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A mathematical model of spontaneous calcium(II) oscillations in astrocytes

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Abstract

Astrocytes exhibit oscillations and waves of Ca^{2+} ions within their cytosol and it appears that this behavior helps facilitate the astrocyte's interaction with its environment, including its neighboring neurons. Often changes in the oscillatory behavior are initiated by an external stimulus such as glutamate, recently however, it has been observed that oscillations are also initiated spontaneously. We propose here a mathematical model of how spontaneous Ca^{2+} oscillations arise in astrocytes. This model uses the calcium-induced calcium release and inositol cross-coupling mechanisms coupled with a receptor-independent method for producing inositol (1,4,5)-trisphosphate as the heart of the model. By computationally mimicking experimental constraints we have found that this model provides results that are qualitatively similar to experiment.

1. Introduction

In the past few decades, the suggested role of astrocytes in the central nervous system has increased dramatically. Initially thought of as being a passive structural element that held the neurons together, they are now found to play a much more active part in the signaling process (Charles et al., 1991; Cornell-Bell et al., 1990; Dani et al., 1992). The evidence that indicates that astrocytes interact with neurons has come from experiments *in situ* (Kang et al., 1998; Newman and Zahs, 1998; Pasti et al., 1997), and with neuron–astrocyte co-cultures (Araque et al., 1998; Neder-gaard, 1994). The work has shown that stimulated changes in the astrocyte's cytosolic Ca^{2+} concentration can alter the surrounding neural activity by releasing chemicals such as glutamate and ATP. This leads to the idea that the synapse is tripartite, where the pre- and postsynaptic neural elements, as well as the astrocyte, respond to one another via neuro- and gliotransmitter release (Haak et al., 1997; Holtzclaw et al., 2002; McHugh et al., 2000; Parri et al.,

2001). These interactions can have profound results, with effects that can apparently alter long-term depression (LTD) and play a role in disease states such as epilepsy (Massey et al., 2004; Tian et al., 2005). In many of these cases where astrocytes are seen to interact with their environment, a change in the concentration or oscillatory behavior of the astrocyte's $[Ca^{2+}]_{cyt}$ appears to be an integral step in the process.

While the changes in the astrocyte's oscillatory Ca^{2+} behavior is often found to be a result of external stimulation, these oscillations can also be formed spontaneously. Spontaneous Ca^{2+} oscillations have been observed in the astrocyte's cytosol both in culture (Charles, 1994; Fatatis and Russell, 1992; Harris-White et al., 1998) and *in situ* from cells originating in several different parts of the brain, such as the ventrobasal (VB) thalamus, hippocampus and cortex (Aguado et al., 2002; Nett et al., 2002; Parri et al., 2001). When the neural input to the astrocyte is blocked, the timing of these Ca^{2+} spikes appears to be relatively random within the astrocytic field; however, when the neurons were allowed to interact, the spontaneous behavior became more correlated between the astrocytes (Aguado et al., 2002; Parri et al., 2001).

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Thus, while the functional significance of these spontaneous oscillations is unknown, it appears that in conjunction with neuronal input, the behavior may help correlate the activity of both the astrocytes and the neurons.

In this study, we investigated key mechanistic steps by which these spontaneous Ca^{2+} oscillations could occur using numerical simulation. Despite the previous experimental studies into this area, few models have been put forth for the generation of this type of Ca^{2+} oscillations (Goto et al., 2004). We propose a model for this behavior that is triggered by small changes in the cytosolic calcium concentrations brought on by the flux of calcium ions through the astrocyte's membrane. The oscillations are sustained by the interaction of inositol (1,4,5)-trisphosphate (IP_3) and extracellular, cytosolic and endoplasmic Ca^{2+} through the inositol cross-coupling (ICC) (Meyer and Stryer, 1988, 1991) and the calcium-induced calcium release (CICR) (Dupont et al., 1991; Dupont and Goldbeter, 1993; Goldbeter et al., 1990) mechanisms. Our simulations have produced results that are qualitatively similar to experiment with appropriate frequency, amplitude and behavioral dependence as parameters controlling various physical attributes are changed.

