Long-Time Simulation of Calcium Waves in a Heart Cell to Study the Effects of Calcium Release Flux Density and of Coefficients in the Pump and Leak Mechanisms on Self-Organizing Wave Behavior

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Abstract

Spontaneous calcium sparks can lead to propagation of a self-initiated calcium wave under certain conditions in a heart cell. A model for diffusion waves of calcium ions in a heart cell is given by a system of coupled, time-dependent reaction-diffusion equations. The key term of the model quantifies the release of calcium at the calcium release units by a flux density. The model also includes pump and leak mechanisms that model the extruding and entering of calcium throughout the cell, respectively. Previous simulations for this model with extreme values of the flux density demonstrate that no wave will self-organize for a small value and that a wave will self-organize for a large value; in the latter case, it also becomes apparent that the total concentration of calcium throughout the cell grows without bound. This report shows that the original conclusions with respect to wave self-organization are correct qualitatively, and it identifies the range of values of the flux density quantitatively for which we can be confident about the observation. Additionally, a range of values for the parameters of the pump mechanism is studied. We can conclude that the growth of the total calcium concentration is affected by the choice of coefficients, but that, for the parameters studied here, the growth cannot be avoided for the cases in which a wave self-organizes.

1 Introduction

Calcium sparks are visualized as fluorescent flashes of calcium released from internal cellular stores. The release is routinely triggered by calcium entering from the extracellular space during the course of the heart's electrical impluse signaling muscle contractions. However, spontaneous sparks can form and lead to propagation of a self-initiated calcium wave under certain conditions [1].

1.1 The Calcium Flow Model

A model for diffusion waves of calcium ions in a heart cell is given by a system of coupled, time-dependent reaction-diffusion equations

$$\frac{\partial u^{(i)}}{\partial t} - \nabla \cdot \left(D^{(i)} \nabla u^{(i)} \right) = r^{(i)} + \left(- J_{\text{pump}} + J_{\text{leak}} + J_{\text{SR}} \right) \delta_{i0} \tag{1.1}$$

for the concentrations $u^{(i)}(\mathbf{x}, t)$ of the n_s chemical species $i = 0, 1, \ldots, n_s - 1$ as functions of space $\mathbf{x} \in \Omega \subset \mathbb{R}^3$ and time $0 \le t \le t_{\text{fin}}$. The system (1.1) is coupled with no flow boundary conditions, and the concentrations at the initial time are given. The studies in this report follow those in [2]. Additionally, see the appendix in [3] as well as [4, 5, 6] for more references on background material.

The problem of calcium flow in a cell is a multiscale problem in both space and time. For the simulation of calcium waves through an entire cell, the domain needs to be on the scale of the cell, which is on the order of 10×10 μm^2 in cross-section and at least between 50 and 100 μm in length. Thus, we choose the domain $\Omega \subset \mathbb{R}^3$ of the differential equation model (1.1) as the interior of one cell as $\Omega = (-6.4, 6.4) \times (-6.4, 6.4) \times (-32.0, 32.0)$ in units of μm. On the scale of a cell, the points where calcium ions are released into the cytosol, are represented as point sources, i.e., mathematically discrete points of size 0. On the time scale of the waves we intend to simulate, which have a duration of about 100 ms, the opening and closing of calcium release units appears as instantaneous switching in time, and a final simulation time that may capture multiple wave initiations is desirable such as $t_{\text{fin}} = 1{,}000$ ms.

The time and space derivatives on the left-hand side of (1.1) model the diffusive transport of each chemical species with diffusivities given by the diagonal, positive definite matrices $D^{(i)} \in \mathbb{R}^{3\times 3}$, $i = 0, 1, \ldots, n_s - 1$. The reaction terms $r^{(i)} \equiv r^{(i)}(u^{(0)}, \ldots, u^{(n_s-1)})$ on the right-hand side are in general non-linear functions of all species and couple all reaction-diffusion equations in (1.1).

Crucial effects related to the calcium species, labeled with index $i = 0$, are contained in the right-hand side terms associated with the Kronecker delta function δ_{i0} (defined as $\delta_{ij} = 0$ for all $i \neq j$ and $\delta_{ij} = 1$ for $i = j$). Calcium leaves the cytosol through the non-linear drain term [4, p. 89]

$$J_{\text{pump}}(u^{(0)}) = \frac{V_{\text{pump}}\,(u^{(0)})^{n_{\text{pump}}}}{(K_{\text{pump}})^{n_{\text{pump}}} + (u^{(0)})^{n_{\text{pump}}}}. \tag{1.2}$$

At rest, that is, for the calcium concentration $u^{(0)} = 0.1$ μM, the constant source term J_{leak} balances the pump term such that $J_{\text{leak}} = J_{\text{pump}}(u^{(0)})$ [4, p. 89]. This effect is modeled by the source term J_{SR} that is described in more detail in the following subsection.

1.2 The model of the spark mechanism

The key term of the model is the term $J_{\text{SR}}(u^{(0)}, \mathbf{x}, t)$ in the equation for the calcium concentration (labeled as species $i = 0$) in (1.1) that describes the release of calcium at the calcium release units (CRUs), referred to as spark events [4, 6]. On the spatial scale of a cell, the CRUs appear as discrete points distributed uniformly throughout the cell. Specifically, we take the arrangement of the CRUs as a three-dimensional lattice with spacings of $\Delta x_s = \Delta y_s = 0.8$ μm in the x- and y-dimensions and of $\Delta z_s = 2.0$ μm in the z-dimension of the cell with no CRUs on the boundary of the cell [6, p. 105]. For our domain of $\Omega = (-6.4, 6.4)\times(-6.4, 6.4)\times(-32.0, 32.0)$ with length units of μm, this means that the CRUs form a $15\times 15\times 31$ lattice with a total of 6,975 CRUs in the cell.

