The Generation of Oscillations in Networks of Electrically Coupled Cells

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Reproducing the work of Y. Loewenstein, Y. Yarom, and H. Sompolinsky:

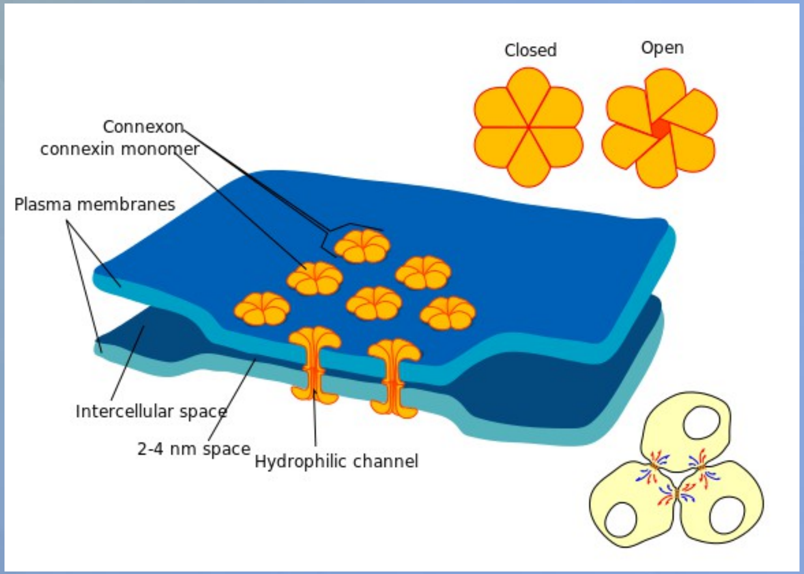
Loewenstein, Y., Yarom, Y., & Sompolinsky, H. (2001). The generation of oscillations in networks of electrically coupled cells. *Proceedings of the National Academy of Sciences*, *98*(14), 8095-8100.

Outline

- Introduction and motivation
- Description of the model
- Simulation Results
- Conclusions

Electrical Coupling

- Cells are coupled via a gap junction
- Directly connects the cytoplasm
- Relatively fast acting to allow for quick inter-cellular signaling



http://en.wikipedia.org/wiki/File:Gap_cell_junction-en.svg

Where are electrically coupled cells?

- Found in nearly all touching animal cells and in most tissues
- Oscillations in hippocampal slices that are independent of chemical synapses
- Inferior Olive – subthreshold oscillations
- Aortic smooth muscles cells

The Model

- Biologically feasible model based on calcium dynamics
- Characteristics of the model:
  - Individual cells are completely described by their membrane potential and internal variables
  - Internal variables have a natural tendency to oscillate
  - Membrane potential provides negative feedback that suppresses these oscillations
  - Electrical coupling increases membrane conductance and disrupts the feedback