2. Methods and materials

Simulations were performed using the double precision Livermore solver of ordinary differential equations (DLSODE) routine from Lawrence Livermore National Laboratory's Center for Applied Scientific Computing as well as Berkeley Madonna, an ODE solving package that used the Rosenbrock algorithm. All diagrams were produced from the results of the DSLODE routine.

3. Presentation of the model

We have developed a model of spontaneous calcium oscillations in astrocytes based on experimental observations and previous theory. This model involves three variables: Ca^{2+} concentration in the cytosol (X), Ca^{2+} concentration in the endoplasmic reticulum (ER) (Y), and the IP_3 concentration in the cell (Z).

Within this model, the oscillatory behavior is initiated by small changes in $[Ca^{2+}]_{cyt}$ that is caused by varying the flux of extracellular Ca^{2+} across the plasma membrane into the cytosol. The possibility that small changes in the cytosolic calcium concentration could cause such a dynamical change is supported by experiment (Aguado et al., 2002). The primary self-perpetuating mechanism for the oscillations is two coupled feedback loops in which the feedback species are Ca^{2+} and IP_3. The feedback loops center on the release of calcium ions from the ER to the cytosol via the type-2 inositol trisphosphate receptor (IP_3R-2) (Holtzclaw et al., 2002; Sharp et al., 1999). The generation and continuation of the oscillatory events are aided by the receptor's activation by IP_3 and its modulation by cytosolic Ca^{2+}. IP_3 is a known intracellular messenger and after its

production is initiated, possibly by the delta-isoform of phospholipase C (PLC), it can bind to the IP_3 receptors on the membrane of the ER. As cytosolic calcium ions can also bind to these receptors, the ion can feedback and is able to both enhance and reduce the flow of other Ca^{2+} ions passing through the channel. The cytosolic calcium ions can also positively feedback on the activation process of PLC and enhance the production of IP_3, which in turn enhances Ca^{2+} release from the ER (Meyer and Stryer, 1988, 1991). In our model, the sequestration of Ca^{2+} ions in the ER occurs through the sarco(endo)plasmic calcium ATPase (SERCA) pump. The importance of the ER and of the IP_3R is supported by pharmacological experiments that show a significant decrease in the number of spontaneous events upon the Ca^{2+} depletion of the ER by blocking the SERCA pump (Aguado et al., 2002; Nett et al., 2002; Parri et al., 2001) or inhibition of the IP_3 receptor (Nett et al., 2002; Parri and Crunelli, 2003). The details of the model are further discussed after the presentation of the equations.

The model is governed by three ordinary differential equations which represent interactions in the microdomain between the cell membrane and the ER (illustrated in Fig. 1):

$(X = [Ca^{2+}]_{cyt}, \ Y = [Ca^{2+}]_{ER}, \ \text{and} \ Z = [IP_3]_{cyt})$,

$$\frac{dX}{dt} = v_{in} - k_{out}X + v_{CICR} - v_{serca} + k_f(Y - X),$$
$$\frac{dY}{dt} = v_{serca} - v_{CICR} - k_f(Y - X),$$
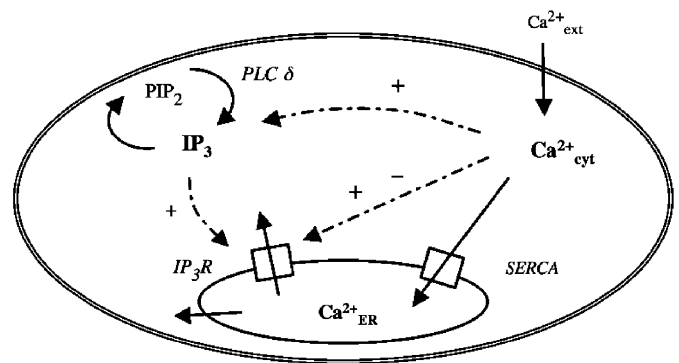$$\frac{dZ}{dt} = v_{PLC} - k_{deg}Z,$$

