Synchronous Calcium Induced Calcium Release (CICR) in a Multiple Site Model of the Cardiac myocyte

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The behavior of the muscle of the heart depends upon changes in free Ca^{2+} concentration in the sarcoplasm and cytoplasm of a ventricular myocyte. We present a model of the free Ca^{2+} concentration across twenty components: ten adjacent sarcoplasmic/cytoplasmic junctions. It incorporates diffusion both in the cytoplasm and the sarcoplasmic reticulum. The model shows qualitative agreement with experimental observations on the effects of altering the rate of calcium input to a cell, the efficiency of the SERCA pump, the threshold setting for CICR, and the rate of a cells calcium loss. In addition it displays spontaneous recurring calcium peaks in the presence of sufficient extracellular calcium, and these peaks are seen to synchronize across the junctions. The model confirms the importance the SR by demonstrating that this robust synchronization across sites does not occur in the absence of SR diffusion.

1. Introduction

Ca^{2+} serves as the predominant ionic messenger within the cardiac myocyte. As a result, Ca^{2+} plays a significant role in controlling Excitation Contraction Coupling (ECC). This is a process by which an increase of cytoplasmic calcium near a particular type of receptor on the sarcoplasmic reticulum results in a release of calcium into the cytoplasm. The receptors responsible for both ECC and sequestering of calcium in the SR are clustered at junctional areas called t-tubules distributed along the length of the myocyte. Though well studied, the literature currently contains few, if any, models that qualitatively describe the synchronicity of Ca^{2+} release across junctional sites within the myocyte.

Most mathematical models, such as those studied by Zahradnikova,[1] Faber,[2] Greenstein,[3] Dupont,[4] and others (Falke,[5] Shannon,[6] Tang,[7] Hinch,[8] Spiro,[9] Keizer,[10] Jafri,[11] Tuan[12]) describe the role of Ca^{2+} in ECC by relying on so-called calcium release units. These units include the cardiac t-tubule and a closely juxtaposed junctional sarcoplasmic reticulum (JSR). Ca^{2+} can enter the cytoplasm as the result of the opening of a Ca^{2+} channel in the t-tubule. The entry of Ca^{2+} into the cytoplasm may then lead to Ca^{2+} release from a nearby SR junction.[13] This process, termed Calcium Induced Calcium Release (CICR), depends on the movement of Ca^{2+} throughout the cell and influx of Ca^{2+} into the cell.[14] In addition, myocytes utilize Ca^{2+} leaks to maintain homeostasis. These leaks emanate from both the SR into the cytoplasm and from the cytoplasm into the extra-cellular medium (ECM).

The sarcoplasmic reticulum (SR) plays a pivotal role in Ca^{2+} homeostasis by sequestering Ca^{2+}, and is implicated in both normal and abnormal heart cell function[15][16].[17] The SR accomplishes this requisition by activating a Ca^{2+}ATPase pump, termed the SERCA pump, and by releasing Ca^{2+} via both passive and active means. These Ca^{2+} releases can only occur when the Ca^{2+} concentration in the SR reaches a threshold level.[18] A physiologically observed time lag exists between the time when the region of the SR closest to the site of the spark undergoes CICR and when the region of the SR furthest from the spark undergoes CICR.[19] Similarly, because Ca^{2+} moves through the SR as a wave,[20] the SR Ca^{2+} concentration is not equal at every point of the SR in the time directly following a Ca^{2+} spark. Calcium waves in the SR have also been observed directly.[21] Physiological studies show that in time the oscillations in Ca^{2+} concentration of both the SR and the cytoplasm synchronize.[22]

Whereas previous attempts at modeling Ca^{2+} dynamics within a myocyte have succeeded in accounting for calcium release units and other complexities of this system, no previous models demonstrate this experimentally observed synchronization. Our model consists of a set of twenty ordinary differential equations and is based on a model first developed by B. V. Williams.[23] This model differs from others by coupling ten cytoplasm-SR junctions that show an initial lag in the onset of CICR dependent upon distance from Ca^{2+} input site as well as an eventual synchronization of Ca^{2+} concentration oscillations. Each junctional model is based on an early model of Goldbeter *et al.*[24]

