Calcium Induced Calcium Release with Stochastic Uniform Flux Density in a Heart Cell

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ABSTRACT
Calcium is a critical component in many cellular functions. It serves many important functions such as signal transduction, contraction of muscles, enzyme function, and maintaining potential difference across excitable membranes. We examine the self-organization of calcium waves in a heart cell and how they propagate through the cell. Specifically, the crucial parameter of flux density that controls the amount of calcium released at each calcium release unit is assumed a known constant in the original model. In reality, this value is not known exactly, thus we design parameter studies where the flux density is made a stochastic parameter for each simulation. This technique from uncertainty quantification allows for determining the range of the flux density, in which calcium waves are likely to self-organize, but without physiologically unrealistic saturation of the cell and without electrical stimulation.

Author Keywords
Calcium Induced Calcium Release (CICR), calcium waves, heart cell, uncertainty quantification (UQ)

1. INTRODUCTION

Calcium is a critical component in many cellular functions. It serves many important functions such as signal transduction, contraction of muscles, enzyme function, and maintaining potential difference across excitable membranes. Calcium in mammals is stored in their bones and the calcium ions are released from the bone under controlled conditions and are then transported through the blood stream. In this study we examine calcium waves in a heart cell and how they propagate. Calcium sparks are intracellular Ca^{2+} release events which are important in converting electrical stimuli into mechanical responses. However, under certain pathological conditions such as Ca^{2+} overload release can occur spontaneously. The evolution of spontaneously released calcium into self-organized waves underlies certain proposed mechanisms of cardiac arrhythmias [3].

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The existing model for calcium flow in a heart cell Ω is given by a system of coupled, time-dependent advection-reaction-diffusion equations

$$\frac{\partial u^{(i)}}{\partial t} - \nabla \cdot \left(D^{(i)} \nabla u^{(i)}\right) = r^{(i)} + s^{(i)} \qquad (1)$$

for concentrations $u^{(i)}(\mathbf{x}, t)$ in μM of the $n_s = 3$ chemical species, $i = 1, \ldots, n_s$, as functions of space $\mathbf{x} \in \Omega \subset \mathbb{R}^3$ and time $0 \le t \le t_{\text{fin}} = 1{,}000$ ms. Here, $i = 1$ represents calcium, $i = 2$ an endogenous calcium buffer, and $i = 3$ a fluorescent indicator dye. The cell itself has elongated shape and is reasonably represented as

$$\Omega = (-6.4, 6.4) \times (-6.4, 6.4) \times (-32.0, 32.0)$$

in units of μm. For the complete model description including model parameters, the numerical method, and its parallel implementation, see [5,10]. This model is coupled with no-flux boundary conditions in the cell wall, and the concentrations at the initial time are set at basal levels, which is 0.1 μM for the calcium concentration.

The second term in (1) models diffusion with diffusivity $D^{(i)} \in \mathbb{R}^{3\times 3}$. The coupling among the species is modeled by the non-linear reaction terms $r^{(i)}$ that depend on all species [5], given by

$$r^{(i)}(u^{(1)}, \ldots, u^{(n_s)}) = \sum_{j=2}^{n_s} R^{(j)}(u^{(1)}, u^{(j)})$$

for $i = 1$ and

$$r^{(i)}(u^{(1)}, \ldots, u^{(n_s)}) = R^{(i)}(u^{(1)}, u^{(i)})$$

for $i = 2, \ldots, n_s$ with reaction rates

$$R^{(i)} = -k_i^+ u^{(1)} u^{(i)} + k_i^- \left(\overline{u}_i - u^{(i)}\right)$$

for $i = 2, \ldots, n_s$.

For species $i > 1$ other than calcium in (1), the term $s^{(i)} \equiv 0$. For the calcium species $i = 1$, the term

$$s^{(1)} = -J_{\text{pump}} + J_{\text{leak}} + J_{\text{SR}}$$

contains pump and leak effects with the calcium store inside the cell as well as the key term of the model that describes the release of calcium from the sarcoplasmic reticulum (SR) into the cytosol of the cell at all calcium release units (CRUs) located at [5, 6, 8, 10]. Specifically,

the J_{pump} term is given by the equation

$$J_{\text{pump}}(u^{(1)}) = \frac{V_{\text{pump}}(u^{(1)})^{n_{\text{pump}}}}{(K_{\text{pump}})^{n_{\text{pump}}} + (u^{(1)})^{n_{\text{pump}}}}.$$

and $J_{\text{leak}} = J_{\text{pump}}(0.1) \equiv const.$ for the calcium concentration at basal level 0.1 μM.

