# Calcium

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**Abstract**

Calcium-induced Calcium release is a crucial biological process that allows our cardiac muscle to contract and relax. The key of the process is a control function F. The function F takes the value of $Ca^{2+}$ concentration in the cytoplasm and determines the rate at which $Ca^{2+}$ flows out of the Endoplasmic Reticulum into the cytoplasm. In this project, we model the $Ca^{2+}$ concentration to study some necessary properties of F for the cardiac muscle to contract periodically. The project also includes a stochastic model and the comparison of the two models.

## 1 Introduction

The contraction of a muscle cell is controlled by the Calcium concentration in it. When a high $Ca^{2+}$ is present, the sliding filaments binds with the $Ca^{2+}$ and contracts. When the concentration drops, the $Ca^{2+}$ detaches from the sliding filament which causes it to relax. Therefore, contraction and relaxation of a muscle cell is achieved by regulating the $Ca^{2+}$ concentration. In a cardiac cell, a contraction is initiated by electrical impulses known as action potentials. The signal triggers some ion channels on the membrane to open and allows the $Ca^{2+}$ contained in the extracellular fluids to enter ($Ca^{2+}$ concentration of extracellular fluids is much higher than that of the cytoplasm). The rate at which these impulses fire controls the rate of cardiac contraction, that is, the heart rate. The cells that create these rhythmic impulses, setting the pace for blood pumping, are called pacemaker cells, and they directly control the heart rate.

Since a pacemaker cell receives no incoming signal, its contraction and relaxation depends only on its internal mechanisms. In order to have a periodic heartbeat, these internal mechanisms must make the $Ca^{2+}$ concentration of the cytoplasm periodic with respect to time. In this project, we will use two different model, a continuous model and a stochastic model, to simulate the change of $Ca^{2+}$ concentration is a pacemaker cell. We will then study the conditions under which the $Ca^{2+}$ concentration is periodic.

## 2 Preliminaries: Calcium-induced calcium release

The intracellular concentration of ionized calcium is roughly 100 nM within a typical cell, while the calcium concentration of the extracellular fluid is approximately $10^6$ nM. Past experiments showed that heart muscle will not continue to beat in the absence of external $Ca^{2+}$. It suggests that there are channels on the membrane of a cardiac cell that allows external $Ca^{2+}$ to enter the

cell. However, it is estimated that not enough $Ca^{2+}$ comes from this source. Some experiments suggested that there are intracellular Calcium stores, called the Endoplasmic Reticulum (ER), and when external $Ca^{2+}$ passes through the membrane, it triggers a release of the $Ca^{2+}$ stored in the ER. This process is called Calcium-induced calcium release.

# 3 Continuous Model

## 3.1 Model

Figure 1 is the model we employed to simulate the $Ca^{2+}$ concentration in a pacemaker cell. The Endoplasmic Reticulum is split into two compartments. $Ca^{2+}$ enters the ER through Compartment 2 and leaves the ER through Compartment 1. There are five independent $Ca^{2+}$ flows in our model. The flow from Compartment 1 to the cytoplasm depends on F and is therefore non-linear. The other 4 flows are all linear.

- C1*[out] is the amount of external $Ca^{2+}$ entering the cell.
- C2*[cyto] is the amount of $Ca^{2+}$ pumped out of the cell in unit time.
- C3*[cyto] is the amount of $Ca^{2+}$ pumped into the ER in unit time.
- F([cyto])*[comp1] is the amount of $Ca^{2+}$ released from the ER in unit time.
- C4*[comp2] is the amount of $Ca^{2+}$ transferred from one compartment of the ER to another in unit time.

Note: The notation $[\cdot] is the amount of \mathrm{Ca}^{2+}$ in that section and has unit nMol (nanomoles). For example, [cyto] is the number of nanomoles of $Ca^{2+}$ in the cytoplasm (not including the ER). C1, C2, C3, C4 are all constants.

As previously stated, the $Ca^{2+}$ concentration in extracellular fluids is approximately 1000 times larger than that in the cell. Due to this large ratio, the amount of $Ca^{2+}$ passing through the membrane into and out of the cell has little effect on the $Ca^{2+}$ concentration in extracellular fluids. Therefore, we assume [out], the concentration of extracellular fluids to be a constant in our model.