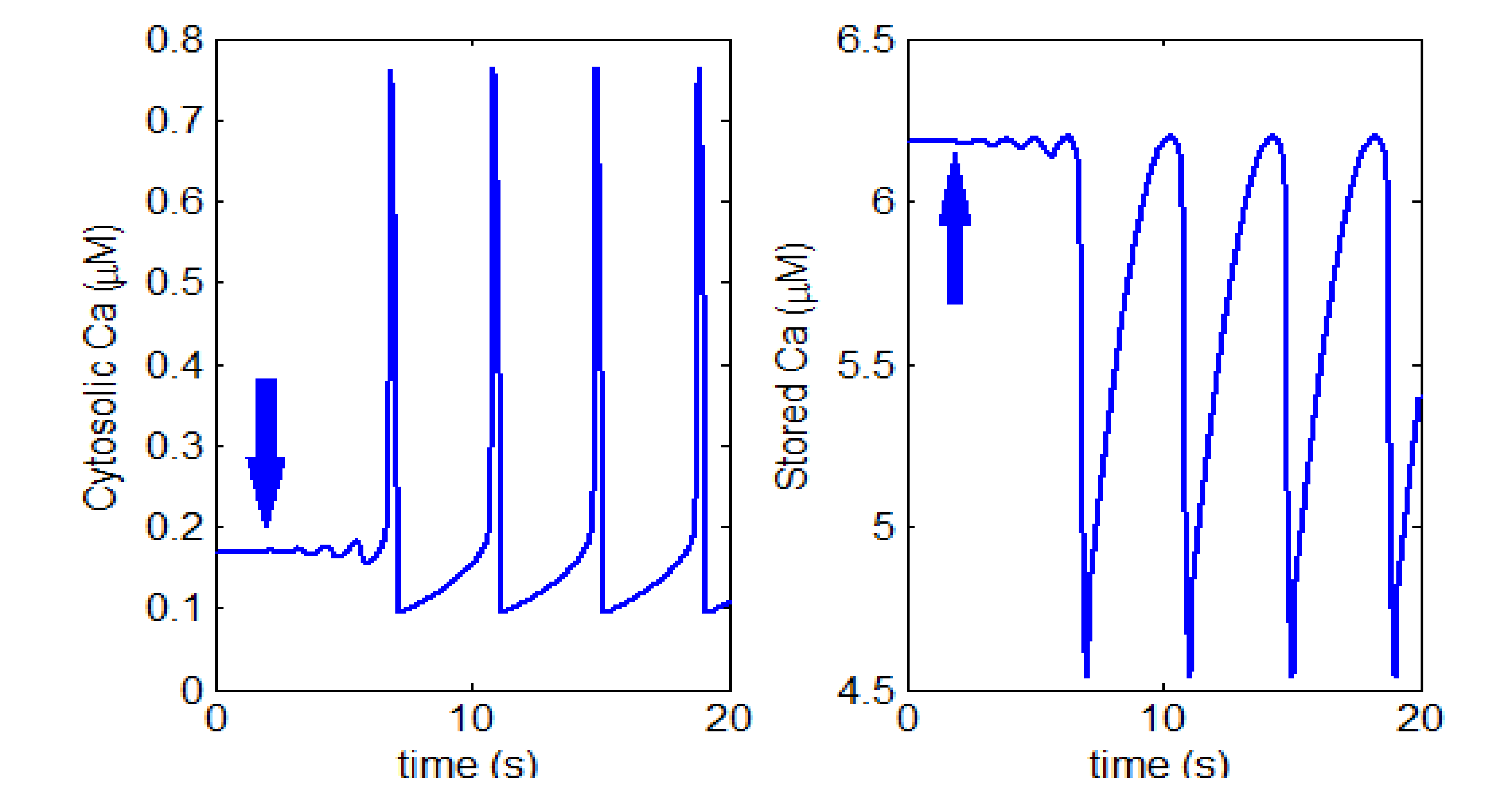
Internal Model

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

$$\frac{dY}{dt} = -J(X,Y)$$

- *X* is the cytosolic Ca concentration
- *Y* is the concentration of stored Ca

Internal Dynamics



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

Single Cell Model

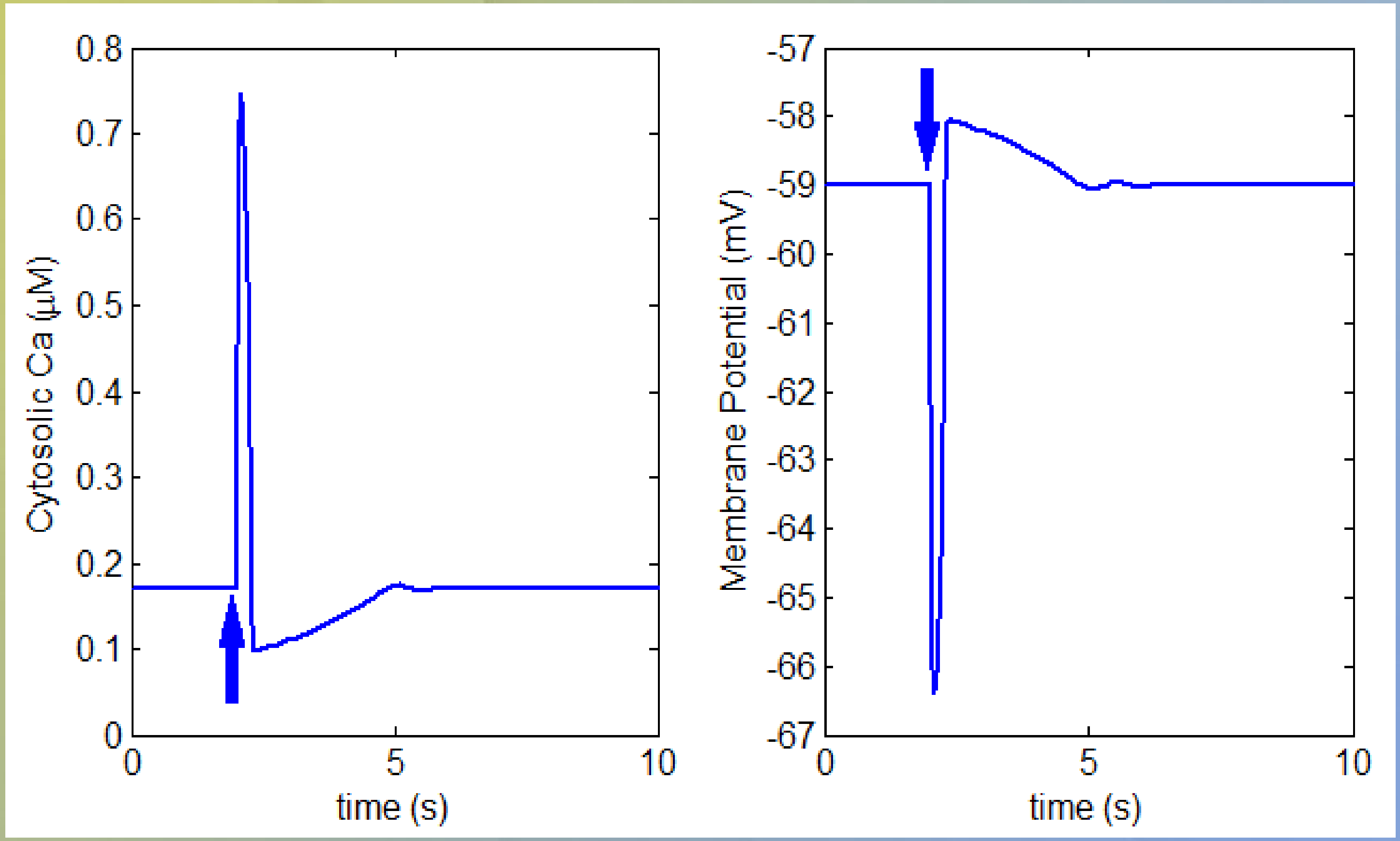
- Complete model for an isolated cell
- Membrane potential is a source of negative feedback which suppresses oscillations

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

$$\frac{dX}{dt} = J(X,Y) - K \cdot X - \phi \cdot I_{Ca}(V)$$

$$\frac{dY}{dt} = -J(X,Y)$$

Single Cell Dynamics



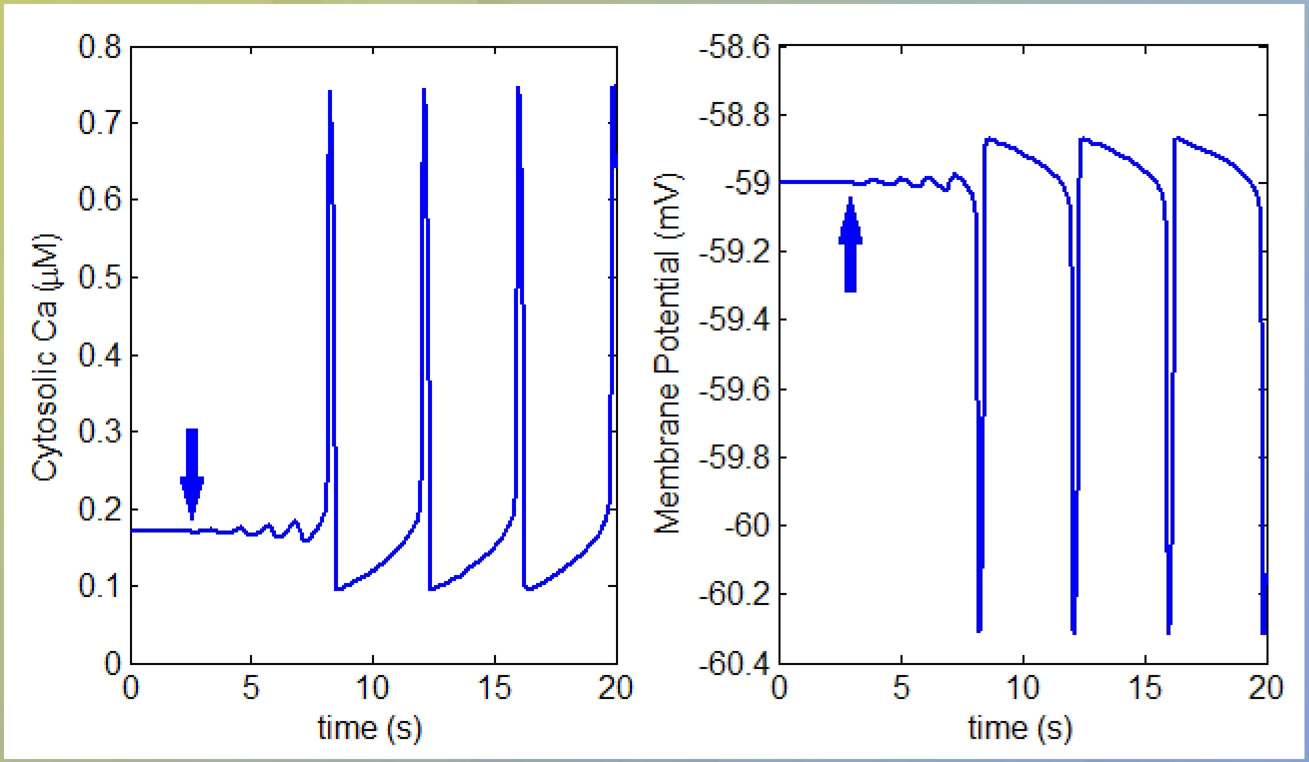
An increase in cytosolic Ca by 0.1 μM at time t = 2 sec causes only transient behavior; the cell soon returns to equilibrium. The membrane potential is able to suppress the tendency of the internal variables to oscillate.

Single Cell with Shunt Current

- Claim that the membrane potential is what is suppressing the oscillations
- Increasing the membrane conductance with a shunt current should inhibit this effect
- Electrical coupling is then modeled in a single cell as a shunt current with a reversal potential equal to the equilibrium potential

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

Shunted Cell Dynamics



A small increase in cytosolic Ca by 0.001 μM at time t = 2 sec drives the cell away from the equilibrium into stable oscillations. Shunt conductance taken to be 2e4 $\mu S/cm^2$