The key term of the model

$$J_{\text{SR}}(u^{(1)}, \mathbf{x}, t) = \sum_{\hat{\mathbf{x}} \in \Omega_{\text{s}}} g\, S_{\hat{\mathbf{x}}}(u^{(1)}, t)\, \delta(\mathbf{x} - \hat{\mathbf{x}}) \qquad (2)$$

describes the release of calcium from the sarcoplasmic reticulum (SR) into the cytosol of the cell at all calcium release units (CRUs) located at $\hat{\mathbf{x}} \in \Omega_s \subset \Omega$ [6,8]. There are thousands of CRUs in one heart cell, and they are arranged along a three-dimensional lattice throughout the cell, whose points are collected in the set Ω_{s}. The effect of a CRU at $\hat{\mathbf{x}} \in \Omega_{\text{s}}$ switching on and off is incorporated by the indicator function $S_{\hat{\mathbf{x}}}$, where $S_{\hat{\mathbf{x}}} = 1$ when the CRU is turned on and $S_{\hat{\mathbf{x}}} = 0$ when it is turned off. A CRU switches on (it 'fires'), when a uniform random number is less than a threshold function that gets larger with calcium concentration. In this way, the opening of a CRU becomes more likely in an environment of high calcium concentration. A CRU stays open for 5 ms and then is refractory for 100 ms, before being able to open again [6, 8]. This avoids details of the mechanism of CRU termination such as by junctional SR depletion [12]. The amount of calcium released per unit of time at each open CRU $\hat{\mathbf{x}}$ is modeled as a point source on the spatial scale of the cell and is represented mathematically as a Dirac delta distribution $\delta(\mathbf{x}-\hat{\mathbf{x}})$ for a CRU located at $\hat{\mathbf{x}}$. The definition of the Dirac delta distribution provides that (i) $\delta(\mathbf{x} - \hat{\mathbf{x}}) = 0$ when $\mathbf{x} \neq \hat{\mathbf{x}}$ and (ii) $\int_\Omega \psi(\mathbf{x})\, \delta(\mathbf{x} - \hat{\mathbf{x}})\, d\mathbf{x} = \psi(\hat{\mathbf{x}})$ for any continuous function $\psi(\mathbf{x})$. Thus, the amount of calcium released into the cytosol of the cell at $\hat{\mathbf{x}}$ is given by the flux density g, since $\int_\Omega g\, \delta(\mathbf{x} - \hat{\mathbf{x}})\, d\mathbf{x} = g$ by the definition of delta distribution.

In the original model and simulations [5,6,8,10], the flux density $g \equiv const.$ in (2) was kept constant uniformly for all CRUs. We refer to this as the Uniform CRU Flux Density (UCFD) implementation. It is apparent that parameters in physiological models obtained from experiments cannot be precisely reliable in their exact values. In uncertainty quantification (UQ), one tries to gain more certainty about the overall model behavior by running a large number of simulations, with one (or more) key parameters allowed to vary statistically. With the underlying assumption that there is a correct value or range, a normal distribution $N(\mu_g, \sigma_g)$ with mean μ_g and standard deviation σ_g is a reasonable choice.

This work focuses on uncertainty quantification applied to the flux density g, since this is a particularly important parameter to the question of wave initiation in this model. The thesis [2] and this work generalize (2) to a Stochastic Uniform CRU Flux Density (SUCFD) implementation, in which the flux density in (2) is sampled stochastically $g \in N(\mu_g, \sigma_g)$, but still uniformly for all CRUs. The purpose of this work is to demonstrate the steps needed to perform uncertainty quantification on a model. That is, we demonstrate first how one might choose μ_g and σ_g in $N(\mu_g, \sigma_g)$ and then how many statistical samples of this distribution might be needed to gain confidence in the results. We finish by the example of wave initiation to demonstrate the types of conclusions possible in uncertainty quantification.