Fig. 1. Schematic illustration of the model. Aside from the entry of Ca^{2+} from the extracellular medium, no other external influences are needed for the generation of spontaneous oscillations. This model takes into account one internal Ca^{2+} store, the endoplasmic reticulum (ER), and that IP_3 is created with help from PLCδ. The dashed lines indicate feedback or cooperative effects. IP_3 cooperatively opens the IP_3 receptor (IP_3R) allowing Ca^{2+} to flow out of the ER. This receptor is also influenced by the concentration of cytosolic Ca^{2+}; at lower concentrations the Ca^{2+} ions activate the opening of the receptor and at higher concentrations they are inhibitory. The Ca^{2+} ions also help activate PLCδ, which in turn will help produce more IP_3.

$$v_{serca} = v_{M2}\left(\frac{X^2}{X^2 + k_2^2}\right),$$

$$v_{PLC} = v_p\left(\frac{X^2}{X^2 + k_p^2}\right),$$

$$v_{CICR} = 4v_{M3}\left(\frac{k_{CaA}^n X^n}{(X^n + k_{CaA}^n)(X^n + k_{CaI}^n)}\right)$$

$$\times \left(\frac{Z^m}{Z^m + k_{ip3}^m}\right)(Y - X).$$

The term v_{in} represents the flow of calcium from the extracellular space through the astrocyte's membrane and into the cytosol. This flow is essential to the creation of the spontaneous oscillations as they are virtually eliminated when the specimen is bathed in Ca^{2+}-free medium (Parri et al., 2001). (The few oscillations that occur in Ca^{2+}-free medium are due to release of the ion from intercellular stores.) Similar loss of activity occurs after the application of Co^{2+}, a non-specific voltage gated Ca channel blocker. Although the N, P, Q high-voltage-activated channels cause a decrease in the oscillations, a more significant decrease is caused by a block of the L-type channels (Aguado et al., 2002; Parri and Crunelli, 2003; Parri et al., 2001). By changing the value associated with the v_{in} term, the simulated flow of Ca^{2+} ions into the cytosol is being modified, and based on experiment, this appears to mainly correspond to an inactivation of L-type channels and to a lesser degree the high-voltage-activated channels. The range of values used in this study are of the same magnitude as those used in Hofer et al. (2002) and are representative of the relatively small flux that occurs during spontaneous oscillations in the absence of agonist stimulated Ca^{2+} ion flux.

The term $k_{out}X$ represents the rate of calcium efflux from the cytosol into the extracellular space. The values for these constants were determined by fitting the Hofer et al. (2002) model to experimental measurements of Venance et al. (1997).

v_{CICR} represents the IP$_3$R-mediated flux of calcium from the ER to the cytosol and is specifically built to accommodate the evidence that the IP$_3$R-2 is preferentially expressed in astrocytes (Holtzclaw et al., 2002; Sharp et al., 1999). As this receptor is influenced by IP$_3$ and calcium ions from both the ER and cytosol, its dynamics will depend on 3 main terms. Fitting experimental data show the IP$_3$R-2 to have a sigmoidal dependence on IP$_3$ that is slightly steeper than that seen for the other isoforms (Tu et al., 2005b). Further experiments show that all isoforms of the IP$_3$R display bell-shaped cytosolic Ca^{2+}-dependence in the physiological range (Bezprozvanny et al., 1991). For the type-2 isoform, the activating and inhibiting affinities, k_{CaA} and k_{CaI}, as well as the Hill coefficient, n, came from experimental evidence fitted to the modified model for the IP$_3$R proposed in papers by Tu et al. (2005a, b) In the third term, the receptor will depend on the gradient of the calcium concentration between the ER and cytosol ($Y - X$).