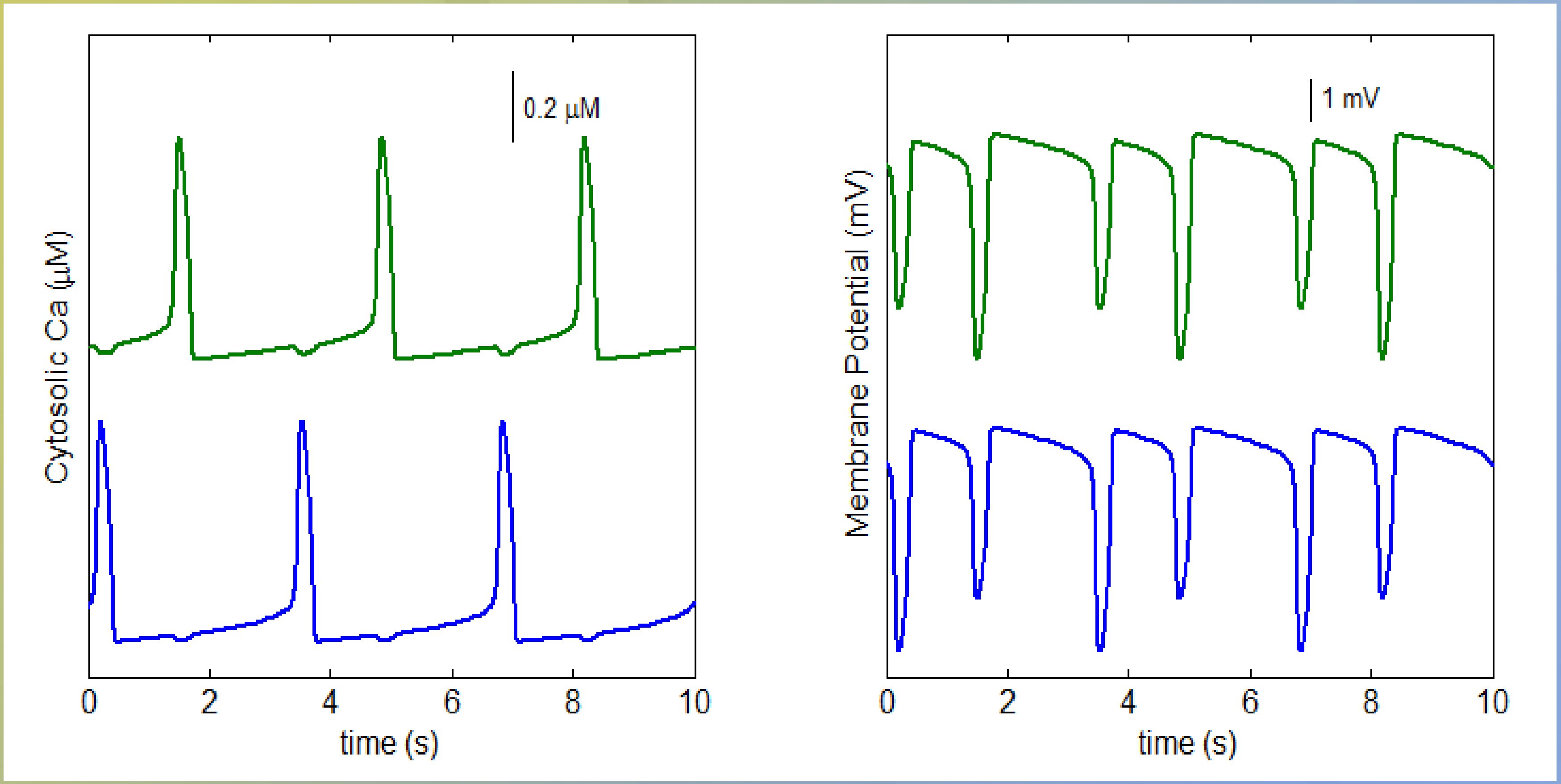
Electrically Coupled Cells

- Electrical coupling can be thought of as a shunt current
- Coupling is provided by an additional coupling current

$$C\frac{dV^i}{dt} = -(I^i_{Ca} + I^i_{K\_Ca} + I^i_{leak} + I^i_{coupling})$$

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

Coupled Cell Dynamics



Steady state oscillations of two electrically coupled cells with a coupling conductance of 1e4 µS/cm^2

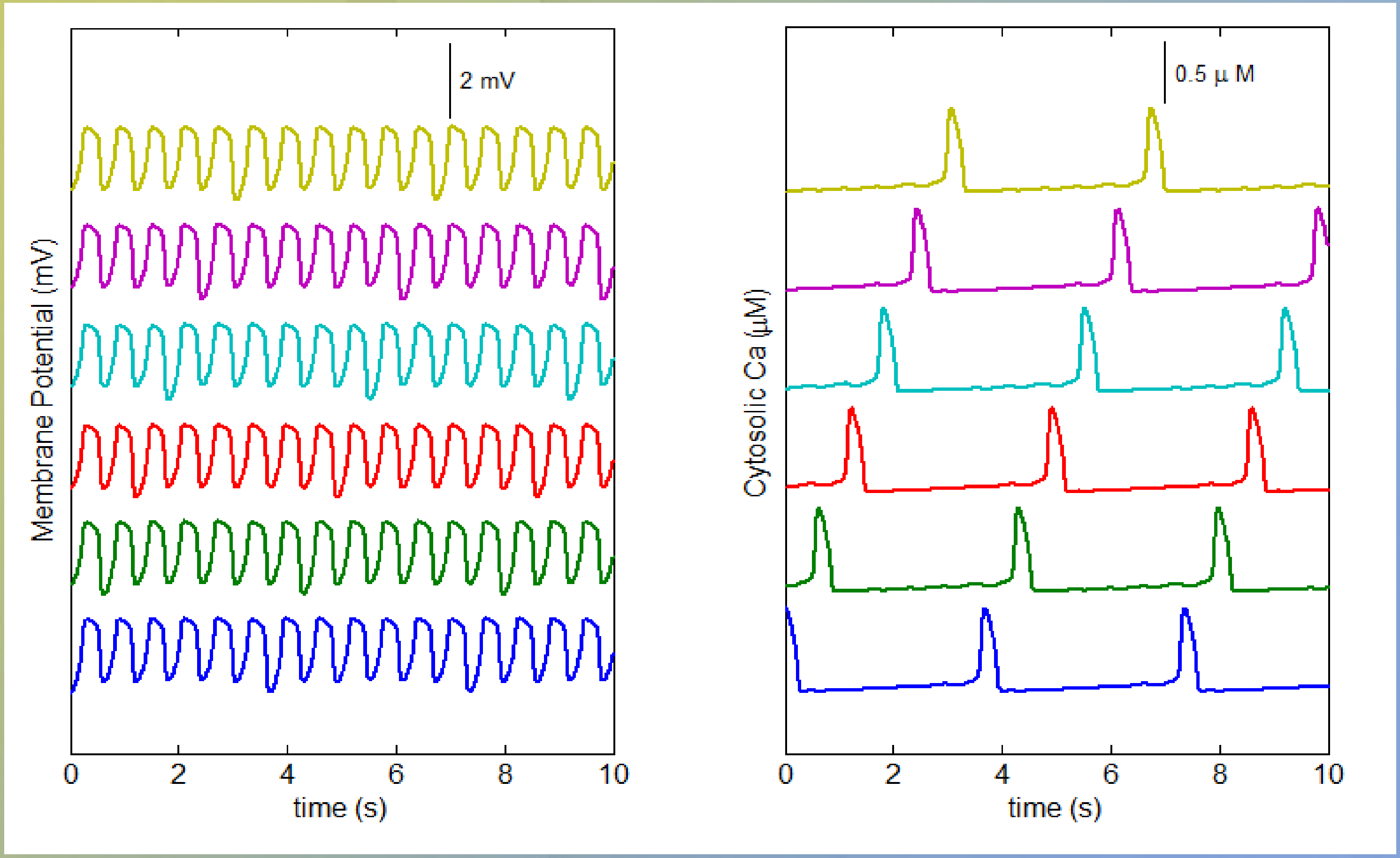
Network Model

- Can generalize the network to an arbitrary number of cells
- Electrical coupling produces interesting network dynamics
- Coupling conductance given by the followig expression:

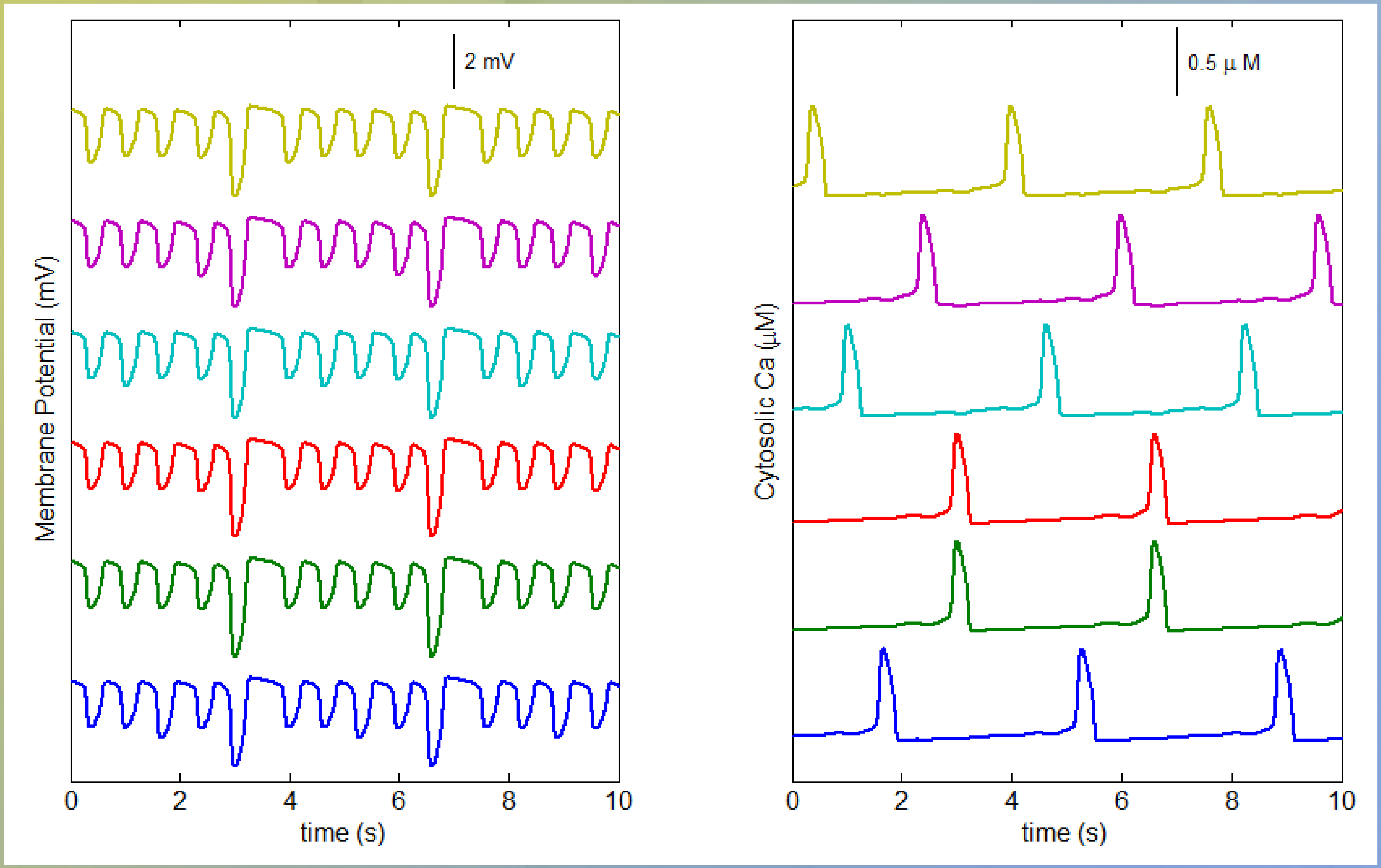
$$g_{ij} = (4 + 2 \cdot i + 2 \cdot j) \cdot 10^3 \mu S/cm$$

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

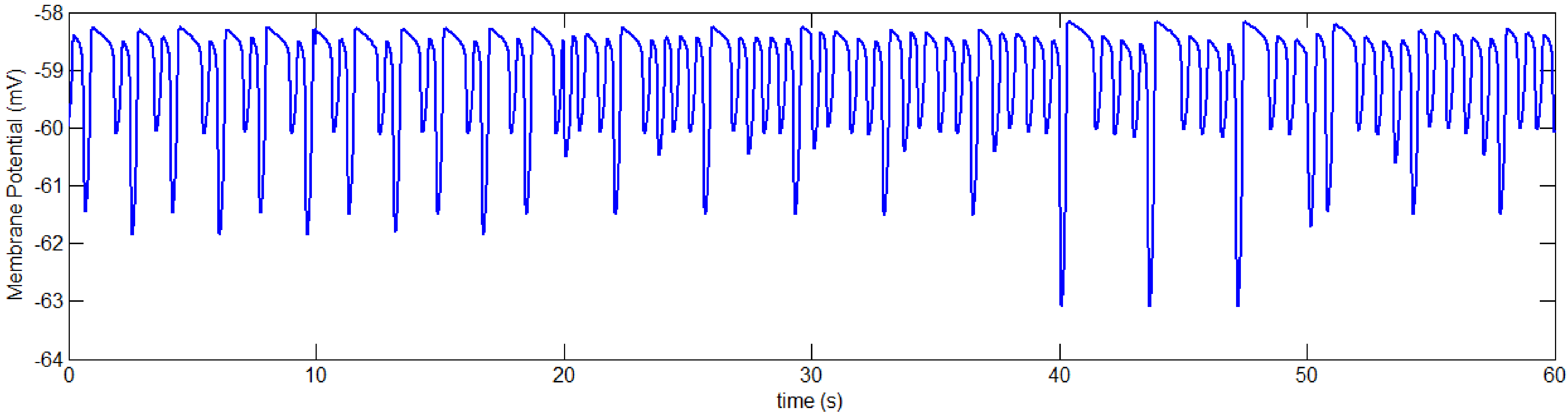
Stable State (6 spikes)



Stable State (5 spikes)

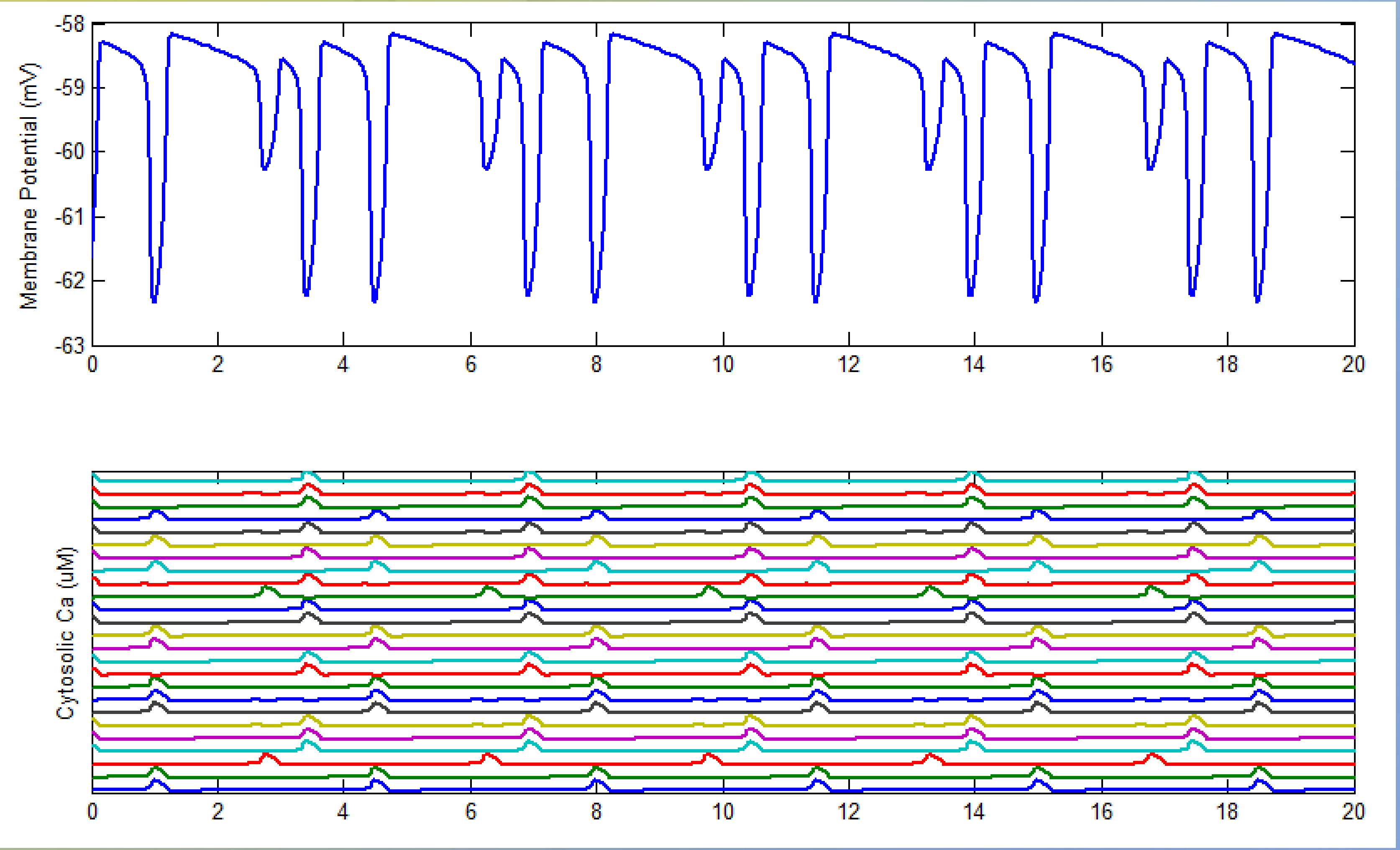


Changing States



Membrane potential of a cell showing changes in the stable state as it is kicked at 10sec intervals by a perturbative increase in cytosolic Ca concentration of 0.1 μM

Larger Networks



Conclusions

- This model of electrical coupling can create very interesting dynamics in a network of identical non-oscillating cells
- Cells form clusters within the network that have synchronous oscillations separate from other clusters
- Electrical coupling is much more than just a synchronizing device or communication pathway

Questions?