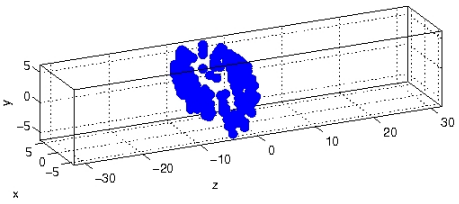
2. RESULTS

2.1 Visualization of Simulations of CICR

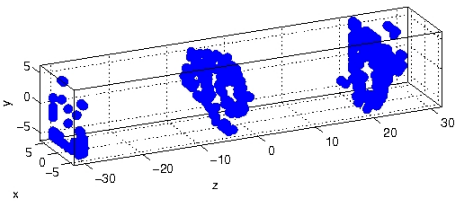
We solve the model of calcium induced calcium release given by the system of coupled, time-dependent advection-reaction-diffusion equations (1), where the calcium release is modeled by (2) with a constant uniform CRU flux density (UCFD) $g = 110$ μM μm^3 / ms at all CRUs. Figures 1 and 2 show two ways to visualize the initiation of calcium waves through the cell by plotting at the times from $t = 100$ ms to $t = 500$ ms. In this simulation, we have several waves self initiate and propagate throughout the cell.

The first plotting method is called a CRU plot, shown in Figure 1. The fat dots in this plot mark which CRUs are open at a particular time in the simulation. Figure 1 (a) shows that by $t = 100$ ms, a group of CRUs are open near the middle of the cell. The fundamental mechanism of the model (2) favors opening of CRUs close to already-open CRUs, since their released calcium diffuses through the cell, increases the concentration at nearby CRUs, and makes their opening more likely. Thus, at a slightly later time $t = 200$ ms in Figure 1 (b), the open CRUs have traveled in both directions from the middle, and the CRUs in the middle have opened for the second time. Interrupted by the rest period of 100 ms of each CRU, the increasing calcium concentration forms a diffusion wave through the cell, and the CRUs follow this effect by opening and closing.

The second plotting method is called isosurface plot, shown in Figure 2. This plot shows the same times as the CRU plots, but on the calcium concentration. The isosurface plot gives us a three-dimensional representation of how the calcium diffuses through the cell. Inside the surface, the concentration is higher than $u_{\text{crit}} = 65$ μM, while outside the plotted area the concentration is lower than u_{crit}. Where the surface with $u_1 = u_{\text{crit}}$ touches the boundary of the domain, the concentration may be higher than u_{crit}, and this is indicated by the color palette increasing from blue over yellow to red on the cell boundary. This plot indicates that the concentration around open CRUs increases due to the release from the calcium store, but decreases again due to diffusion and reactions with the other species to the basal level away from active CRUs. Over time, this forms a diffusion wave of increasing calcium concentration that self-organize without electrical stimulation. Since the heart



$t = 100$ ms



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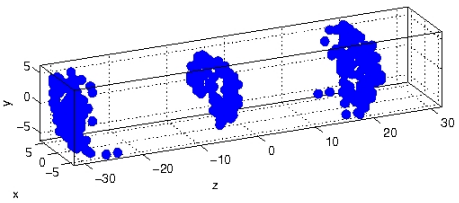

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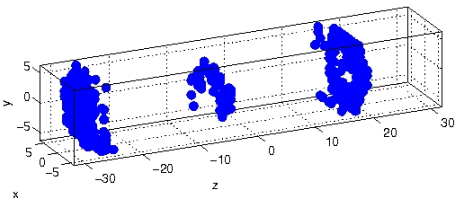
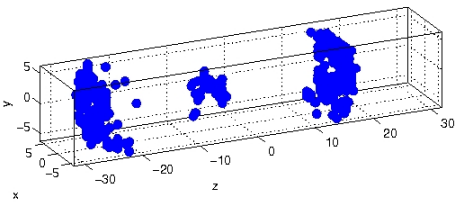
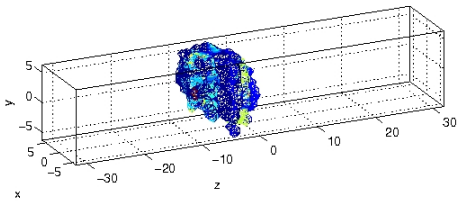


$t = 400$ ms

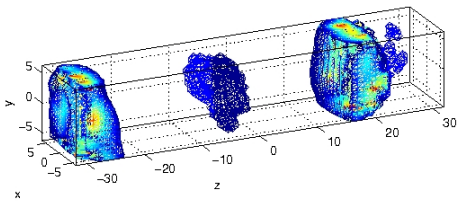


$t = 500$ ms

Figure 1. CRU plots for $g = 110$.