The release of calcium concentration at each CRU is modeled as a point source on the spatial scale of the cell, mathematically represented as a Dirac delta distribution $\delta(\mathbf{x} - \hat{\mathbf{x}})$ for a CRU located at $\hat{\mathbf{x}}$ [4, p. 89]. The Dirac delta distribution is understood here in a three-dimensional sense for short, that is, $\delta(\mathbf{x} - \hat{\mathbf{x}}) := \delta(x - \hat{x})\,\delta(y - \hat{y})\,\delta(z - \hat{z})$, where we also write $\mathbf{x} = (x, y, z)$ and $\hat{\mathbf{x}} = (\hat{x}, \hat{y}, \hat{z})$. We recall that $\delta(\mathbf{x})$ is defined by requiring (i) $\delta(\mathbf{x} - \hat{\mathbf{x}}) = 0$ for all $\mathbf{x} \neq \hat{\mathbf{x}}$ and (ii) $\int \psi(\mathbf{x})\,\delta(\mathbf{x} - \hat{\mathbf{x}})\,d\mathbf{x} = \psi(\hat{\mathbf{x}})$ for any continuous function $\psi(\mathbf{x})$; this definition implies in particular that $\delta(\hat{\mathbf{x}})$ tends to ∞ and is thus not a function in the mathematical sense. The amount of calcium injected into the cell at one point $\hat{\mathbf{x}}$ is given by the flux density σ, that is, $\int_\Omega \sigma\,\delta(\mathbf{x} - \hat{\mathbf{x}})\,d\mathbf{x} = \sigma$, by the definition of the delta distribution, gives the amount of calcium released into the cell in 1 ms. The effect of a CRU switching on and off is incorporated by an indicator function in time. More specifically, let the set $\Omega_s = \{\hat{\mathbf{x}} \in \Omega \,|\, \hat{\mathbf{x}} \text{ is a CRU}\}$ denote the set of all CRU locations. Then [5, p. 96]

$$J_{\text{SR}}(u^{(0)}, \mathbf{x}, t) = \sum_{\hat{\mathbf{x}}\in\Omega_s} \sigma\, S_{\hat{\mathbf{x}}}(u^{(0)}, t)\,\delta(\mathbf{x} - \hat{\mathbf{x}}) \tag{1.3}$$

is the superposition of the release of calcium at all CRUs.

The indicator function $S_{\hat{\mathbf{x}}}(u^{(0)}, t)$ in each term of the sum in (1.3) houses the stochastic aspect of the sparking mechanism of the CRU at $\hat{\mathbf{x}}$. The model allows the CRU to open with probability

$$J_{\text{prob}}(u^{(0)}) = \frac{P_{\max}\,(u^{(0)})^{n_{\text{prob}}}}{(K_{\text{prob}})^{n_{\text{prob}}} + (u^{(0)})^{n_{\text{prob}}}} \tag{1.4}$$

as a function of the local calcium concentration $u^{(0)}$ [6, p. 104]. This probabilistic model is checked at the spark times that are every unit in time $\Delta t_s = 1$ ms apart. That is, for all CRUs that is eligible to open, $J_{\text{prob}}(u^{(0)})$ is compared to a random number $0 \leq r \leq 1$, and if $J_{\text{prob}} > r$ the CRU is switched on by setting $S_{\hat{\mathbf{x}}}$ to 1. We use uniformly distributed random numbers generated by the popular Mersenne twister code [7]. If a CRU opens at a time $t = \hat{t}$, it stays open for a duration $t_{\text{open}} = 5$ ms, that is, the indicator function $S_{\hat{\mathbf{x}}} = 1$ for $t \in [\hat{t}, \hat{t} + t_{\text{open}}]$. The desired effect of this design is that the calcium released at one CRU diffuses

to a neighboring CRU, whose probability for opening increases with the increased calcium concentration. If the calcium concentration then reaches a third CRU and it opens, the effect is that of a wave forming throughout the cell [3, 6]. After a CRU closes again, it stays closed for a time period $t_{\text{closed}} = 100$ ms before it is eligible to open again. Therefore, calcium waves through the cell are separated in time by at least 100 ms. We see that to simulate a sequence of repeated calcium waves, we need to be able to calculate for long times, such as, up to the final time $t_{\text{fin}} = 1{,}000$ ms.

The experimentally obtained coefficient σ models the amount of calcium released at one CRU [4, 6]. It is a function of the calcium current I_{SR} by $\sigma = I_{\text{SR}}/(2F)$, where F denotes the Faraday constant and the factor of 2 is the valence of a calcium ion (i.e., Ca^{2+}). The range of I_{SR} from 10 to 20 pA is "back-calculated from the size of sparks" [5, p. 96]. This quantity has crucial influence on whether calcium waves self-organize or not because it determines how much calcium is released into the cell at one CRU, σ, which via diffusion raises the value of J_{prob} in (1.4) at nearby CRUs and thus influences strongly whether they open or not.

1.3 Outline

One interesting validation for this model of calcium waves is to consider several values of σ in I_{SR} and observe whether calcium waves self-organize. This is the purpose of Section 2, in which we consider several values of σ, while keeping all other model parameters as in Table 2.1 of [2]. The application studies in [2] indicate that too much calcium seems to be released into the cytosol at the CRUs with the current model parameters. Using a value of σ, which consistently leads to a self-initiating wave, in Section 3 we vary parameters in the pump and leak mechanism (1.2) to try to control the increase of total calcium concentration in the cell.

2 Critical Flux Density Interval Determination via Simulations

As stated in Section 1.2, one parameter that influences self-initiation of calcium waves in the cell is the flux density σ in (1.3), which is a function of the calcium current I_{SR}. Since our main goal is to study the self-initiation of calcium waves as a function of the problem parameters in (1.1), we vary the flux density in this section and observe for which values a calcium wave self-initiates. From [2, Section 4.4], we know that for $\sigma \approx 51.82$ μmol/L μm^3/s, which corresponds to $I_{SR} = 10$ pA, simulation runs resulted in no wave self-organization; and for $\sigma = 103.64$ μmol/L μm^3/s, which corresponds to $I_{SR} = 20$ pA, simulation runs resulted in a wave self-organization.

2.1 Simulation Method

The model can be used to approximate a critical σ range above which a wave is likely to self-initiate and below which a wave is not likely to self-initiate. One way of locating this critical σ range is to run multiple simulations with different values of σ and determine the percentage of simulations in which a wave self-organizes. We use $\sigma = 50, 60, 70, 80, 90$, and 100, while maintaining all other model parameters as in Table 2.1 in [2]. We consider two spacial discretizations of the domain $\Omega = (-6.4, 6.4)\times(-6.4, 6.4)\times(-32, 32)$ in the studies, one with $16 \times 16 \times 64$ finite elements resulting in 56,355 degrees of freedom for the 3-species model and one with $32 \times 32 \times 128$ yielding 421,443 degrees of freedom. Since a pseudo-random number generator is involved in each simulation, we run the simulations for each value of σ with 20 different seeds to the pseudo-random number generator.