Appendix: The Calcium Dynamics Cell Model

The calcium dynamics in Eqs. 1 and 2 is: $J(X,Y) = -V_2 + (V_3 + K_s) \cdot Y$ with

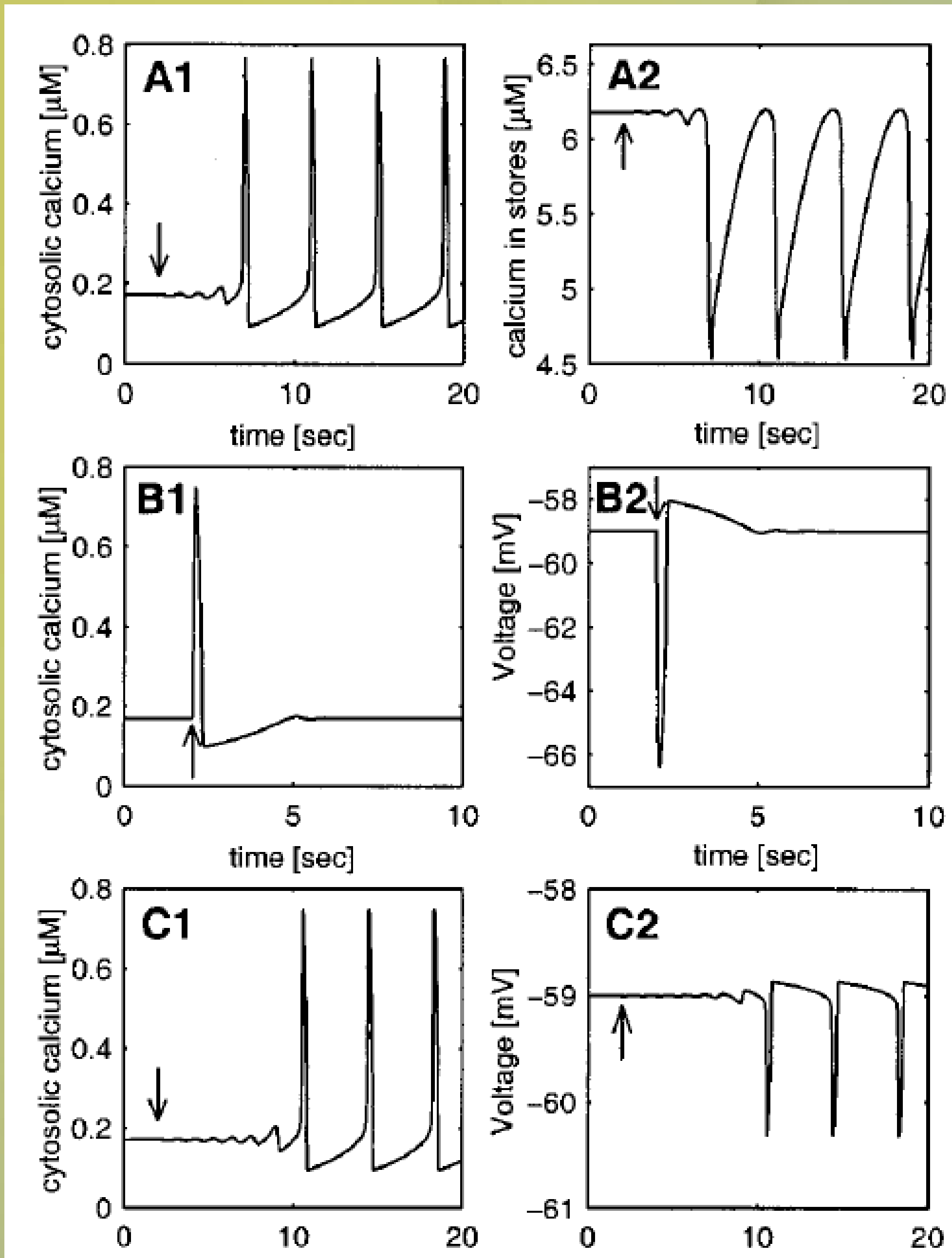
$$V_2 = V_{M2}\frac{(X^2)}{(K_2)^2 + X^2}; V_3 = V_{M3}\frac{(K_4X)^3}{(X + K_4)^6};$$

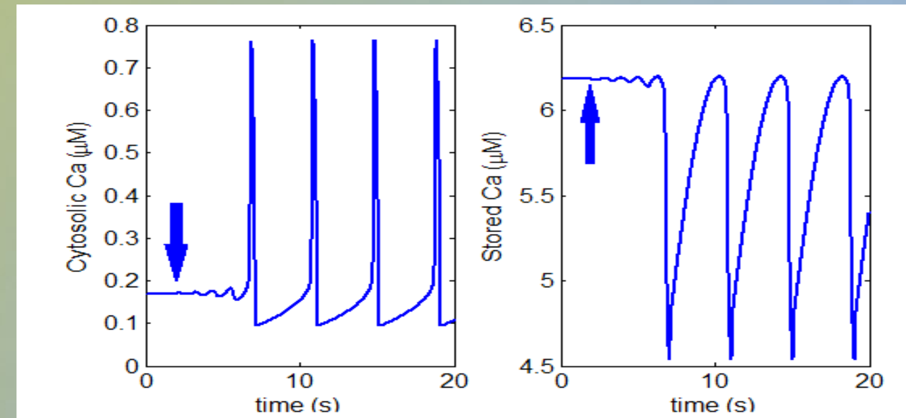
$K_s = 1\ \mathrm{sec}^{-1}$; $V_{M2} = 50\ \mu\mathrm{M/sec}$; $K_2 = 0.2\ \mu\mathrm{M}$; $V_{M3} = 600\ \mathrm{sec}^{-1}$; $K_4 = 0.69\ \mu\mathrm{M}$. The parameters of J and K were taken from ref. 30 assuming that the inositol triphosphate concentration is constant and equal to 0.14 μM. The calcium efflux constant, $K = 10\ \mathrm{sec}^{-1}$ and $\phi = 9.221 \cdot 10^{-3}\ \mu\mathrm{Mcm}^2/(\mathrm{sec{\cdot}nA})$ is the conversion factor from calcium current to change in cytosolic calcium concentration. For an appropriate regime of values of X and Y, the derivative of $J(X,Y)$ with respect to X is positive, implying that X exhibits a positive feedback loop mediated by the calcium-induced calcium release. This positive feedback is terminated when the stores are depleted and the excess calcium is pumped out of the cell. The influx of calcium into the cell via voltage-dependent calcium current restores the necessary calcium for the next cycle. The currents in Eq. 2 are: $I_{leak} = g_{leak}(V - V_{leak})$; $I_{Ca} = g_{Ca}m_\infty{}^3h_\infty(V - V_{Ca})$; $I_{K\_Ca} = g_{K\_Ca}\sigma(V - V_K)$ with