$t = 100$ ms



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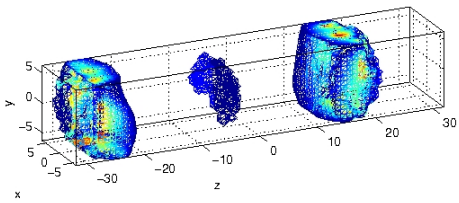

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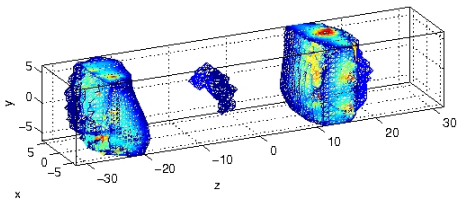

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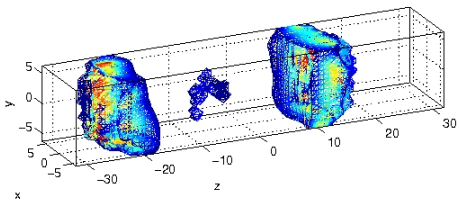


$t = 500$ ms

Figure 2. Calcium isosurface plots for $g = 110$.

beat is supposed to be controlled by electrical stimulation, self-organization of waves without it can potentially lead to irregular heart beat.

2.2 Stochastic Uniform CRU Flux Density

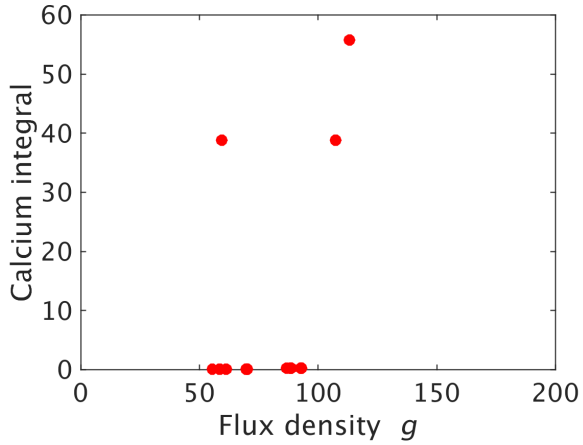
Simulations for a smaller value of flux density $g = 50$ μM μm^3 / ms do not result in self-organization of calcium waves [2, 5]. We conclude from the simulations for $g = 110$ and $g = 50$ that there must be a critical value of the flux density between these values at which waves self-organize. The purpose of the following work is to use a parameter study to identify the critical value. We also note that it is possible for g to be simply so high that the cell will get saturated in the model beyond physiological reasonableness, so we are prepared for a second critical value that would limit the range of g values with reasonable physiological behavior.

To reduce the overall number of simulations needed, the parameter study uses a normal distribution of values of g to concentrate the effort in a rational way around the most likely value. Based on the values of g used above, we choose the mean value $\mu_g = 75$ and standard deviation $\sigma_g = 25$ in the normal distribution $N(\mu_g, \sigma_g)$ used in the parameter study for g, defining the Stochastic Uniform CRU Flux Density (SUCFD) of (2).

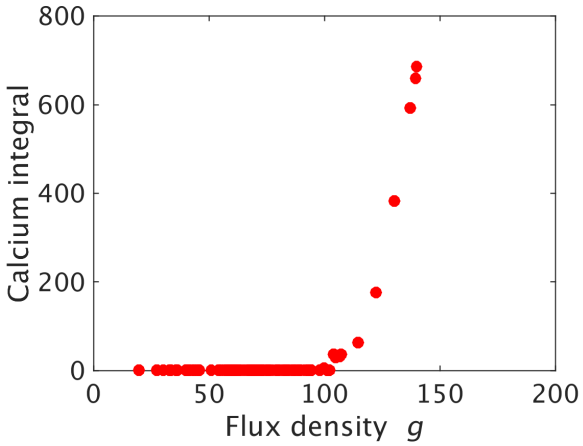
We analyze the results of running the SUCFD to get a more complete picture of how g influences the behavior of the model. To examine the effect of stochastic g values we will look at the correlation between them and the total number of moles of calcium over the entire domain Ω, given by $I^{(1)} = \int_\Omega u^{(1)}(\mathbf{x}, t)\, d\mathbf{x}$ [1, 4, 9]. This calcium integral over the entire cell is in particular an indicator of cases where the value of g is higher than is physiological reasonable and is taken at $t = 1000$ ms in the figures.