2.2 Simulation Results

Simulation runs gave equivalent results when either of the Ω domain discretization was used. Therefore, this section presents simulation results obtained using the spacial discretization of the Ω domain with $32\times32\times128$ finite elements.

Figures 1 and 2 show results for the case study with $\sigma = 50$. The studies for $\sigma = 50$ here consider essentially the same case as for $\sigma \approx 51.82$ in [2, Section 4.4], when no wave self-organization occurred. Figure 1 shows the number of open CRU at different spark time for a simulation ran with a σ value of

50. Each dot indicates that the CRU at the spatial point is open (and does not represent the value of any quantity). For the duration of the simulation, very few CRUs are open without discernible pattern. Clearly the number of open CRUs isn't enough to initiate a wave. Figure 2 shows the corresponding isosurface plot of calcium concentration with a critical isolevel of 65 μmol/L. We can clearly see that the critical isolevel is crossed at very few CRUs and only for the duration that the CRU at the location is firing. Equivalent results for the self-initiation of a wave were observed for all 20 simulation runs for this σ value. In looking for a criterion to determine if a calcium wave occurs during the simulation that is more immediate than considering several subplots in figures such as Figures 1 and 2, we plot the total number of open CRUs throughout the cell as a function of time in Figure 3 (a) for $\sigma = 50$. It is evident that no more than about 16 CRUs are ever open at any given moment, which is a very small number compared to the total of about 7,000 CRUs throughout the cell.

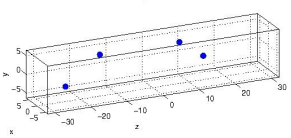
Figures 4 and 5 show results for the case study with $\sigma = 70$. Figure 4 shows the locations of open CRUs at different times. We see that from $t = 100$ ms to $t = 400$ ms a number of CRUs are open without discernible pattern. At $t = 600$ ms, two waves of CRU have self-organized; at some time between 500 and 600 ms, the concentration near the center and left side of the domain has reached higher levels that caused several other CRUs to open. This, in turn, engendered more CRUs to be open; by $t = 600$ ms, we have a wave traveling throughout the cell. Figure 5 shows the corresponding isosurface with a critical isolevel of 65 μmol/L. We see that from $t = 100$ ms to $t = 500$ ms, the concentration has crossed the critical isolevel only at a few CRUs. By $t = 600$ ms, however, in the wake of both waves, we see significantly increased levels of calcium, which by $t = 1{,}000$ ms have reached levels above the critical isolevel throughout the entire domain. Looking at the number of open CRUs in Figure 3 (d) for $\sigma = 70$, we observe that somewhere between $t = 500$ ms and 600 ms, the number of open CRUs reaches more than 300 and oscillates between 400 and 200 for the remainder of the simulation. This exhibits a wave self-initiation. Equivalent results were consistently obtained for all 20 simulation runs for this σ value, with only slight variations from simulation to simulation. For all larger $\sigma = 80, 90$, and 100, a wave self-organization occurred in a manner similar to the case of $\sigma = 70$. This conclusion was originally drawn from plots analogous to Figures 4 and 5. But we find that it can be reached directly from the plots of total number of open CRUs throughout the domain as function of time in Figures 3 (e), (f), and (g), which all show an oscillatory behavior around a mean of several hundreds of open CRUs. Therefore, we will use plots of the total number of open CRUs throughout the cell as function of time in the following to conclude whether a calcium wave self-organized or not.

For $\sigma = 60$, some of the 20 simulation runs performed resulted in no wave self-organization (as in the $\sigma = 50$ case) within the 1,000 ms simulation time, while the remaining runs might eventually result in wave self-organization (as in the $\sigma = 70$ case). More precisely, in 18 out of the 20 simulations performed, we observed no self-organization of a calcium wave; a representative plot of the number of open CRUs is presented in Figure 3 (b) for $\sigma = 60$, which shows that never more than about 16 CRUs are open at any moment in time. In the remaining 2 out of the 20 simulations, we observe in the representative Figure 3 (c) that the total number of open CRUs eventually increases for a time greater than 900 ms; we claim a wave has initiated. While the self-organization of a wave is not conclusive, the case of $\sigma = 60$ demonstrates that different runs can lead to different results and that one may consider this value of σ in the critical transition range.

Based on the simulation results, we can summarize the following conclusions:

- For σ values less than or equal to about 50 μmol/L μm^3/s, no wave self-organization can be expected.
- For σ values between 50 and 70 μmol/L μm^3/s, waves may or may not self-organize.
- For σ values greater than or equal to about 70 μmol/L μm^3/s, wave self-organization is virtually assured.

Therefore, for the purpose of studying wave self-initiation as function of problem parameters, we choose a value of $\sigma = 70$ μmol/L μm^3/s in the following, as this value virtually guarantees self-initiation of a wave throughout the cell. The results of this section also demonstrate that one can use the plot of the total number of open CRUs throughout the cell as a function of time as a criterion for judging whether a calcium wave self-organizes or not in a particular simulation.