## 3.2 Systems of ODE

Based on our model, we can derive a system of ODEs. To simply the equations, we replace [cyto], [comp1], [comp2] with x, y, z respectively. Since C1 and [out] are both constants, we will also replace C1*[out] with $\alpha$.

- $\frac{dx}{dt} = \alpha - (C2 + C3) * x + F(x) * y$
- $\frac{dy}{dt} = C4 * z - F(x) * y$
- $\frac{dz}{dt} = C3 * x - C4 * z$

To simply subsequent calculations, we assign real values to the constants. Let $\alpha = 1$ and C2 = C3 + C4 = $\frac{1}{4}$. Then the equations become:

- $\frac{dx}{dt} = 2 - \frac{1}{2}x + F(x)y$

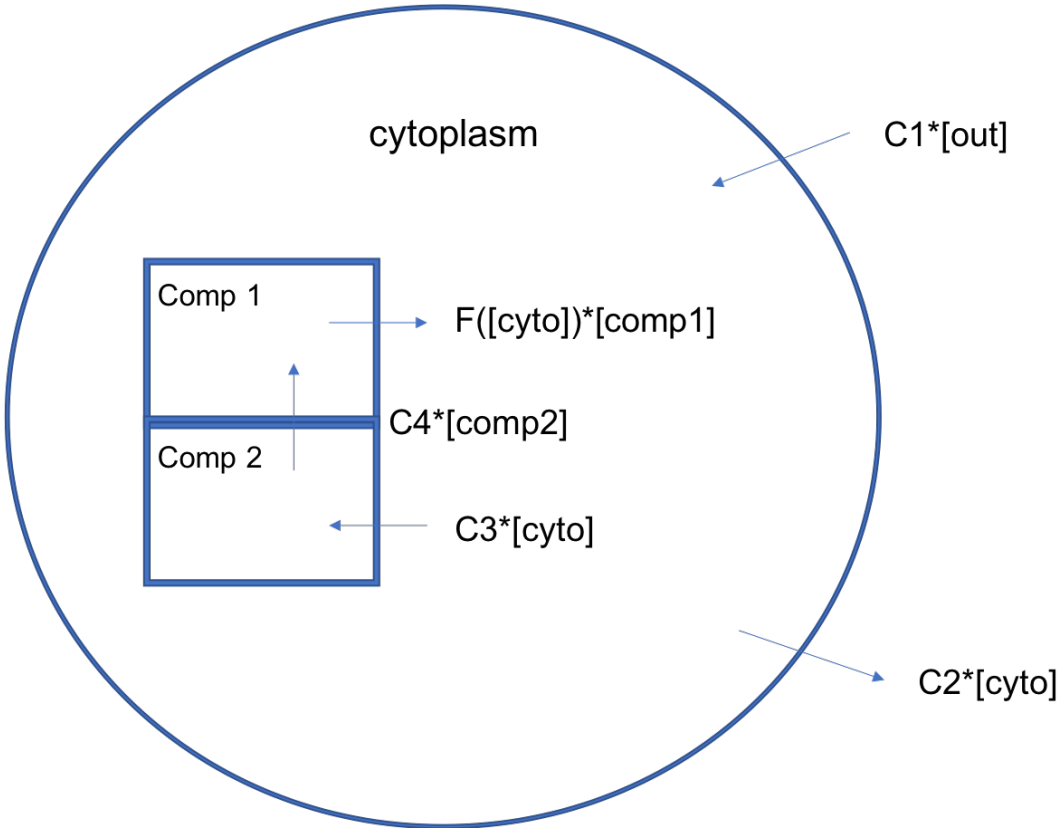



Figure 1

- $\frac{dy}{dt} = \frac{1}{4}z - F(x)y$
- $\frac{dz}{dt} = \frac{1}{4}x - \frac{1}{4}z$

### 3.3 Steady State

The system reaches the steady state when $\frac{dx}{dt} = \frac{dy}{dt} = \frac{dz}{dt} = 0$. Therefore we have:

- $2 - \frac{1}{2}x + F(x)y = 0$
- $\frac{1}{4}z - F(x)y = 0$
- $\frac{1}{4}x - \frac{1}{4}z = 0$

The solution to the steady state is

- $x_0 = 8$
- $y_0 = \frac{2}{F(8)}$
- $z_0 = 8$

## 3.4 Stability at the Steady State

In this section, we examine the stability of the system at the steady state. We further assume that F is a sigmoid function with the following expression.

$$F(x) = \frac{(\frac{x}{M*V})^n}{1+(\frac{x}{M*V})^n} \qquad \text{where V is the volume of the cell excluding the ER.}$$

We include the volume V in the function so that F is a function on the concentration of $Ca^{2+}$ instead of the amount of $Ca^{2+}$ in the cytoplasm.

We first linearize the ODEs at the steady state point. Since $\frac{dx}{dt}, \frac{dy}{dt}, \frac{dz}{dt}$ are all differentiable, we use the Jacobian matrix presented below to approximate are near the steady state point.

$$J = \begin{pmatrix} -\frac{1}{2} + \frac{2F^{'}(8)}{F(8)} & F(8) & 0 \\ -\frac{2F^{'}(8)}{F(8)} & -F(8) & \frac{1}{4} \\ \frac{1}{4} & 0 & -\frac{1}{4} \end{pmatrix},$$

The jacobian matrix provides a linear approximation around the steady state.

$$\frac{du}{dt} = \begin{pmatrix} -\frac{1}{2} + \frac{2F^{'}(8)}{F(8)} & F(8) & 0 \\ -\frac{2F^{'}(8)}{F(8)} & -F(8) & \frac{1}{4} \\ \frac{1}{4} & 0 & -\frac{1}{4} \end{pmatrix} * \begin{pmatrix} x - x_0 \\ y - y_0 \\ z - z_0 \end{pmatrix} \qquad \text{where } \frac{du}{dt} = \begin{pmatrix} \frac{dx}{dt} \\ \frac{dy}{dt} \\ \frac{dz}{dt} \end{pmatrix}$$

Denote $u = (x, y, z)^T$ The linear system is said to be stable at $u_0$ if $\forall \epsilon > 0, \exists \delta > 0$ such that every solution $u(t)$ having initial conditions within distance $\delta i.e. \parallel u(t_0) - u_0 \parallel < \delta$ of the equilibrium remains within distance $\epsilon$ i.e. $\parallel u(t) - u_0 \parallel < \epsilon$. And it is said to be asymptotically stable if it is stable and, in addition, there exists $\delta_0$ such that whenever $\parallel u(t_0) - u_0 \parallel < \delta_0$, then $u(t) \to u_0$ as $t \to \infty$. According to the stability theory, if all eigenvalues of J, the Jacobian at the equilibrium point, have negative real parts, then the solution is asymptotically stable; if at least one of the eigenvalues of the matrix has positive real part, then the equilibrium point is unstable.

Therefore, to acquire periodicity in x, the system has to be unstable at the steady state $u_0$, that is, the Jacobian matrix J must have at least one eigenvalue with positive real part. I calculated the eigenvalues of J with different values of n and M. The result is shown in Figure 2. The horizontal axis is the value of n and the vertical axis is the value of M. The yellow part are the pairs (n, M) that make the steady state unstable and the blue part are the pairs that make it stable (the boundary of the two colors is considered to be yellow).

As mentioned above, having at least one eigenvalue with positive real part is only a necessary condition. Having instability at the steady state doesn't guarantee periodicity of the system. The eigenvalue analysis above only describes the local behavior of the system and tells us nothing about the global properties. However, if F is the Sigmoid function as we assumed in this section, this eigenvalue analysis accurately predicts the periodicity of the system. For example, $\{n = 4, M = 2.7\}$ is on the boundary. And the graphs in Figure 3 show that the system is periodic when $M < 2.7$ and converges to the steady state when $M \geq 2.7$. (Figure 3 are the graphs of the $Ca^{2+}$ concentration of the cytoplasm with respect to time)

Another result from the tests is the larger n (or M) is, the larger the magnitude of the peak and the length of the interval between two consecutive peaks are. Here I present two examples in Figure 4 (fixing n and changing M in the first one, and fixing M and changing n in the second one), but the result is true for all (n, M).