First, we examine the results after taking $M = 10$ samples shown in Figure 3 (a). We see that there is no noticeable trend in the data, so we increase the number of samples to $M = 100$. Figure 3 (b) shows the data for $M = 100$ samples and we see that as g increases the total amount of calcium in the cell also increases. We also see that there is a critical point at approximately $g = 100$ where calcium begins to increase dramatically; this is the value, beyond which the calcium concentration is reasonable, since the concentration in between waves is not restored to basal levels any more. To gain a better understanding of this trend, we take $M = 1000$ samples. Figure 3 (c) shows the data for $M = 1000$ samples. We see that the trend observed with $M = 100$ samples is sustained and that as the value of g increases the total amount of calcium increases.

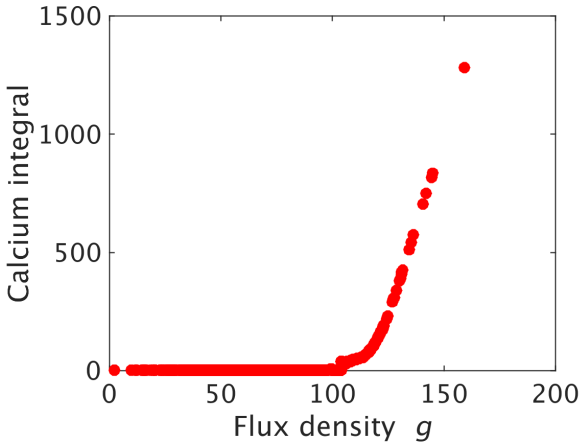
Next, we use the data from the full simulations with $M = 1000$ samples, but we scale the value calcium integral on the vertical axis by the volume of the cell $V = 10000$ μm^3, since $I^{(1)}/V$ in units of μM can be compared to the basal level 0.1 μM to indicate if waves begin to self-organize and propagate. Figure 4 (a) shows the full data from Figure 3, but with the vertical axis



(a) $M = 10$ samples



(b) $M = 100$ samples



(c) $M = 1000$ samples

Figure 3. Plots of total moles $I^{(1)}$ vs. g for different sample sizes.

scaled by V and the horizontal axis restricted so as to avoid the values of g which overload the cell. After scaling the vertical axis, we search for the critical point at which calcium integral becomes greater than

basal level 0.1μM. One critical value at about $g \approx 104$ is visible, beyond which the calcium concentration simply grows unreasonably. Closer inspection of the data themselves also indicates another critical value at about $g \approx 71.1$ μM μm^3 / ms. Figure 4 (b) shows that this critical point is one where activation starts occurring, that is, below $g \approx 71.1$, no CRUs are regularly captured open, while above this value individual CRUs open, clusters of CRUs open, and waves form, which is indicated by $I^{(1)}/V$ greater than the basal level 0.1 μM. In addition, we investigate the region in which the calcium integral begins to blow up. Looking at Figure 4 (c), we see calcium indeed begins to blow up at $g \approx 104$ μM μm^3 / ms, where $I^{(1)}/V$ reaches much larger values than the basal level 0.1 μM.

3. CONCLUSIONS

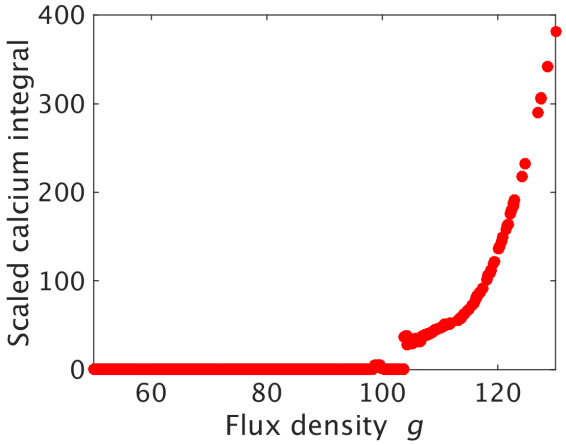
This brief note shows the steps involved in applying the concept of uncertainty quantification to a key parameter of a physiological model. The results of our Stochastic Uniform CRU Flux Density (SUCFD) studies show that patterns can be identified in the data if a sufficient number of samples are used. Specifically, we are able to quantify the range of g values, in which it is likely that calcium waves form in a physiologically realistic way, that is, while returning to basal levels in between waves. By contrast, if g is outside this range, either no waves form or the cell concentration increases without bound, which is physiologically unrealistic.