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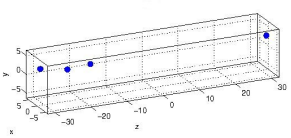

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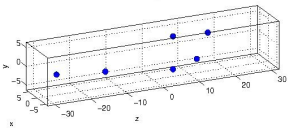
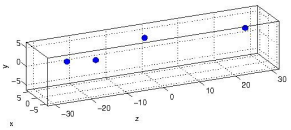
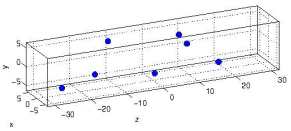


$t = 300$



$t = 400$



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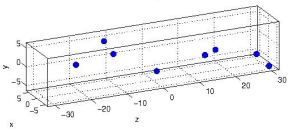

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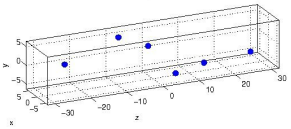

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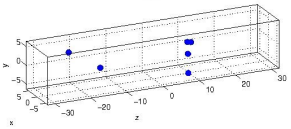

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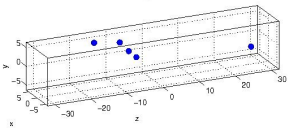

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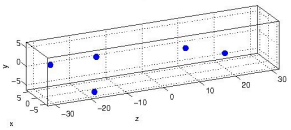
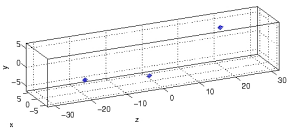
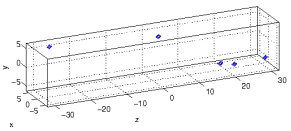


$t = 1{,}000$

Figure 1: Open calcium release units throughout the cell with $\sigma = 50$.



$t = 100$



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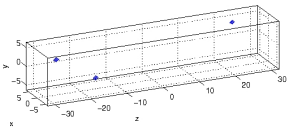

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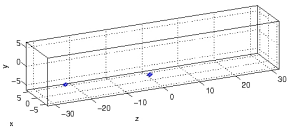

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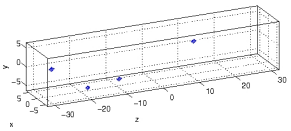

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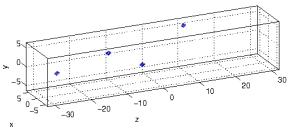

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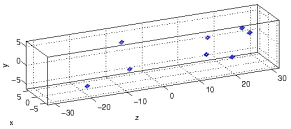

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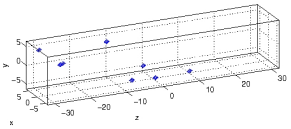

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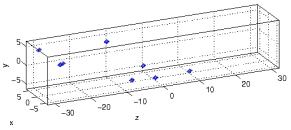

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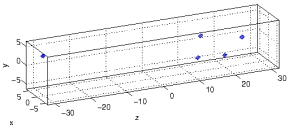
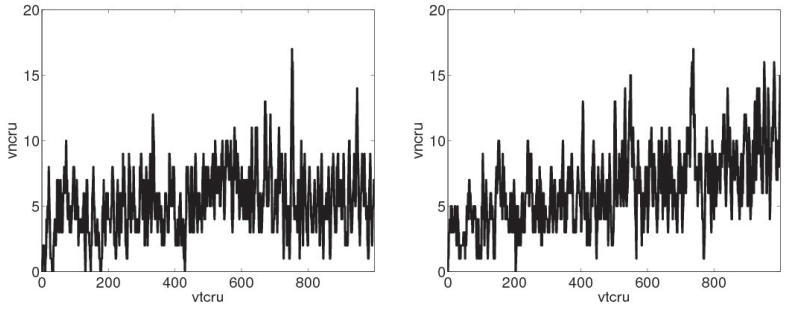


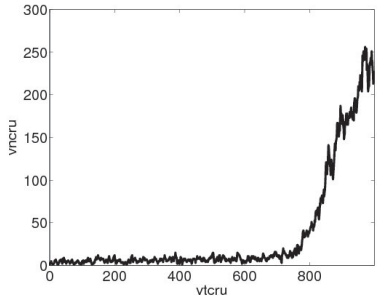
$t = 1{,}000$

Figure 2: Isosurface plots of the calcium concentration throughout the cell with $\sigma = 50$.

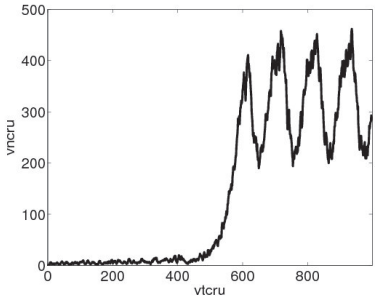


(a) $\sigma = 50$

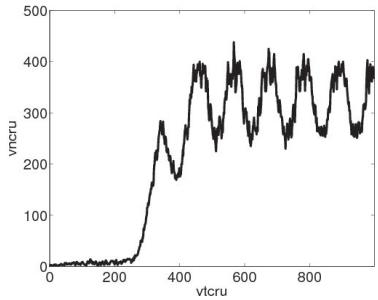
(b) $\sigma = 60$ — dominant case



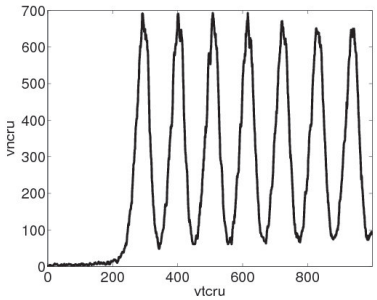
(c) $\sigma = 60$ — subordinate case



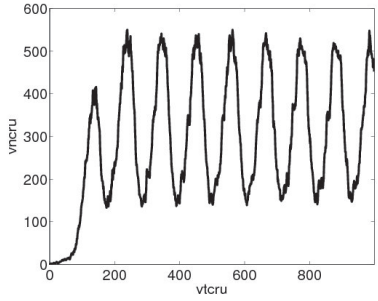
(d) $\sigma = 70$.



(e) $\sigma = 80$

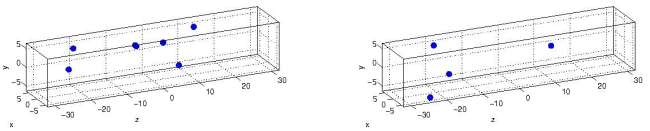


(f) $\sigma = 90$

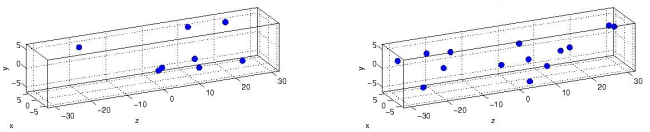


(g) $\sigma = 100$

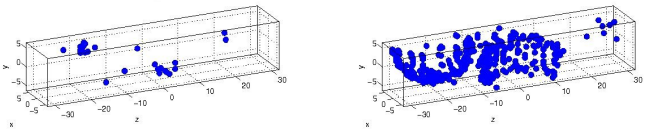
Figure 3: Plots of the number of open CRUs vs. time for $\sigma = 50, 60(\text{two cases}), 70, 80, 90$, and 100.