The coupled mathematical model was tested against four research findings that demonstrated different outcomes based upon experimental vari-

ations that correspond to changes in parameters or initial conditions of heart cell activity. First, we confirmed the writings of Klabunde[25] by concluding that the amount of input Ca^{2+} controlled the ability of the heart cell to undergo ECC. Second, we confirmed the findings of Jiang *et al*[26] by concluding that reducing the SERCA pump activity in the SR led to heart failure. In this study, heart failure was measured as a cessation of synchronous Ca^{2+} oscillations in both the SR and the cytoplasm. We further confirmed the findings of Marks *et al*[27,28] by concluding that changing the threshold at which RyR channels embedded in the SR membrane release Ca^{2+} similarly led to heart failure. Finally, we confirmed the descriptions in Marin-García's text[16] which link an increased Ca^{2+} leak rate (from the cytoplasm to the ECM) to heart failure.

2. Model Formulation

The model described here includes the following features:

(i) variable Ca^{2+} concentration in both the cytoplasm and the sarcoplasmic reticulum
(ii) uptake of Ca^{2+} from the cytoplasm to the SR via the SERCA pump
(iii) discharge of Ca^{2+} from the SR to the cytoplasm via CICR
(iv) passive diffusion within both the cytoplasm and the SR
(v) external input of Ca^{2+} to the cytoplasm

There are many molecular pumps and exchangers besides these, both from the SR to the cytoplasm and from the cytoplasm to the cell exterior. These are not modeled explicitly but summarized in two single linear leaks from the SR to the cytoplasm and from the cytoplasm out of the cell. This model assumes that a portion of the calcium dynamic can be captured by a relatively simple local model coupled with itself to include multiple local t-tubule/SR junctional sites. It also treats all the SERCA pumps in one site as a single unit with one over-riding dynamic, and does the same with the CICR pumps.

Our model consists of twenty coupled ordinary differential equations describing changes in the concentrations of both cytoplasmic (C) and sarcoplasmic (S) Ca^{2+} concentrations in a cardiac myocyte. Fig. 1 illustrates the interactions of these components. The arrows denote the movement of Ca^{2+} throughout the myocyte. The Ca^{2+} input to the system is denoted by the R arrow. Ca^{2+} is added to the cell, which then travels through the cytoplasm as a wave. As the Ca^{2+} reaches the different JSRs, the Ca^{2+}

threshold for CICR is reached. We assume that the makeup of both the cytoplasm and the SR are uniform throughout.

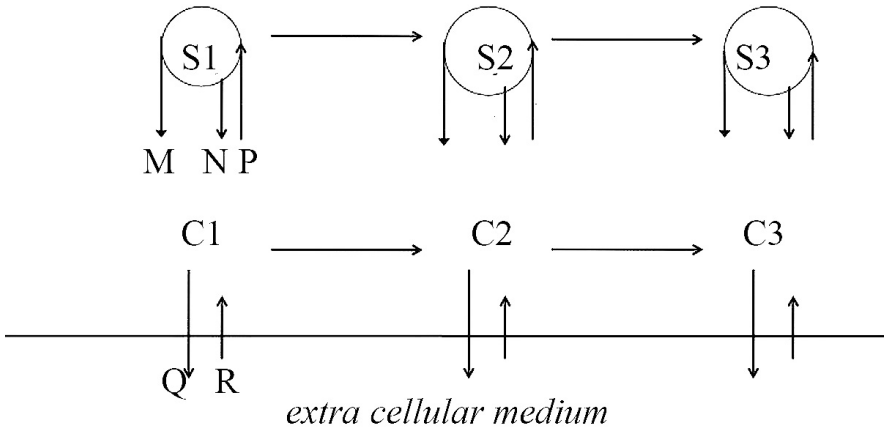

Fig. 1. The box model pictures three of the ten junctions in the model, which includes CICR from the SR junction denoted M, SERCA uptake P, other leaks N from the SR, input R from the extracellular medium and discharge Q from cytoplasm to the extracellular medium.