A further generalization to the case of Stochastic Independent CRU Flux Density (SICFD), where the flux density g can be different at every CRU, show that the model reacts correctly to spatially non-uniform values of g, as studied in [2] and has been shown to be important in previous work [7, 11]. This is demonstrated by a test case, in which CRUs in one half of the cell are fixed, while they are varied in the other half; for this setup, waves predominantly occur in the half with the higher values of g. This confirms that spatially non-uniform values of g have the correct effect. The test case in that thesis sets the stage for fully stochastic simulations using the SICFD code.

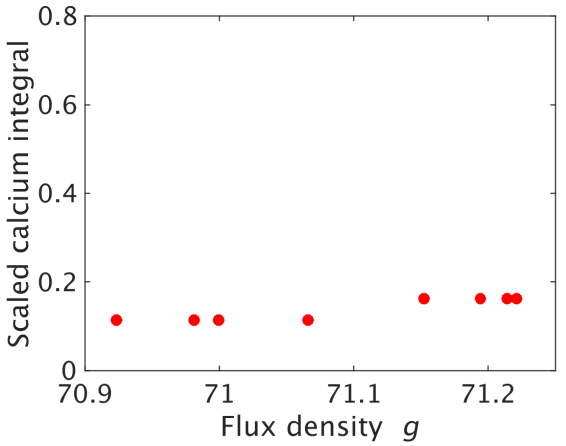
APPENDIX

A. NUMERICAL METHOD

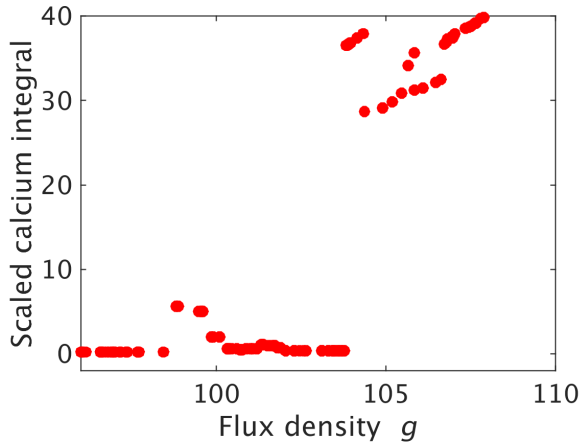
In order to simulate the calcium spark model, memory-efficient numerical methods are implemented. The uniform rectangular CRU lattice is used to create a regular numerical mesh. The model uses constant diffusion coefficients. We use the finite volume method for spatial discretization. The parameters to control the timestep selection in the time-stepping NDFk method are $\tau_{rel}^{ode} = 10^{-6}$ and $\tau_{abs}^{ode} = 10^{-8}$, and the tolerance for the Newton solver is $\tau^{newt} = 10^{-4}$. The Krylov subspace method used to solve the system of linear equations is BiCGSTAB with tolerance $\tau^{lin} = 10^{-2}$.



(a) Scaled vertical axis



(b) Initial region of calcium activity



(c) Calcium blow up region

Figure 4. Plots of scaled total moles $I^{(1)}/V$ vs. g with $M = 1000$.

The C code used to perform the parallel computations uses MPI for parallel communications. The computations for this study are preformed on a cluster using C/MPI under the Linux operating system on multiple

nodes. Each node features two quad-core Intel Nehalem X5550 processors (2.66 GHz, 8 MB cache) with 24 GB of memory. To distribute the vector of unknowns among p processes, we split the mesh in the z-direction and distribute the unknowns into p subdomains for p parallel processes. For more specifics refer on how this problem was parallelized refer to [10]. The parallelization of the method is vital to decrease the simulation time for each of the parameters to 3 to 5 minutes, so that large numbers of samples can be analyzed in reasonable time.

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