Finally, the value to guide the maximum flux of calcium ions into the cytosol, v_{M3}, comes from work on hepatocytes (Hofer, 1999).

v_{serca} describes the sarco(endo)plasmic reticulum ATPase that fills the ER with calcium ions from the cytosol. Based on experiment, the rate of inflow appears to follow sigmoidal dynamics and the Hill form is used for its description. The Hill coefficient is found to have a value of two (Falcke, 2004) and the maximum flux of calcium ions out of the pump, v_{M2}, is based on experimental data for SERCA pumps in chicken cerebellums (Falcke, 2004; Schatzmann, 1989). The parameter describing the half-maximal value effect is of the same order of magnitude as many experimental results for SERCA pumps and has also been used in other models (Falcke, 2004; Houart et al., 1999).

Finally, $k_f(Y-X)$ represents the leak flux from the ER into the cytosol due to the concentration gradient. The high relative Ca^{2+} concentration in the ER makes passive diffusion through the membrane possible and there are suggestions that Ca^{2+} may be able to leak through unactivated IP$_3$Rs (Parri and Crunelli, 2003; Simpson and Russell, 1997). (To account for the Ca^{2+} buffering encountered in the ER, the initial concentration for the simulation is set to the low end of the range of what has been encountered experimentally.) Although many models make the assumption that the actual concentration gradient ($[Ca^{2+}]_{ER}-[Ca^{2+}]_{cyt}$) can be simplified to $[Ca^{2+}]_{ER}$ due to the negligible concentration of Ca^{2+} in the cytosol, other simulations from our lab have shown that at times the dynamical behavior is sensitive to this simplification.

The fluctuations in the IP$_3$ concentration is modeled by a production and degradation term. Although IP$_3$ is typically formed through a path initiated by an external signal, in the case of spontaneously generated oscillations, production must be initiated by a mechanism internal to the cell. It has been shown that these oscillations are not dependent on *receptor*-mediated PLC activity, but PLC activity is nonetheless indicated (Parri and Crunelli, 2003), and for that reason, our work focuses on the delta-isoform of PLC (PLCδ1). Studies indicate that this isoform is not as closely situated to the stimulating receptor sites as the beta and gamma forms, and consequently does not appear to be activated via the normal external signals (Rebecchi and Pentyala, 2000). It does, however, appear to be activated by changes in the physiological levels of cytosolic Ca^{2+}, which suggests that the IP$_3$ formation in astrocytes undergoing spontaneous activity is the result of the internal stimulation of PLCδ1 by cytosolic calcium ions (Allen et al., 1997; Pandey et al., 1996; Parri and Crunelli, 2003). (This process is described in our IP$_3$ production term, v_{PLC}.) Assuming sigmoidal dynamics for this process, we followed the PLCδ1 kinetics found in the Hofer model (Hofer et al., 2002; Parri and Crunelli, 2003), which uses parameters fit from experiment (Pawelczyk and Matecki, 1997). The degradation of IP$_3$ ($k_{deg}Z$) is based on the linear

dependence of IP_3 degradation by 5-phosphatase and is also seen in models (Hofer et al., 2002; Houart et al., 1999).

Although PKC action is primarily thought to be driven by external signals, it can also respond to internal forces. To that end, experimental evidence shows that the inhibition of PKC results in the spontaneously generated behavior changing from a spiking regime to one that results in sustained, elevated calcium ion concentration (relative to baseline) (Allen et al., 1997; Pawelczyk and Matecki, 1997). This indicates that PKC does have a role in the formation of this behavior in astrocytes and appears to at least indirectly interact with the IP_3R. Although that work did not directly connect the behavior to a particular cellular structure, studies with PKC on various cell types show that it can influence L-type channels in a variety of ways depending on what isoform is present, the expression level, etc. (Kang and Walker, 2005; McHugh et al., 2000). However, in contrast to the astrocyte work noted above, several studies have indicated that it can inhibit L-type calcium channels and thus decrease the rate of Ca^{2+} influx from the extracellular matrix in both astrocytes and cardiac cells (Haak et al., 1997; Kang and Walker, 2005; McHugh et al., 2000). Although the experimental work is still inconclusive, our simulations suggest that PKC is intimately involved in generating the spontaneous behavior.