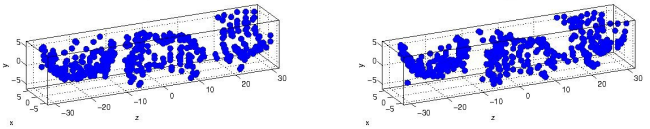
$t = 100$ $t = 200$



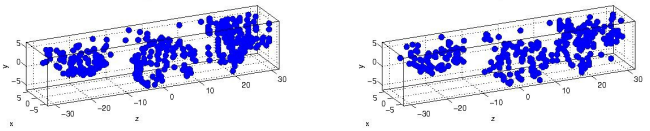
$t = 300$ $t = 400$



$t = 500$ $t = 600$

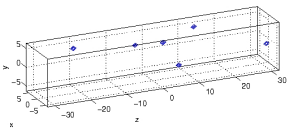


$t = 700$ $t = 800$

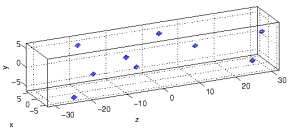


$t = 900$ $t = 1{,}000$

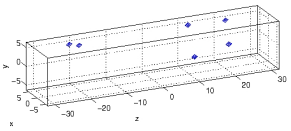
Figure 4: Open calcium release units throughout the cell with $\sigma = 70$.



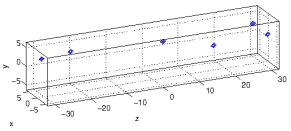
$t = 100$



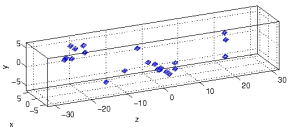
$t = 200$



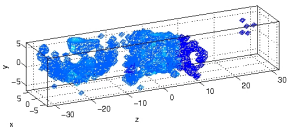
$t = 300$



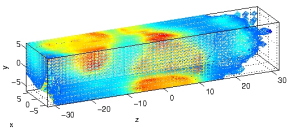
$t = 400$



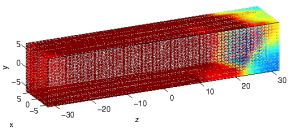
$t = 500$



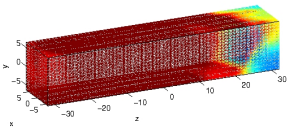
$t = 600$



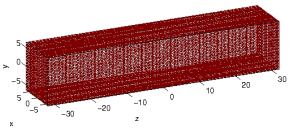
$t = 700$



$t = 800$



$t = 900$



$t = 1{,}000$

Figure 5: Isosurface plots of the calcium concentration throughout the cell with $\sigma = 70$.

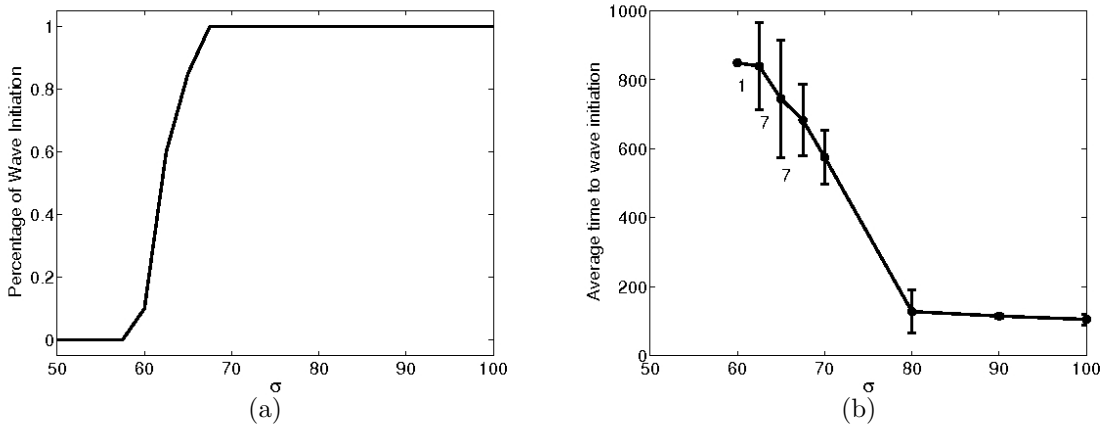


Figure 6: (a) Fraction of simulation runs resulting in wave self-initiation for each σ. (b) Average time for wave self-initiation and its standard deviation as error bar for each σ.

Each plot in Figure 3 displays the total number of open CRUs vs. time for a representative run for each σ into one plot and information on self-initiation of a wave can be gleaned from it. In Figure 6, we summarize this information for all 20 runs for all σ values in one plot. For more detail, additional values of σ between 50 and 70 were considered for this figure. In Figure 6 (a), we start by plotting the fraction of simulation runs resulting in wave self-initiation for each value of σ considered in the studies. The transition of the fraction from 0 to 1 indicates that the critical transition value for σ lies around 60. Figure 6 (b) expands on the information of Figure 6 (a) for those cases of σ that resulted in runs with self-initiated waves. Namely, it shows the average time for wave self-initiation and its standard deviation as error bar among the runs for each σ that resulted in a self-organized wave; if the number of these runs is fewer than the 20 runs performed for that σ, Figure 6 (b) indicates the number. That is, the average and its standard deviation is computed only when, for a specific value of σ, a wave does self-organize in at least one run of the 20 performed for each σ. We consider a wave to have self-initiated for a particular run, if the total number of open CRUs becomes greater than or equal to 100 at any point in time during the simulation. Then, in a plot of the type in Figure 3, the initiation time is the first time that the total number of open CRUs is greater than or equal to 100. Figure 6 (b) indicates that the average time for wave self-initiation decreases as σ increases.