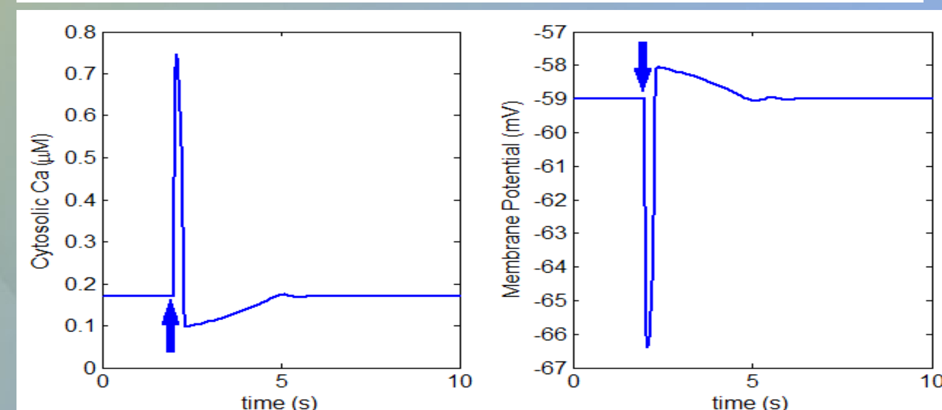
$$m_\infty = \frac{1}{1 + e^{-(V - V_m)/T_m}}; h_\infty = \frac{1}{1 + e^{(V - V_h)/T_h}};$$

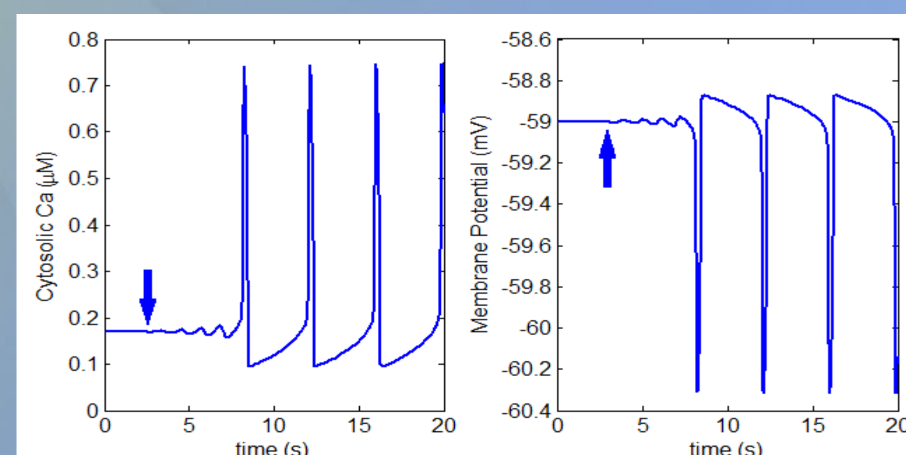
$$\sigma = \frac{1}{2}\{1 + \tanh[\beta(X - X^*)]\};$$

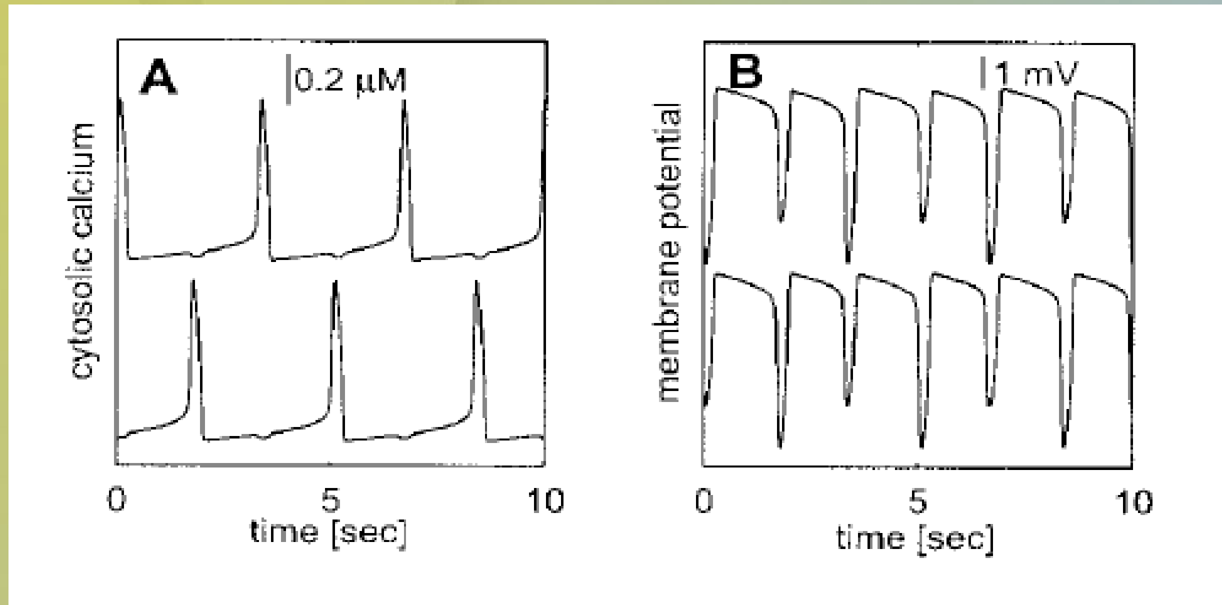
with the parameters: $V_{leak} = -55$ mV; $g_{leak} = 2{,}701\ \mu\mathrm{S/cm}^2$; $V_m = -61$ mV; $T_m = 4.2$ mV; $V_h = -85.5$ mV; $T_h = 8.6$ mV; $V_{Ca} = 120$ mV; $g_{Ca} = 100\ \mu\mathrm{S/cm}^2$; $\beta = 2.5\ \mu\mathrm{M}^{-1}$; $X^* = 0.4334\ \mu\mathrm{M}$; $V_K = -85$ mV; $g_{K\_Ca} = 2{,}000\ \mu\mathrm{S/cm}^2$, $C = 1\ \mu\mathrm{F/cm}^2$. The parameters of I_{Ca} were taken from *in vitro* measurements in the IO (11), assuming an instantaneous inactivation term.

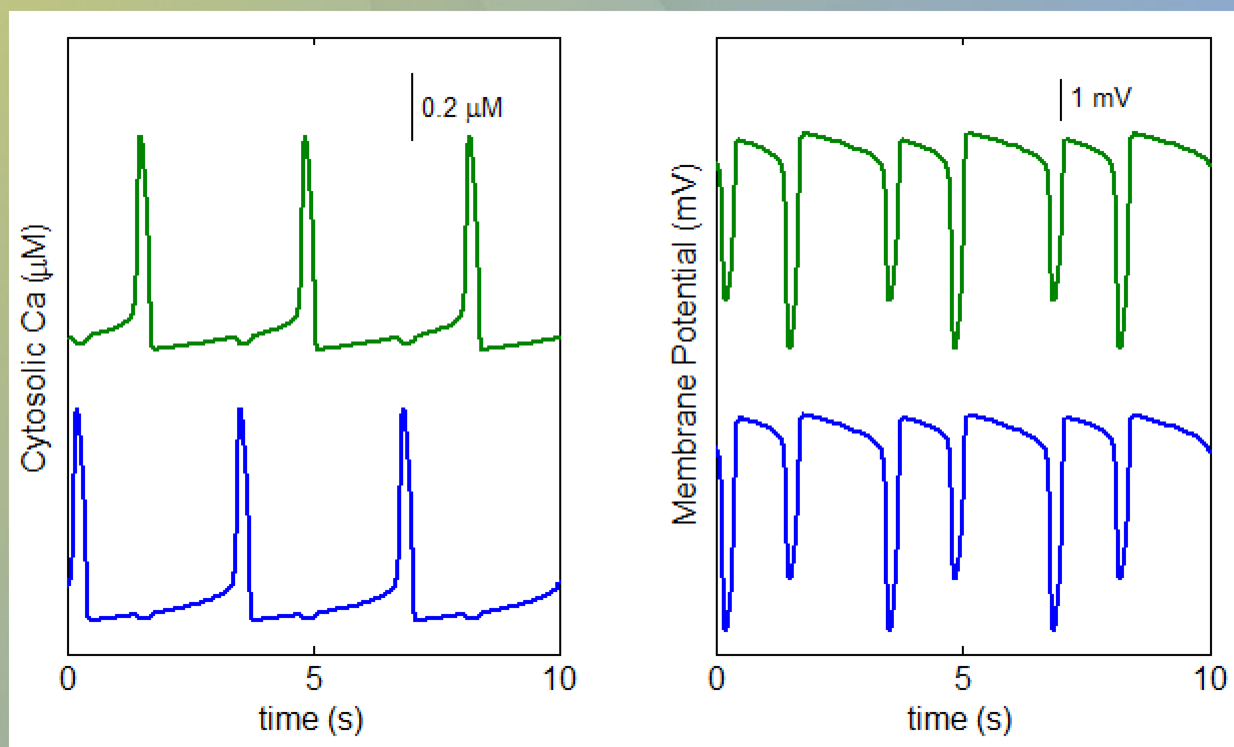

A1
cytosolic calcium [µM]
time [sec]
A2
calcium in stores [µM]
time [sec]
B1
cytosolic calcium [µM]
time [sec]
B2
Voltage [mV]
time [sec]
C1
cytosolic calcium [µM]
time [sec]
C2
Voltage [mV]
time [sec]