4. Results and discussion

This model supports the idea that spontaneous Ca^{2+} oscillations can be generated without the aid of external stimulation (Parri and Crunelli, 2003). Small changes in the rate of Ca^{2+} entry through the plasma membrane cause enough change in the local $[Ca^{2+}]_{cyt}$ to activate the ICC–CICR mechanisms, which are key to the development and propagation of oscillatory behavior. This agrees with experimental observations that more cells exhibit spontaneous behavior after an increase in the cytosolic concentration of Ca^{2+}, thus giving experimental indications that the concentration of the calcium ions in the cytosol is closely linked to the ability of a cell to undergo this type of behavior (Parri and Crunelli, 2003). In our model, the cytosolic Ca^{2+} concentration can be most easily manipulated by v_{in}, the parameter representing the influx of the ions from the extracellular matrix. As v_{in} is raised, and consequently the concentration of cytosolic Ca^{2+} is elevated, it is found that the model system moves from a steady state to period-1 behavior (Fig. 3) then back to an elevated steady state. (The bifurcation diagram is represented by the black curve in Fig. 2.) Experimentally the dependence of the spontaneous oscillations on $[Ca^{2+}]_{cyt}$ is noted in Parri and Crunelli (Parri et al., 2001).

The spikes occur with a regular frequency, and the period of oscillation varies from approximately 150 to 700 s, which is characteristic of the relatively slow dynamics seen in most spontaneous activity (Fig. 3). In many of the astrocytes that display spontaneous activity, the time between spikes tends to be longer than 100 s, although in
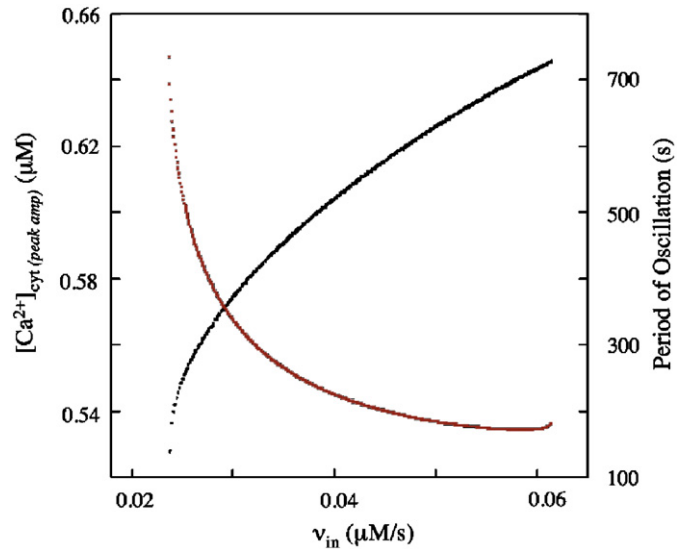