The dynamics of calcium passing between the sarcoplasmic reticulum and the cellular region near a t-tubule have been studied extensively and expressed in various ways. In this model we use two quantities, C and S, to represent the concentrations of Ca^{2+} in the cytoplasm (C) and within the sarcoplasmic reticulum (S) in the region near a t-tubule, respectively indexed by d, as we consider ten of these junctions. The changes in cytoplasmic and SR Ca^{2+} concentrations can therefore be represented by a series of twenty ordinary differential equations. The definitions of the parameters are given along with their physiologically measured default values in Table 1. All parameters are positive and taken from Goldbeter,[24] and Williams.[23]

For each of these pairs, (C_d, S_d), we take into account the SERCA pump that sequesters calcium in the SR, the RyR that is responsible for calcium induced calcium release from the SR into the cytoplasm, and passive diffusion within both the cytoplasm and the SR. All other dynamics are summarized by linear leaks. For each pair we have the following equations.

$$C'_d = i - \frac{V_u C_d^u}{K_u^u + C_d^u} + \frac{V_{ra} S_d^r C_d^a}{(K_r^r + S_d^r)(K_a^a + C_d^a)} + k_1 S_d - q(C_d - C_{d+1} + q(C_{d-1} - C_d) - eC_d \quad (1)$$

C'_d = (Input from cell exterior) - (SR uptake via SERCA pump)+ (CICR release from SR) + (Leak from SR) + (Diffusion within cytoplasm) - (leak to exterior)

$$S'_d = \frac{V_u C_d^u}{K_u^u + C_d^u} - \frac{V_{ra} S_d^r C_d^a}{(K_r^r + S_d^r)(K_a^a + C_d^a)} - k_1 S_d - r_1(S_d - S_{d+1} + r_1(S_{d-1} - S_d) \quad (2)$$

S'_d = (SR uptake via SERCA pump)- (CICR release from SR) - (Leak to cytoplasm) + (Diffusion within SR)

Table 1. Default Parameter Values

Parameter	$Symbol$	$DefaultValue$
Calcium influx form the ECM into the intracellular space	i	3 μM/s
Max rate of calcium uptake from the cytoplasm into the SR	V_u	65 μ M/s
Max rate of calcium release from the SR into the cytoplasm	V_{ra}	500 μ M/s
The threshold constant for calcium uptake into the SR	K_u	1 μ M
The threshold constant for calcium release from the SR into the cytoplasm	K_r	2 μ M
The threshold constant for activation of the SR calcium release	K_a	0.9 μ M
The passive leak form the SR into the cytoplasm	k_1	1/s
Calcium efflux from the cytoplasm to the ECM	e	9/s
Rate of calcium transport between the cytosolic calcium components	q	0.3/s
Rate of calcium transport between the SR calcium components	r_1	0.2/s
The Hill coefficient for calcium uptake	u	2
The Hill coefficient for calcium release	r	4
The Hill coefficient for activation of calcium release	a	2

2.1. *Input from cell exterior*

The first term of Eq. 1, i , describes the influx of Ca^{2+} from the ECM into the intracellular space. For the numerical experiments in this study, i is taken to be constant.

2.2. *SR uptake via SERCA pump*

The second term, $\frac{V_u C_d^u}{K_u^u + C_d^u}$, utilizes a Hill function of degree u to model the rate of Ca^{2+} uptake from the cytoplasm into the SR Ca^{2+} store. Although this model is based on that of Goldbeter,[24] the form of this term is widely agreed upon and present in many models[6 9].[8]

2.3. *CICR release from SR*

The third term, $\frac{V_{ra} S_d^r C_d^a}{(K_r^r + S_d^r)(K_a^a + C_d^a)}$, uses two Hill functions, of degree r and a, respectively, to model the rate of Ca^{2+} release from the SR via a process activated by the cytoplasmic Ca^{2+} concentration. The second of the two Hill functions, that of degree a, denotes the degree of cooperativity of this activation process. Here the model takes its inspiration from a model of Goldbeter.[24]

Other authors use a different term to reflect the action of both the CICR pump and the SERCA pump. This term as in Shannon[6] is the difference between a forward process that releases Ca^{2+} from the SR into the cytoplasm, and the reverse process modeled in the usual way by the SERCA pump term described above. In those models, the forward process gives a larger rate when the Ca^{2+} concentration in the cytoplasm is higher, as is required by CICR. However the forward process in those models gives a lower rate when the Ca^{2+} in the SR is higher. This is not consistent with experimental observations (described in Gyorke,[29] Lukyanenko,[30] Hobai[31] and elsewhere, and summarized in Bers[32]) that report higher Ca^{2+} release when the SR concentration rises.

The functional form for this CICR pump in Goldbeter's model solves this problem, as the response rises with Ca^{2+} concentration in either the cytoplasm or the SR. See Williams' thesis[23] for a graphical representation of this functional response.