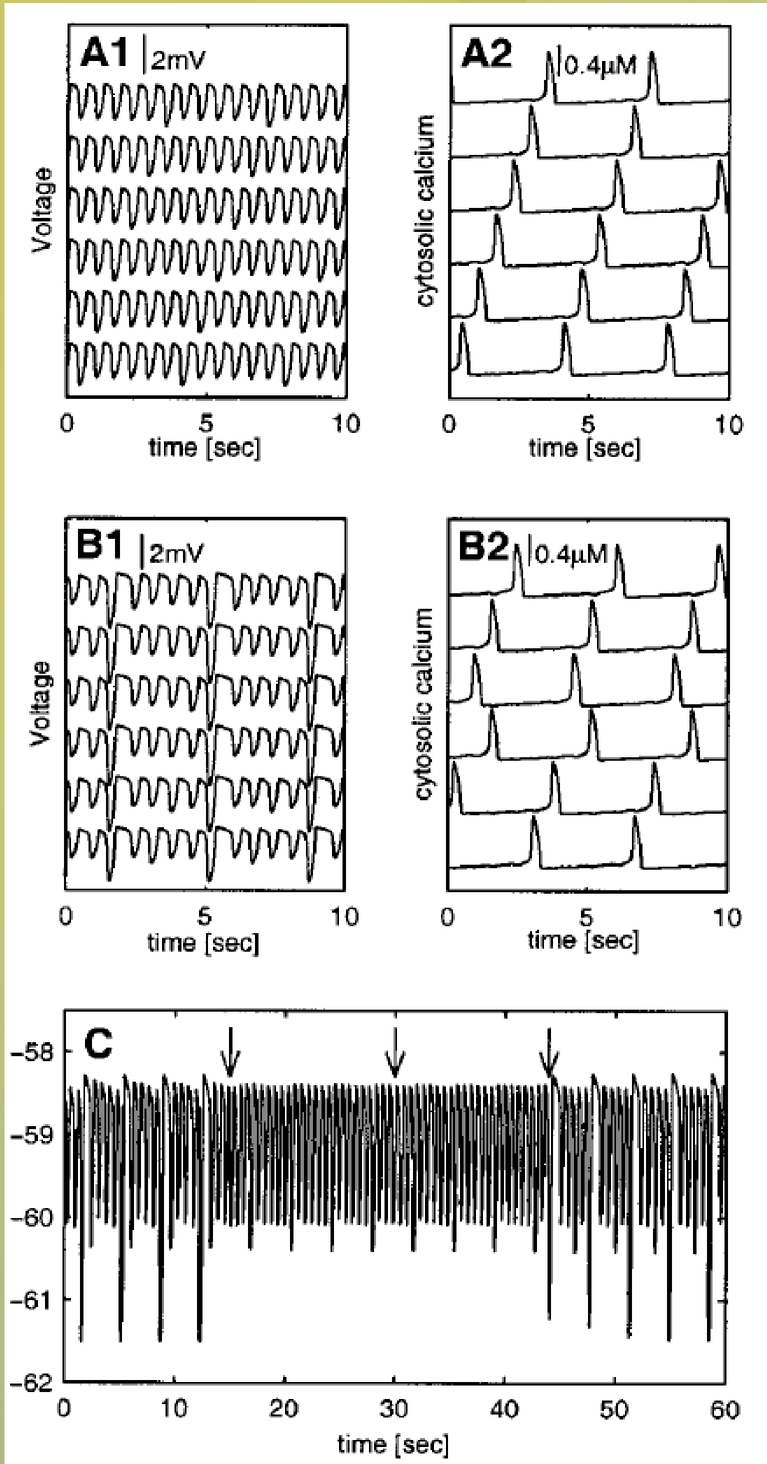

Cytosolic Ca (µM)
time (s)
Stored Ca (µM)
time (s)

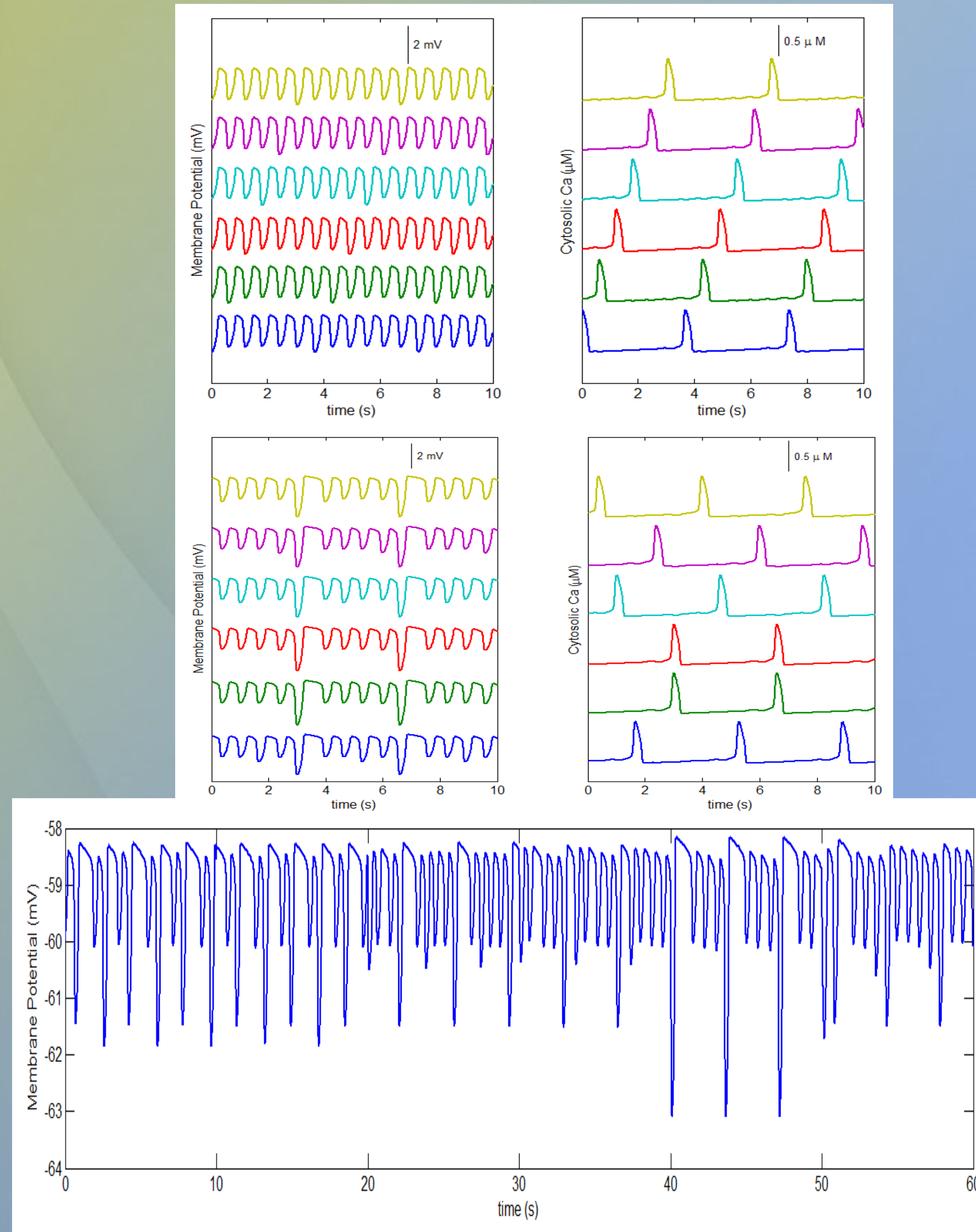

Cytosolic Ca (µM)
time (s)
Membrane Potential (mV)
time (s)