3 Effect of the Pump and Leak Mechanisms on Self-Organizing Wave Behavior and Total Calcium Concentration

The results of long-time simulations for this application problem in Section 4.4 of [2] point to the fact that the calcium concentration in the cell appears to grow without bound. Specifically, isosurface plots of the calcium concentration in Figure 4.5 of [2] for the large value $\sigma \approx 103.64$ show calcium concentration above the critical isolevel of 65 μM throughout the entire cell for times $t \geq 400$ ms. The results of the previous section in this report show the same behavior in Figure 5 for $\sigma = 70$ for times $t \geq 800$ ms. Plotting the total calcium concentration $Q^{(0)} := \int_\Omega u^{(0)}(\mathbf{x}, t)\, d\mathbf{x}$ throughout the cell vs. time t for these simulations confirms that the concentration values are indeed not just above the critical isolevel but indeed grow without apparent limit in the simulations. This behavior is clearly unphysical and this section considers one possible way at controlling the growth of calcium in the cell.

3.1 Simulation Method

As introduced in Section 1, the pump term J_{pump} in (1.1) provides a method in which calcium is extruded from the cytosol. We expect this mechanism to regulate the calcium concentration in the cell and to maintain

Table 1: Value of the constant leak term J_{leak} for each $(V_{\text{pump}}, K_{\text{pump}})$ case.

	$K_{\text{pump}} = 0.2$	$K_{\text{pump}} = 1.6$	$K_{\text{pump}} = 3.2$	$K_{\text{pump}} = 6.4$
$V_{\text{pump}} = 0.2$	0.01176	3.0517e-06	1.9073e-07	1.1920e-08
$V_{\text{pump}} = 1.6$	0.09411	2.4413e-05	1.5258e-06	9.5367e-08
$V_{\text{pump}} = 3.2$	0.18823	4.8827e-05	3.0517e-06	1.9073e-07
$V_{\text{pump}} = 6.4$	0.37647	9.7654e-05	6.1035e-06	3.8146e-07

the total calcium concentration throughout the cell bounded. In (1.2), we see that two parameters are available to be varied in our investigation, namely V_{pump} and K_{pump}. Therefore, we define sixteen cases for comparison by varying both V_{pump} and K_{pump} through the values 0.2, 1.6, 3.2, and 6.4 and listing each case as an ordered pair $(V_{\text{pump}}, K_{\text{pump}})$. The $(V_{\text{pump}}, K_{\text{pump}}) = (0.2, 0.2)$ is the base case with V_{pump} and K_{pump} assuming (approximately) their values specified in Table 2.1 of [2]. Figure 7 shows the plot of $J_{\text{pump}}(u^{(0)})$ as function of the calcium concentration $u^{(0)}$ to visualize concretely the effect of changing V_{pump} and K_{pump} in each of the sixteen cases.

In each of these cases, care was taken to ensure the model's rest point remains at the calcium concentration $u^{(0)} = 0.1$ μM. Therefore, when varying V_{pump} and K_{pump} for each case we set $J_{\text{leak}} = J_{\text{pump}}(u^{(0)})$ in our simulations, as defined in Section 1 after (1.2). This gives the values of J_{leak} specified in Table 1.

As in the previous section, all other model parameters are kept as specified in Table 2.1 of [2], with the exception of setting $\sigma = 70$, identified in the previous section as the smallest value to give rise to a self-organizing wave.

We take the spatial discretization to be $N_x \times N_y \times N_z = 32 \times 32 \times 128$ in all simulations. Since a pseudo-random number generator is involved in each simulation, we perform 4 simulation runs with different seeds to the pseudo-random number generator in each run.

3.2 Simulation Results

Within each case, the 4 simulation runs for different seeds achieved equivalent results, therefore we plot only one representation of the results for each case in Figures 8 and 9.

In Figure 8, we plot the total number of open CRUs throughout the cell as a function of time for each case. This is intended to confirm that a calcium wave self-organizes in each case. For the cases, where $(V_{\text{pump}}, K_{\text{pump}}) = (1.6, 0.2)$, and $(3.2, 0.2)$ in the first column of Figure 8, the number of open CRUs never reaches more than 12 at any point in time, implying that no waves self-organize. The last plot in the first column shows that as V_{pump} is increased to 6.4, the number of open CRUs does start to grow after 600 ms, but this growth is not sufficient to organize a wave. Considering the first two rows of plots in Figure 8, we observe that every combination for $(V_{\text{pump}}, K_{\text{pump}})$ except $(1.6, 0.2)$ shows the number of CRUs eventually oscillate around several hundreds of CRUs. These cases however also exhibit the troubling behavior of unbounded calcium concentration as shown in the first two rows of Figure 9, where we plot the total calcium concentration $Q^{(0)}$ throughout the cell as a function of time for each case. We see that there are rapid increases of total calcium concentration reaching a maximum at the end time with magnitudes of order 10^6.

Examining the last two rows of both Figure 8 and Figure 9, the $(V_{\text{pump}}, K_{\text{pump}})$ cases $(3.2, 1.6)$, $(6.4, 1.6)$ and $(6.4, 3.2)$ show some signs of oscillations in the number of open CRUs and furthermore the calcium concentrations seem to be reaching an asymptotic bound. However, after viewing movies depicting the opening and closing of CRUs over time, we conclude that no waves are organized for these cases in the time frame considered. The remaining three cases for $(V_{\text{pump}}, K_{\text{pump}})$, that is, $(3.2, 3.2)$, $(3.2, 6.4)$ and $(6.4, 6.4)$, definitively show oscillations in the opening and closing of CRUs. Moreover, the oscillatory behavior also shows itself in the calcium concentration. In these three cases the oscillations seem to grow over time. Longer simulation time may be necessary to determine the nature of the amplitude. For the cases $(3.2, 3.2)$ and $(3.2, 6.4)$, the maximum peak of oscillation is of order 10^5. For the $(6.4, 6.4)$ case, the maximum peak is of order 10^4. We note that the second, third, and fourth plots in the first column of Figure 9 show a relatively constant value for the calcium concentration, indicating the absence of a self-organized wave.

In summary, the cases with self-organizing waves and with $V_{\text{pump}} = 0.2$ or 1.6 have total calcium concentrations throughout the cell that grow dramatically over time. For cases with self-organizing waves and with $V_{\text{pump}} = 3.2$ or 6.4, the total calcium concentration throughout the cell oscillates with growing peaks over time.