Some authors model the states of the CICR pumps (e.g. open, closed) separately[8 9 10] or incorporate more of the details of the chemistry, but the model studied here sacrifices some of the local complexity in order to couple multiple sites together.

2.4. *Leak from SR*

The fourth term, $k_1 S_d$, is the passive leak of Ca^{2+} from the SR into the cytoplasm. As stated before, this term is a proxy for a variety of other ways in which Ca^{2+} may move from the SR into the cytoplasm.

2.5. *Leak to exterior*

The final term of Eq. 1, $-eC_d$, models the passive leak of Ca^{2+} from the cytoplasm to the ECM. As stated before, this term is a proxy for a variety of other ways in which Ca^{2+} may leave the cytoplasm.

2.6. *Diffusion within SR and cytoplasm*

Each pair of a C and an S is interconnected not only within itself, but also with the preceding and succeeding C-S pairs. The next two terms of Eq. 1 and Eq. 2, either $-q(C_d - C_{d+1}$ or $q(C_{d-1} - C_d)$, respectively, represent the movement of Ca^{2+} within the cytoplasm and the SR. The t-tubules are assumed to be arranged in a sequence, and appropriate adjustments are made to these terms at the two ends of the sequence. These diffusion terms are taken from Williams.[23] Many models incorporate diffusion within the cytoplasm, but to our knowledge only Swietach *et al*[33] incorporates diffusion within the SR, which must also occur. The rate of diffusion within the SR has not been measured, but this constant would have to take into account not only that rate but the presumed distance between t-tubules. This models takes its constant from Williams' thesis,[23] but it would be misleading to suggest it was experimentally determined. It is comparable in magnitude to the diffusion constant for the cytoplasm.

3. Methods

Fig. 2 shows the synchronization of the Ca^{2+} concentration of the twenty different regions. The presence and stability of this phenomenon in the coupled system was the main result of the thesis of Williams.[23] The oscillations in Fig. 2 represent the oscillation of Ca^{2+} concentration in ten different cytoplasmic or SR regions. Each line represents a unique SR or cytoplasmic region. The Ca^{2+} concentration oscillations appear staggered initially but eventually synchronize. The initial conditions for Fig. 1 were the default parameters listed in Table 1. The default initial Ca^{2+} concentration levels for the twenty different regions are listed in Table 2 and were used to generate Fig. 2.

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chronization displayed in Figure 2 is robust and occurs across a range of parameter values and initial conditions.

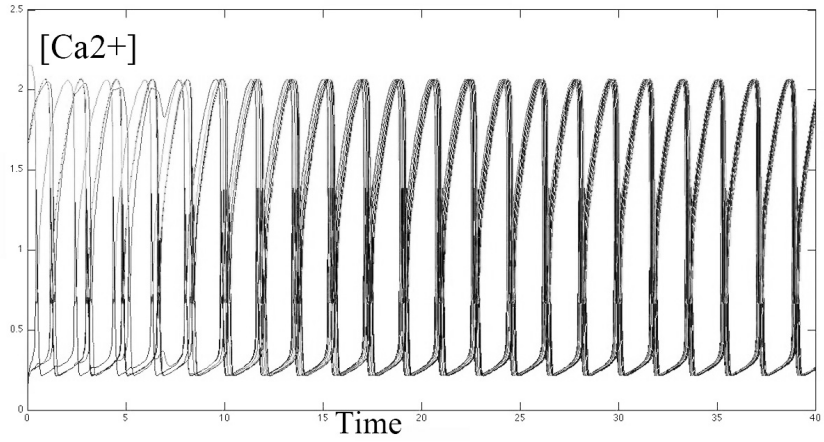

Fig. 2. This image depicts the baseline run of twenty quantities with parameters as in Table 1 and initial conditions as in Table 2.

Table 2. Default Initial Conditions

Region	Initial Value
C_1	0.1 μM
C_2 to C_{10}	0.06 μM
S_1	2.2 μM
S_2 TO S_{10}	1.7 μM

The model was then compared with four distinct results by altering the parameters associated with reported physiological experiments, described below.

(i) The initial Ca^{2+} concentrations of the twenty different regions were varied. Altering the initial Ca^{2+} concentrations of the twenty areas did not change the behavior of the observed baseline in Figure 2.
(ii) Lakatta *et al*[19] showed that the rate of Ca^{2+} influx directly affected the ability of the cardiac myocyte to undergo ECC. The value of the model parameter controlling calcium influx, i was varied from the default value

to determine the range in which sustained oscillations were observed.