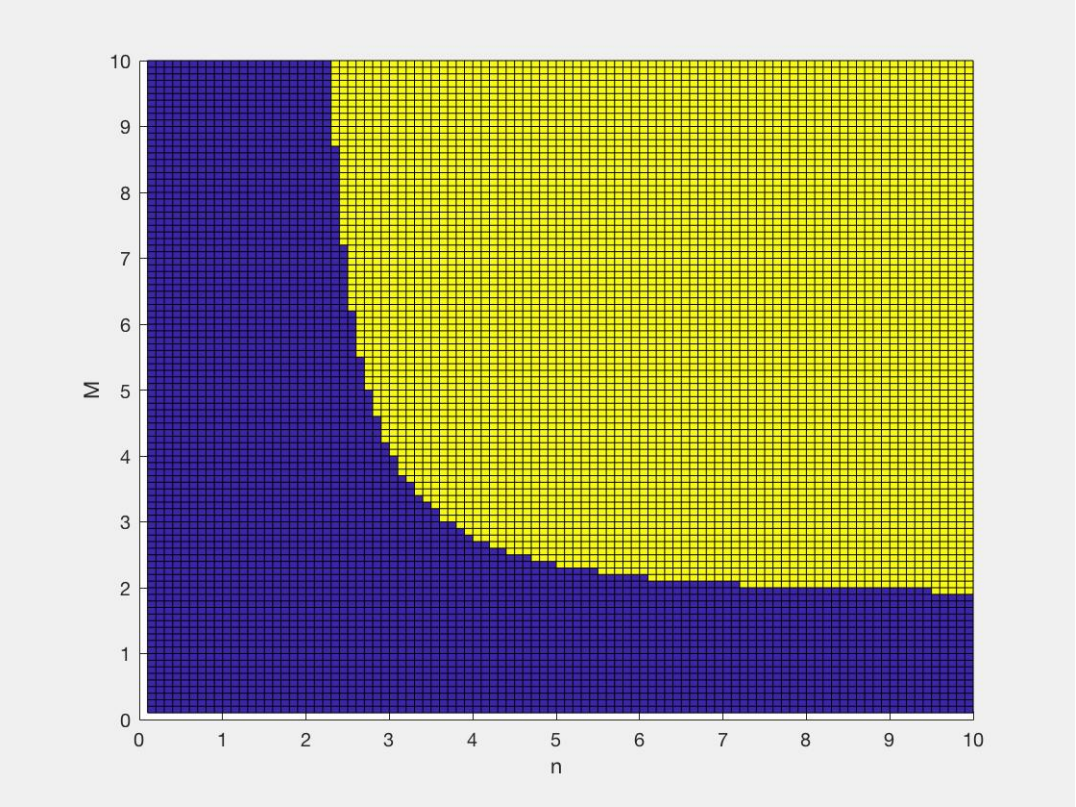



Figure 2

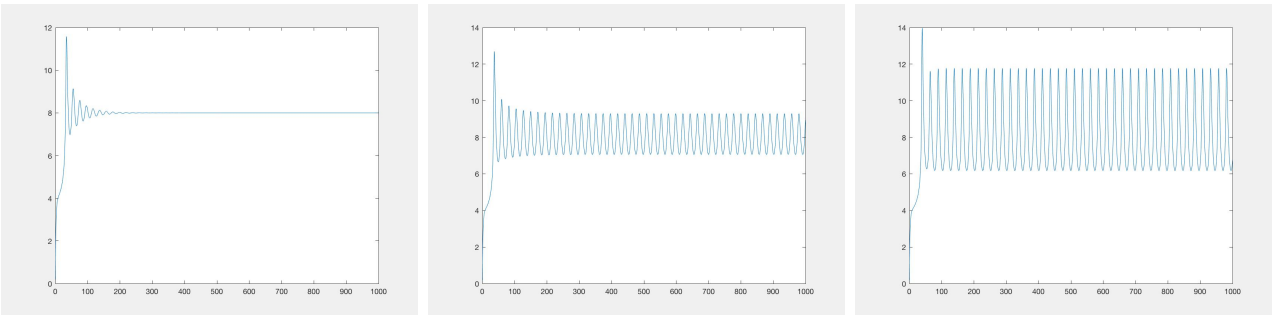
## 3.5 Limit Case

The result of the eigenvalue analysis suggests that we acquire periodicity when n and M are large enough. And both the peak and the period of the function $x(t)$ become bigger when we enlarge n or M. It is natural to ask what happens when $n \to \infty$ (F becomes 0 when $M \to \infty$ and is therefore meaningless).

The system can be solved analytically. When $n \to \infty$, F converges pointwise to the step function $\psi$ defined by

