tanh[\beta(X - X^*)]\right)$$

The constant parameters used in the above expressions are:

$$V_{Ca} = 120\,mV \qquad g_{Ca} = 100\,\mu S/cm^2 \qquad C = 1\,/cm^2 \qquad X^* = 0.4334 \mu M$$
$$V_K = -85\,mV \qquad g_{Ca\_K} = 2000\,\mu S/cm^2 \qquad V_m = -61\,mV \qquad T_m = 4.2\,mV$$
$$V_{leak} = -55\,mV \qquad g_{leak} = 2701\,\mu S/cm^2 \qquad V_h = -85.5\,mV \qquad T_h = 8.6\,mV$$

See the paper for the details and references on where these numbers came from.