(iii) Jiang *et al*[26] showed that reducing the activity of the SERCA pump leads to heart failure. The value of the model parameter controlling the rate of Ca^{2+} uptake, V_u was varied from the default value to determine the range in which sustained oscillations were observed.

(iv) Marks *et al*[27][28] propose that decreasing the threshold constant for SR Ca^{2+} release leads to heart failure. The value of the model parameter controlling the threshold constant for SR Ca^{2+} release, K_r was varied from the default value to determine the range in which sustained oscillations were observed.

(v) Marin-García[16] describes research reporting that an increased rate of Ca^{2+} leaving the cytoplasm led to heart failure. The value of the model parameter controlling the rate of Ca^{2+} removal from the cytoplasm to the ECM, e was varied from the default value to determine the range in which sustained oscillations were observed.

All model simulations were run on MATLAB version 2010(b) using solver ode113. Unless otherwise specified, all parameters and initial conditions were set to the default values given in Table 1 and Table 2.

4. Results

4.1. *Propagation of calcium release*

For a large range of parameter choices the persistent propagation of calcium waves was observed, and these tended to synchronize across all of the (C_d, S_d) pairs, representing a cell whose calcium cycle is synchronized in time across the length of the myocyte. Altering the initial Ca^{2+} concentrations of the twenty areas did not change our observed baseline. The presence and stability of this phenomenon in the coupled system was the main result of the thesis of Williams.[23] Loosely speaking, the cell is "contracting" when this happens, as observed in experiments[34].[21] Synchronous firing is also observed.[22] These spontaneous recurring discharges have been implicated in cardiac pathology.[19] Recurring spontaneous traveling waves have also been observed[35][36][20].[14] This model does not display a noticeable traveling wave, most likely because it would require a much larger number of (C_d, S_d) pairs to simulate the length of a cell. But it clearly displays the regenerative pulse seen in experiments. Initial conditions for the baseline run in Figure 2 were quite similar. Figure 3 below shows synchronization even when the initial conditions vary greatly across sites.

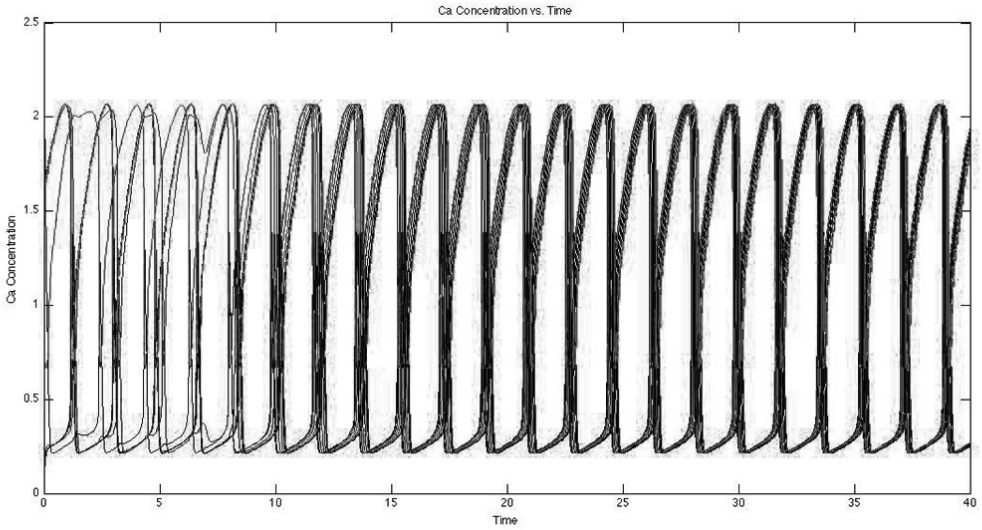

Fig. 3. Slower synchronization with less homogeneous initial conditions. All parameters and initial conditions are as in Figure 2 except $C_1 = 1$, $C_9 = C_{10} = .000005$.

4.2. *Importance of diffusion in the SR*

The parameter r controlling diffusion in the SR is a key parameter in this model. Without it, synchronization is lost, as seen in Figure 4. In this figure, the only synchronized sites are those with identical initial conditions.