Acknowledgments

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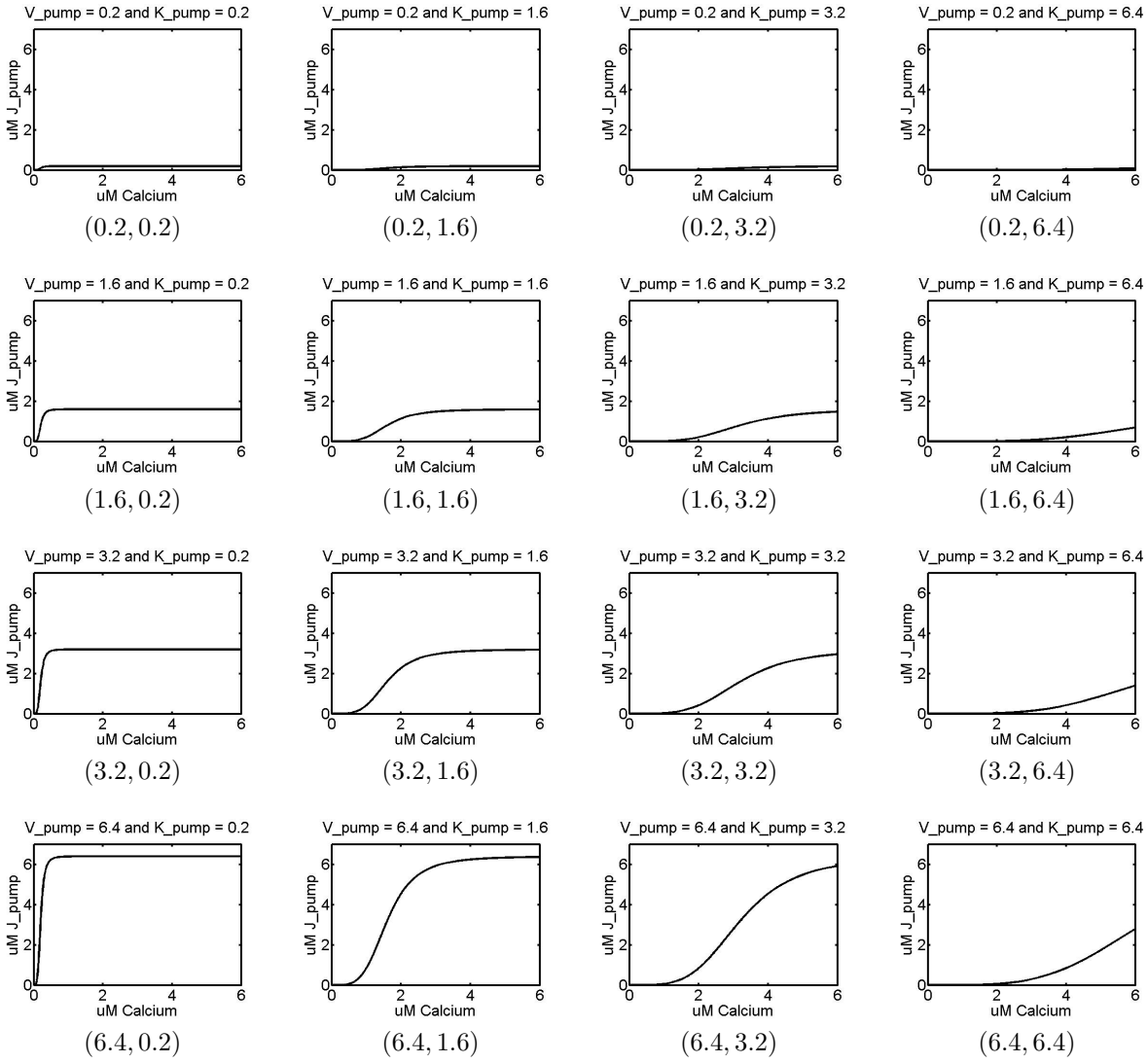

$(0.2, 0.2)$ $(0.2, 1.6)$ $(0.2, 3.2)$ $(0.2, 6.4)$

$(1.6, 0.2)$ $(1.6, 1.6)$ $(1.6, 3.2)$ $(1.6, 6.4)$

$(3.2, 0.2)$ $(3.2, 1.6)$ $(3.2, 3.2)$ $(3.2, 6.4)$

$(6.4, 0.2)$ $(6.4, 1.6)$ $(6.4, 3.2)$ $(6.4, 6.4)$

Figure 7: Plots of J_{pump} vs. calcium concentration for each $(V_{\text{pump}}, K_{\text{pump}})$ case.