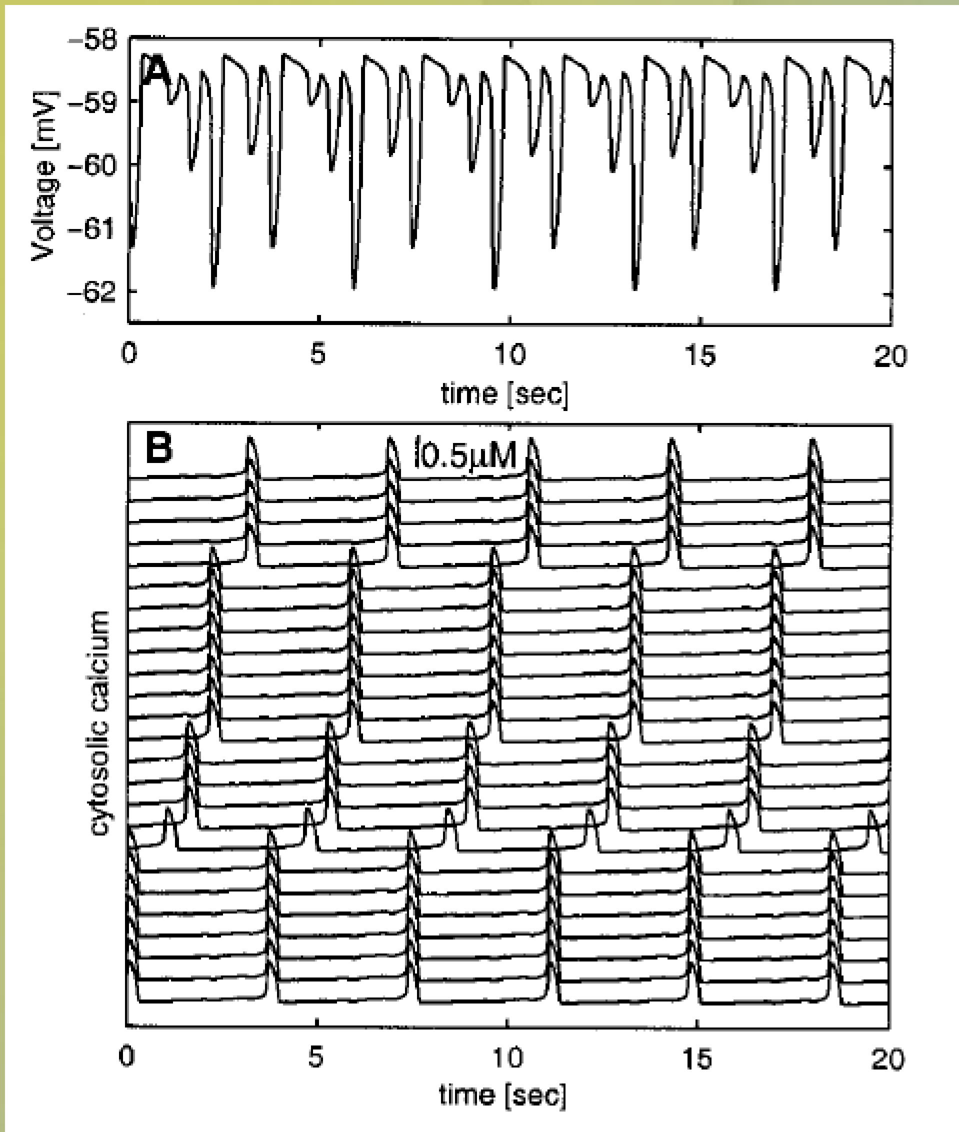

Cytosolic Ca (µM)
time (s)
Membrane Potential (mV)
time (s)

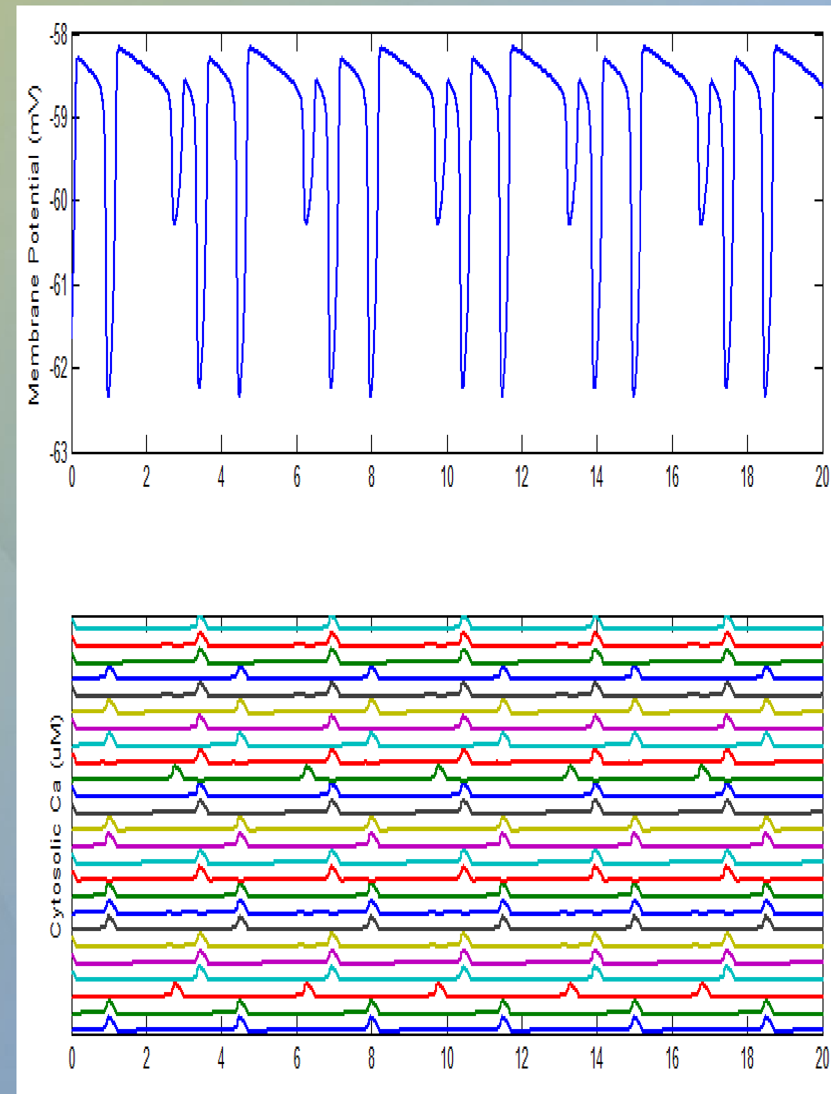

A
0.2 μM
cytosolic calcium
0
5
10
time [sec]
B
1 mV
membrane potential
0
5
10
time [sec]


0.2 μM
Cytosolic Ca (μM)
0
5
10
time (s)
1 mV
Membrane Potential (mV)
0
5
10
time (s)


A1
2mV
Voltage
time [sec]
A2
0.4μM
cytosolic calcium
time [sec]
B1
2mV
Voltage
time [sec]
B2
0.4μM
cytosolic calcium
time [sec]
C
time [sec]


2 mV
Membrane Potential (mV)
time (s)
0.5 μ M
Cytosolic Ca (μM)
time (s)
2 mV
Membrane Potential (mV)
time (s)
0.5 μ M
Cytosolic Ca (μM)
time (s)
Membrane Potential (mV)
time (s)


A
Voltage [mV]
-58
-59
-60
-61
-62
0
5
10
15
20
time [sec]
B
0.5μM
cytosolic calcium
0
5
10
15
20
time [sec]


Membrane Potential (mV)
-58
-59
-60
-61
-62
-63
0
2
4
6
8
10
12
14
16
18
20
Cytosolic Ca (uM)
0
2
4
6
8
10
12
14
16
18
20