4.3. *The Effect of Changing i on CICR*

Klabunde[25] writes that the concentration of Ca^{2+} entering a cardiac myocyte directly influences both CICR and myocyte contractions. Any model that attempts to numerically describe Ca^{2+} dynamics in a cardiac myocyte must therefore show a dependence on the concentration of influxing Ca^{2+} in order to be a viable, working model. As shown in Figure 5, increasing the value of i, the influxing Ca^{2+} in our model, leads to a cessation of CICR. Because CICR has been shown to be the central mechanism of ECC, a cell that can no longer perform CICR will no longer undergo ECC. Similarly, decreasing the value of i leads to a complete cessation of CICR and therefore to termination of ECC. Our results are therefore consistent with Klabunde's text.

Figure 5 shows the effect of changing the influx of calcium on the initi-

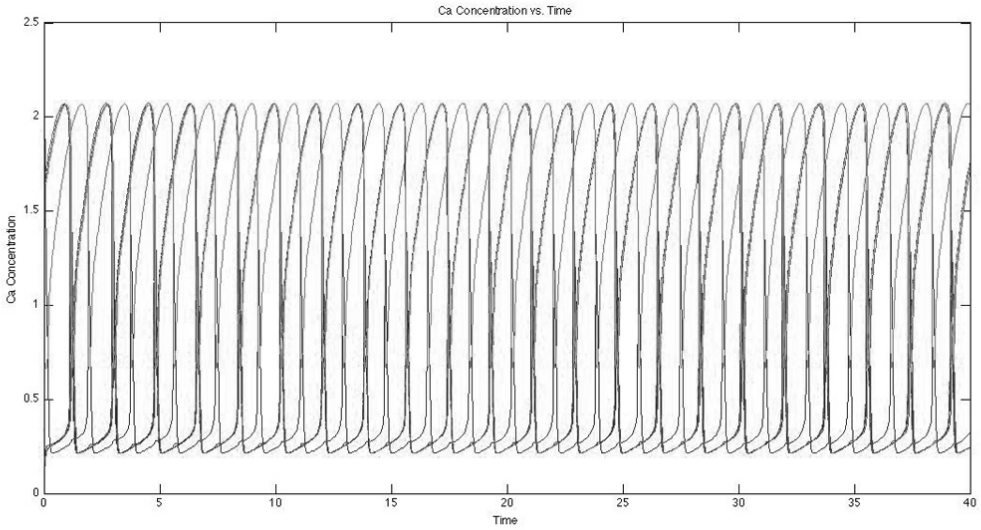

Fig. 4. No synchronization without SR transport. All parameters and initial conditions as in Figure 3, except the rate of calcium transport in the SR, r_1, is set to zero.

ation, propagation, and synchronization of Ca^{2+} concentration oscillations in both the cytoplasm and the SR. The figure shows the lack of CICR when i is substantially below or above limits of sustained, synchronous oscillations. Figure 5 shows that when the value of i is between the lowest value at which sustained, synchronous oscillations occur and the value at which flat lining begins the initial, asynchronous Ca^{2+} concentration oscillations in both the cytoplasm eventually flat line. Figure 5 shows both the lowest and highest values of i for which sustained, synchronous Ca^{2+} concentration oscillations in both the cytoplasm and the SR develop. When the value of i is between the highest value at which sustained, synchronous oscillations occur and the value at which flat lining begins, asynchronous Ca^{2+} concentration oscillations in both the cytoplasm and the SR develop. Finally, Fig 5 illustrates the lack of CICR when i is substantially above the upper limit of sustained, synchronous oscillations. The parameter ranges across which sustained, synchronous Ca^{2+} concentration oscillations occur are presented in Table 3. What is observed in Figure 5 is a Hopf bifurcation, with bifurcation parameter i.

4.4. *Effect of Changing SERCA Pump Activity on CICR*

In the second experiment, the value of V_u was varied from the default value to correspond to the experiments of Jiang *et al*,[26] who demonstrated that decreasing the activity of the SERCA pump directly influences both CICR and myocyte contractions. Specifically, they found that heart failure resulted from a semi-deactivation of the SERCA pump. Therefore, only a model that successfully incorporates this finding represents a truly viable, working model. As shown in Figure 6, decreasing the value of V_u, the maximum rate of Ca^{2+} uptake form the cytoplasm into the SR, leads to a cessation of CICR. As stated above, a cell that can no longer perform CICR will no longer undergo ECC, a process the heart depends upon to maintain normal function. Similarly, we examined how increasing the value of V_u impacted CICR. We found that V_u could not be increased beyond a certain point and still maintain CICR, as increasing V_u by too much led to a complete cessation of CICR. Our results are therefore consistent with the findings of Jiang *et al*.