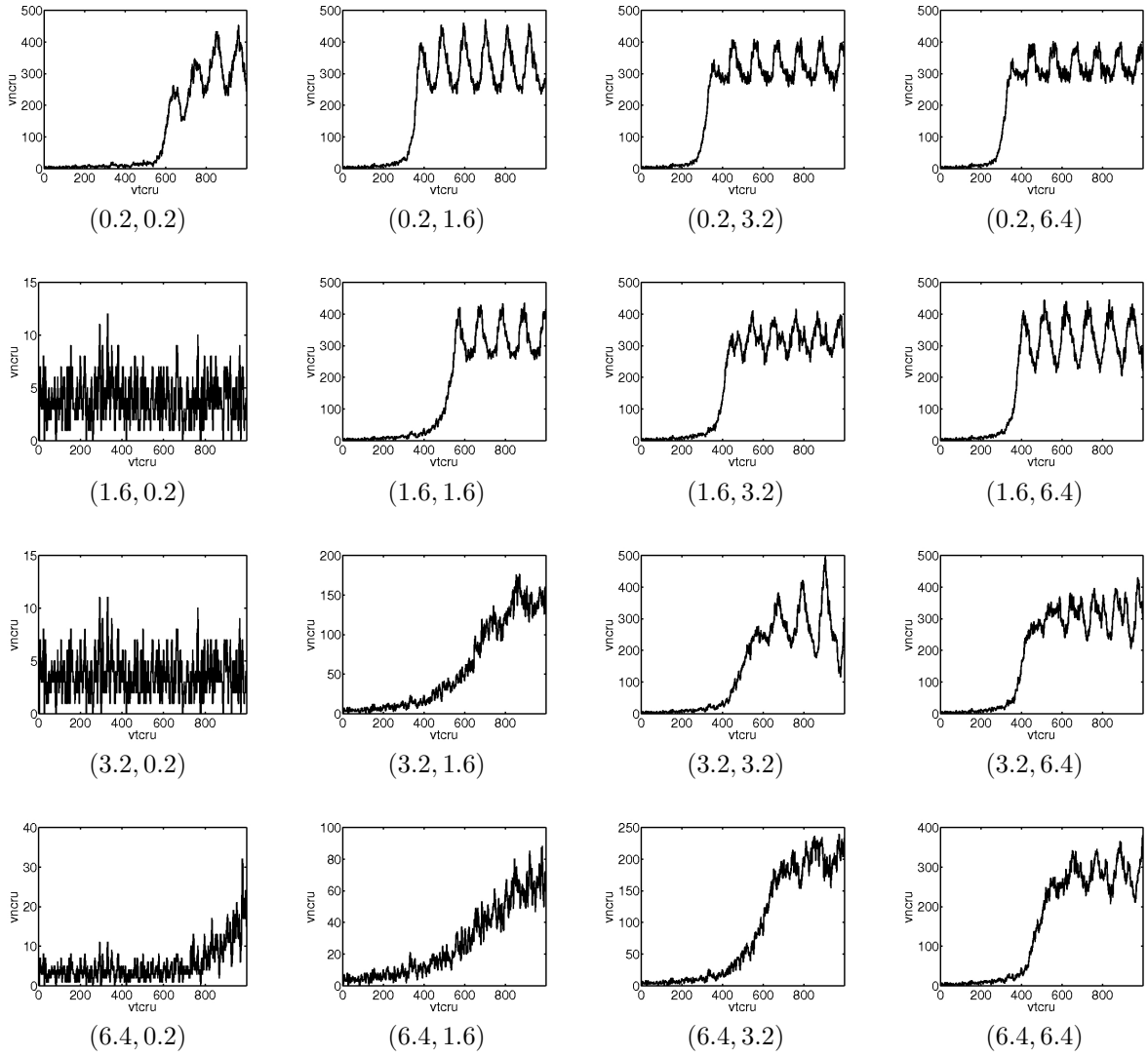

Figure 8: Plots of the total number of open CRUs throughout the cell vs. time for each $(V_{\text{pump}}, K_{\text{pump}})$ case.

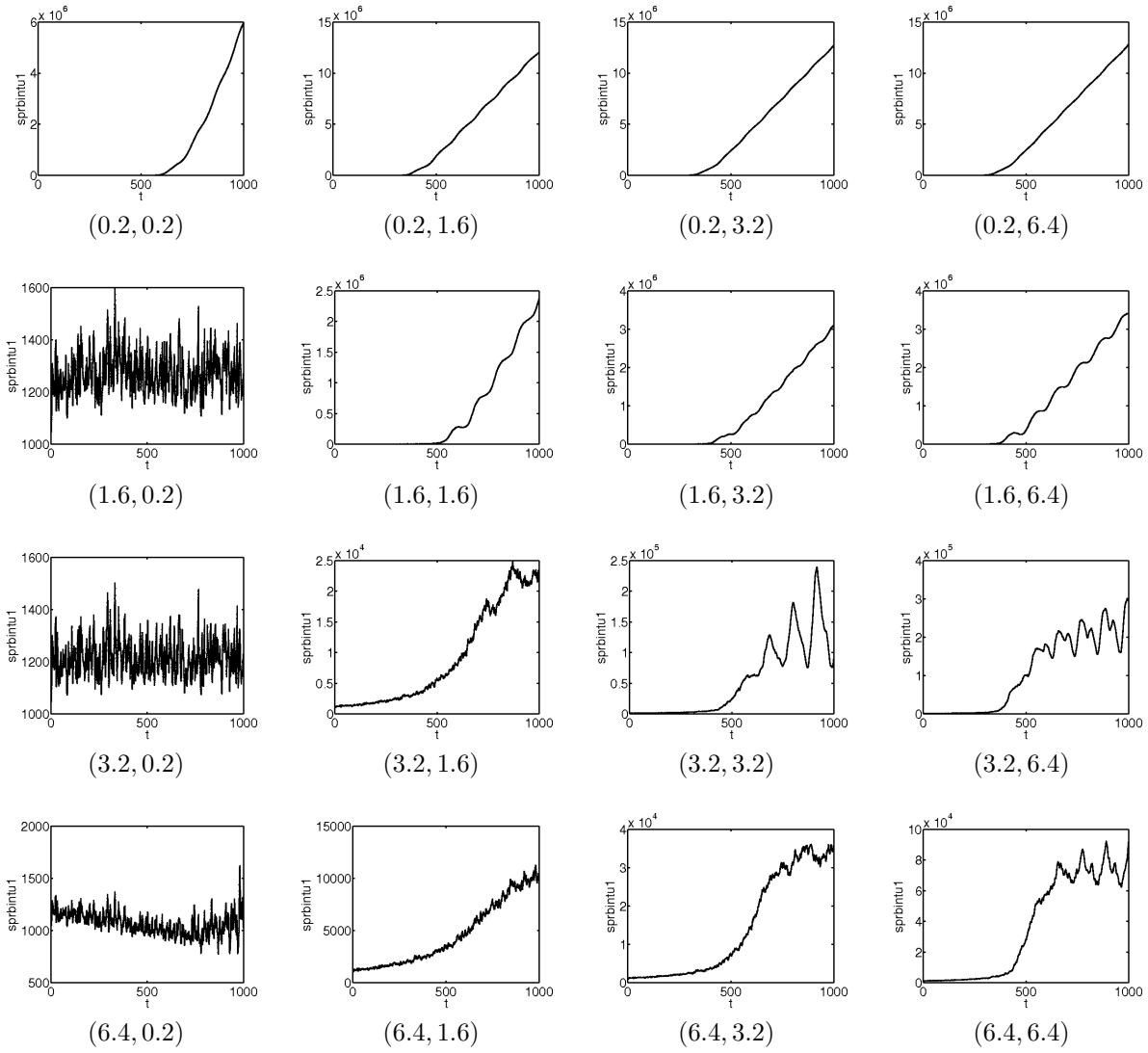

Figure 9: Plots of the total calcium concentration throughout the cell vs. time for each $(V_{\text{pump}}, K_{\text{pump}})$ case.