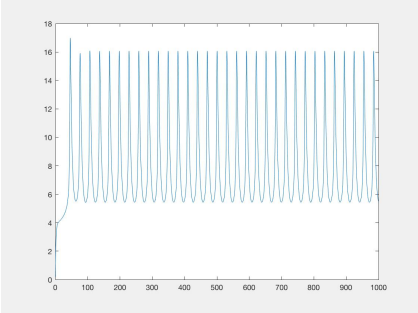
$$\psi(x) = 1_{[N,\infty]} \qquad \text{where N=MV}$$

Note that $\psi(N)$ is in in fact 1/2, but changing the value of $\psi$ at one point makes no difference to

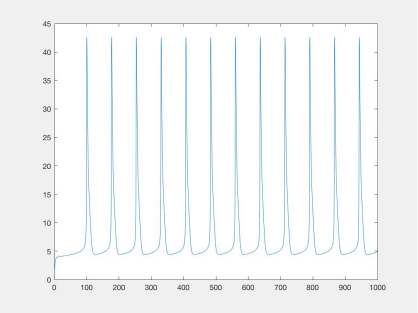


n=4, M=2.6 n=4, M=2.7 n=4, M=2.8

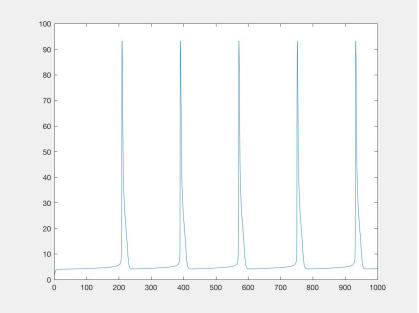
Figure 3



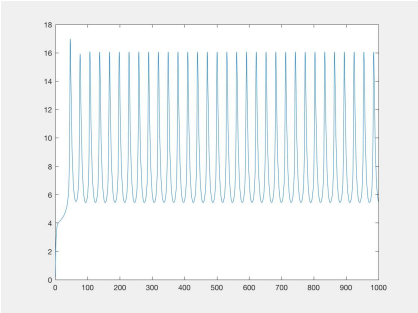
n=4, M=3



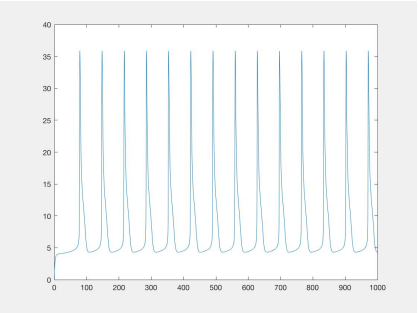
n=4, M=4



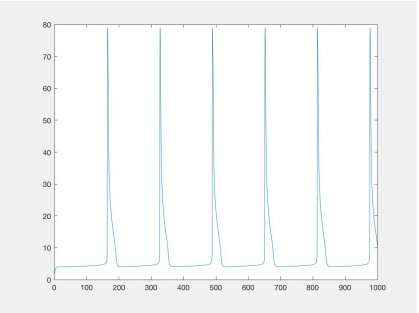
n=4, M=5



n=4, M=3



n=5, M=3



n=6, M=3

Figure 4

the ODEs.