The parameter V_u is also a Hopf bifurcation parameter and the results of varying it are similar to Figure 5, displaying the lack of CICR when V_u is substantially below the lower limit or above the upper limit of sustained, synchronous oscillations. When the value of V_u is between the lowest value at which sustained, synchronous oscillations occur and the value at which flat lining begins, the initial, asynchronous Ca^{2+} concentration oscillations in both the cytoplasm eventually flat line. The parameter ranges across which sustained, synchronous Ca^{2+} concentration oscillations occur are presented in Table 3.

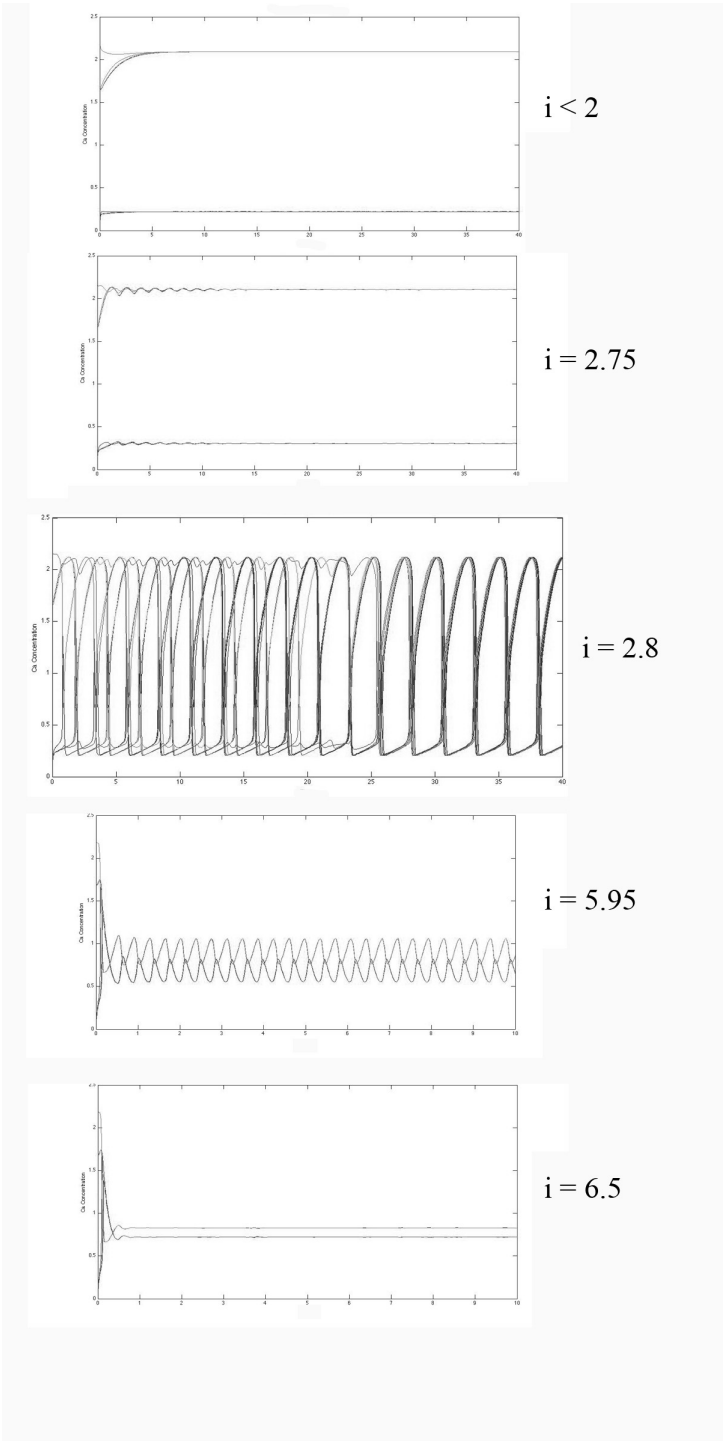

Fig. 5. The Effect of Changing i on CICR

4.5. *Effect of Changing the SR Ca^{2+} Release Threshold on CICR*

Researchers have shown that there is an increase in Ca^{2+} passing from the SR to the cytoplasm in myocytes of animals in chronic heart failure[38,39] which Shannon *et al*[6] attribute to RyR disregulation, based on experiments of Marx[28] and others. Marks *et al*[27,28] demonstrated that increasing the rate of the passive Ca^{2+} leak from the SR into the cytoplasm led to heart failure. Much like the two previous cases, only a model that successfully incorporates this third finding represents a truly viable, working model. As shown in Figure 7, decreasing the value of K_r, the threshold for SR Ca^{2+} release into the cytoplasm, leads to a cessation of CICR. As stated above, a cell that can no longer perform CICR will no longer undergo ECC. Similarly, increasing the value of K_r leads to a complete cessation of CICR and therefore to termination of ECC. Our results are therefore consistent with Marks' findings because our model also predicts heart failure when K_r becomes either too big or too small.

In the third experiment, the value of K_r was varied from the default value. This parameter controls the threshold for CICR response, and the model displays synchronization of Ca^{2+} concentration oscillations only in a range of values again showing a Hopf bifurcation similar to Figure 5. The parameter ranges across which sustained, synchronous Ca^{2+} concentration oscillations occur are presented in Table 3.

4.6. *Effect of Changing the Rate of Cytoplasm to ECM Ca^{2+} Movement on CICR*

Marin-García[16] reported that increasing the rate of Ca^{2+} movement from the cytoplasm to the ECM led to heart failure. In the fourth experiment, we changed the value of e from the default value and examined the effect of this change on the synchronization of Ca^{2+} concentration oscillations in CICR. As in the three previous cases, this model successfully demonstrates this effect. Increasing the value of e, the rate of Ca^{2+} efflux from the cytoplasm into the ECM, leads to a cessation of CICR. A cell that can no longer perform CICR will no longer undergo ECC. Similarly, decreasing the value of e leads to a complete cessation of CICR and therefore to termination of ECC. Our results are therefore consistent with the description in Marin-García's text because our model also predicts heart failure when e becomes either too big or too small. As in previous figures, the system shows a passage from no CICR to asynchronous oscillation, to synchronous

oscillation and back again. The parameter ranges across which sustained, synchronous Ca^{2+} concentration oscillations occur are presented in Table 3.

Table 3. Summary of regions of oscillation as parameters vary

Observation	Study	Parameter	Low Boundary	High Boundary
The amount of input calcium determines ability for CICR	[25]	i	2.8 μM/s	6.275 μM/s
Reduced SERCA pump stops CICR	[26]	V_u	49.5 μM/s	172 μM/s
Decreased threshold for SR Ca release stops CICR	[27]	K_r	0.45 μM	2.8 μM
Increased rate of Ca movement from cytoplasm to ECM stops CICR	[16]	e	4/s	9.6/s

5. Summary

This paper presents a novel model of calcium homeostasis in cardiac myocytes that builds on the work of Goldbeter *et al*[24] and Williams[23] by coupling together ten different junctional release sites. Because the model works on the scale of anywhere from one to ten distinct cytoplasm-SR junctions, it would be possible with sufficient computing power to extend it to the many thousands of junctions that exist in a single cardiac myocyte. This model extends previous work in this field by generating Ca^{2+} concentrations for each cytoplasmic and SR region that initially oscillate independently but ultimately synchronize.

In this study, we compared our model to four different experimental conditions. The analysis of these comparisons is given below. This model exhibits many of the same phenomena observed in the laboratory using only two different kinds of Ca^{2+} pumps. In particular, it

(i) displays spontaneous recurring calcium peaks in the presence of sufficient calcium input
(ii) displays synchronization across sites of these peaks under a range of parameters
(iii) shows appropriate dependence on the efficiency of the SERCA pump, as described in Jiang *et al*[26]
(iv) shows appropriate dependence on the threshold setting for CICR, as described in Marks *et al*[27][28]
(v) shows cessation of oscillations when the calcium leak out of the cell is too large or too small, consistent with the description in Marin-García[16]
(vi) confirms the importance of diffusion in the SR by demonstrating that synchronization ceases without SR diffusion.

This model allows its user to distinguish which observed aspects of myocyte Ca^{2+} dynamics occur because of intracellular communication and which phenomena occur simply because of the local physiological arrangement of the system near each junction. It further demonstrates that the SR, and more specifically the communication between different regions of the SR, plays a key role in the synchronization of Ca^{2+} concentration oscillations.

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