Replacing the function F in the ODE system in section 3.2, we get:

- $\frac{dx}{dt} = 2 - \frac{1}{2}x + \psi(x)y$
- $\frac{dy}{dt} = \frac{1}{4}z - \psi(x)y$
- $\frac{dz}{dt} = \frac{1}{4}x - \frac{1}{4}z$

We start with the initial condition $x(0) = y(0) = z(0) = 0$. Then we have:

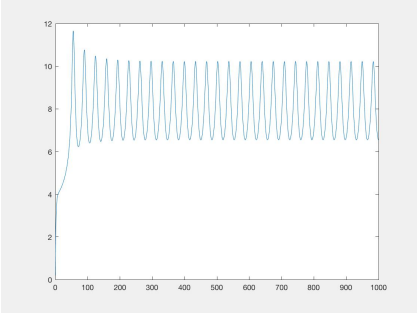
- $\frac{dx}{dt} = 2 - \frac{1}{2}x$
- $\frac{dy}{dt} = \frac{1}{4}z$
- $\frac{dz}{dt} = \frac{1}{4}x - \frac{1}{4}z$

The Initial Value Problem $\frac{dx}{dt} = 2 - \frac{1}{2}x, x(0) = 0$ gives us the solution $x(t) = 4 - 4e^{-\frac{1}{2}t}$. Substituting x into the IVP of z, we get $z(t) = 4 + 4e^{-\frac{1}{2}t} - 8e^{-\frac{1}{4}t}$. Finally, substituting both x and z into the IVP of y, we get $y(t) = t - 2e^{-\frac{1}{2}t} - 8e^{-\frac{1}{4}t} + 10$

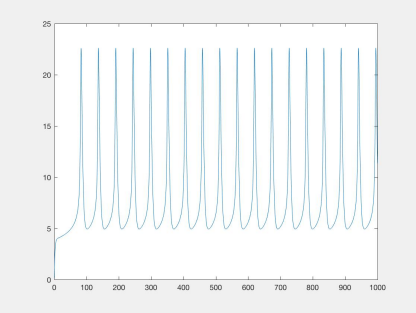
Notice that x is always smaller than 4. Therefore, $\psi$ will not switch to 1 if $N \geq 4$. i.e. if $M \geq 4, x \to 4ast \to \infty$. Note that this is not an equilibrium. As $t \to \infty, z \to 0$ and $y \to \infty$. In other words, $Ca^{2+}$ accumulates in Compartment 1.

When $0 < N < 4$, $x = 4$ when $t = -2ln(1 - \frac{N}{4})$. The switch is then turned on and we get the new ODEs:

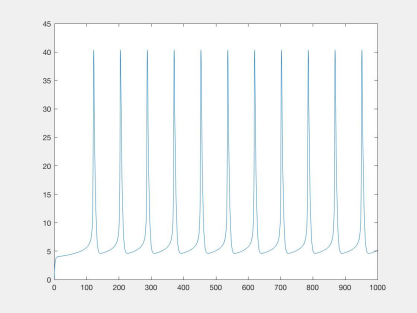
- $\frac{dx}{dt} = 2 - \frac{1}{2}x + y$



Continuous, M=4



Continuous, M=5



Continuous, M=6

- $\frac{dy}{dt} = \frac{1}{4}z - y$
- $\frac{dz}{dt} = \frac{1}{4}x - \frac{1}{4}z$

The new initial values are $x(t_1), y(t_1), z(t_1)$ where $t_1 = -2ln(1 - \frac{N}{4})$. However, the new system is too complicated to solve by hand. Therefore, I used MATLAB to simulate the new system. It turns out the system always converge to the steady state when $0 < N < 4$. I conclude that the system cannot have periodic oscillations when F is the step function.

# 4 Stochastic Model

## 4.1 Model

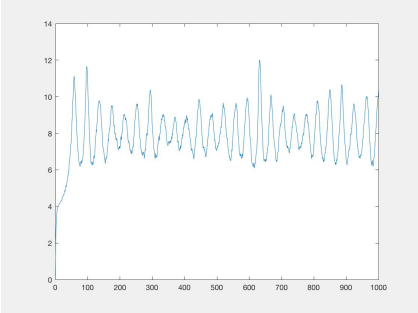
In this model, we replace the $Ca^{2+}$ flow from Compartment 1 to Cytoplasm with a probabilistic structure. Imagine there are 1000 ion channels connecting Compartment 1 and the cytoplasm. Each channel is either open or closed. An open channel has probability $\alpha$ to close (implies probability $1 - \alpha$ to remain open), and a closed channel has probability $\alpha(\frac{x}{MV})^n$ to open. The value of $\alpha$ has no impact on the output of this model. I will show later that we only care about the ratio of the two probabilities. An open channel is considered as a pump with the rate of $\frac{y}{1000}$ nMols per unit time.

The intuition behind this model is to use the ratio of the two probabilities to achieve the effect of F in our first model. At any particular time $t_0$, we have a fixed $x_0$. The number of open and closed channels reach an equilibrium when the expected number of channels going from open to close equals the expected number of channels going from close to open. Let $\lambda_1, \lambda_2$ be the number of open and closed channels respectively. Then the probabilistic structure reaches an equilibrium when

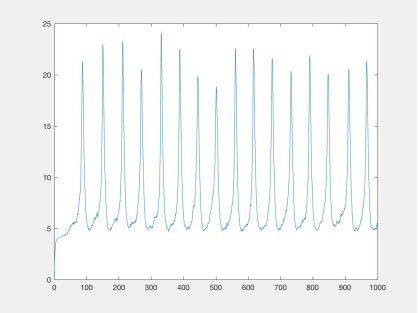
$$\alpha\lambda_1 = \alpha(\frac{x_0}{MV})^n\lambda_2$$

Therefore, $\frac{\lambda_1}{\lambda_2} = (\frac{x_0}{MV})^n$. Since $\lambda_1 + \lambda_2 = 1000$, we have $\lambda_1 = \frac{1000(\frac{x_0}{MV})^n}{1+(\frac{x_0}{MV})^n}$ and therefore the $Ca^{2+}$ flow rate is $\frac{(\frac{x_0}{MV})^n}{1+(\frac{x_0}{MV})^n}$ nMols per unit time.

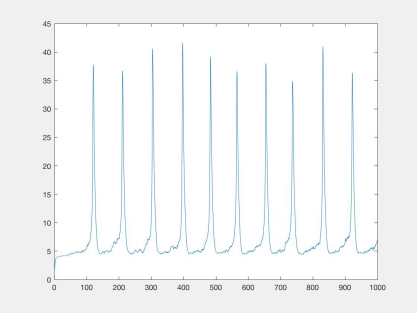
Notice that the expected $Ca^{2+}$ flow is exactly the value of F in our continuous model. Therefore, we expect the output of this model to be similar to that of the continuous model. This turns our to be true. In particular, the outputs of the two models are more similar when we choose large n or M. The graphs in Figure 5 is an example of this phenomenon. In this test, we let $n = 3$ and change M.



Stochastic, M=4



Stochastic, M=5



Stochastic, M=6

Figure 5

# 5 Future studies

- In section 3.4, I stated for a general F, the instability of the equilibrium point does not guarantee a periodic x. But with the specific choice of F we used, the instability seems sufficient. However, I don't know if this is the case for other Sigmoid functions. I haven't had time to test with other choices of F, but it seems that the reason our F worked is .

  I expect the result to hold for some other Sigmoid functions, such as the Logistic Function and the Hyperbolic Tangent Function.

- In this project, I used both models to graph the amount of $Ca^{2+}$ in the cytoplasm. I didn't look at the behavior of the independent ion channels in the stochastic model. Notice that the $Ca^{2+}$ concentration increases and decreases rapidly. Therefore, it would be interesting to see how an independent ion channel behaves when the $Ca^{2+}$ concentration is increasing or decreasing. Does it switch on and off rapidly or does it stay in one state?

# 6 Acknowledgement

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# References

[1] Charles S. Peskin. MATHEMATICAL ASPECTS OF HEART PHYSIOLOGY. Courant Institute of Mathematical Sciences, 1975