Fig. 2. Bifurcation diagram of Ca^{2+} overlaid with the periodicity of oscillations (black curve). The single curve for the bifurcation diagram indicates that this model displays period-1 behavior in $[Ca^{2+}]_{cyt}$ throughout the oscillatory window of v_{in}. At smaller v_{in} values the behavior is steady state, at larger v_{in} values the behavior is also steady state, but at a higher concentration (red curve). In the period-1 region, as the $[Ca^{2+}]_{cyt}$ is increased by raising v_{in}, the oscillatory period decreases as seen in experiment (Parri and Crunelli, 2003). *Parameter values for all figures unless noted*: $v_{M2} = 15.0\,\mu M/s$, $v_{M3} = 40.0\,s^{-1}$, $v_{in} = 0.05\,\mu M/s$, $v_p = 0.05\,\mu M/s$, $k_2 = 0.1\,\mu M$, $k_{CaA} = 0.15\,\mu M$, $k_{CaI} = 0.15\,\mu M$, $k_{ip3} = 0.1\,\mu M$, $k_p = 0.3\,\mu M$, $k_{deg} = 0.08\,s^{-1}$, $k_{out} = 0.5\,s^{-1}$, $k_f = 0.5\,s^{-1}$, $n = 2.02$, $m = 2.2$. *Initial conditions*: $Ca_{cyt}^{2+} = 0.1\,\mu M$, $Ca_{ER}^{2+} = 1.5\,\mu M$, $Ca_{ER}^{2+} = 1.5\,\mu M$, $IP_3 = 0.1\,\mu M$.
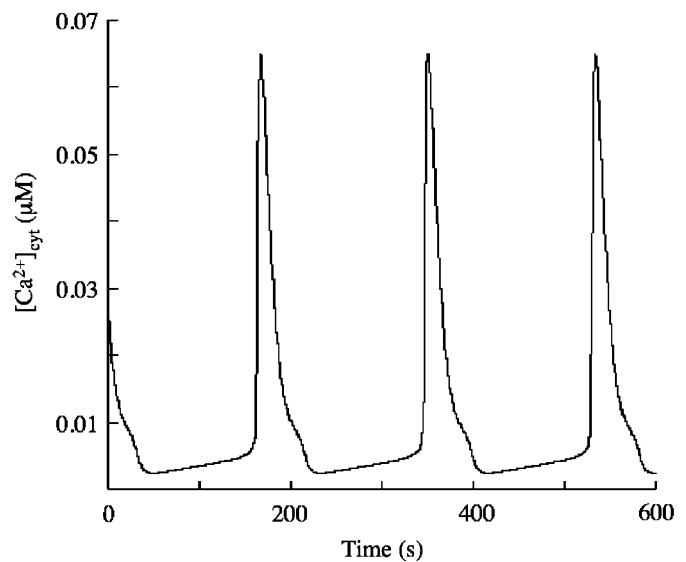

Fig. 3. Typical structure of the simulated oscillations.

terms of frequency, it is often not a regularized process (Aguado et al., 2002; Nett et al., 2002). The regular frequencies seen in our model is a product of its minimalist roots. However, it should be noted that the simple oscillatory behavior seen in Fig. 3 agrees with experimental results from epileptiform tissues, where the calcium oscillations seen after seizure have regular oscillatory

patterns with periods of averaging approximately 100 s (Manning and Sontheimer, 1997; Parri and Crunelli, 2003; Tashiro et al., 2002). While the number of experiments carried out on epileptiform tissue is small, it may be suggested that the regular period of oscillation in these astrocytes may be the result of an oscillatory mechanism that is less complex than that in normal cells.

In addition, the cytosolic Ca^{2+} concentration of the simulations oscillates within physiological levels and the spike shape and peak amplitude is similar to that seen in experiment, especially in the studies done on epileptic tissue (Manning and Sontheimer, 1997). Simulations also show a link between the increase in cytosolic Ca^{2+} and the decrease in the oscillatory period, which have also been seen experimentally (Parri and Crunelli, 2003) (red curve in Fig. 2).

Although PKC is not explicitly modeled within our system, it is possible to mimic this inhibition by changing the term v_{in}. By following the idea that the influx of external Ca^{2+} is indirectly related to the concentration of PKC, PKC inhibition can be modeled by increasing the value of v_{in} (Fig. 4). Our elevated steady-state concentrations do qualitatively represent the physiological results seen in Parri and Crunelli (2003) and thus suggest that PKC does have a role in this process.

With its ability to quickly store and release a large amount of Ca^{2+}, the ER has long been thought to play a key role in the propagation of Ca^{2+} oscillations and waves. Thus, the understanding of the pathways used by Ca^{2+} for entry and exit to the ER, and how these paths affect the dynamical behavior of Ca^{2+} are of importance. The
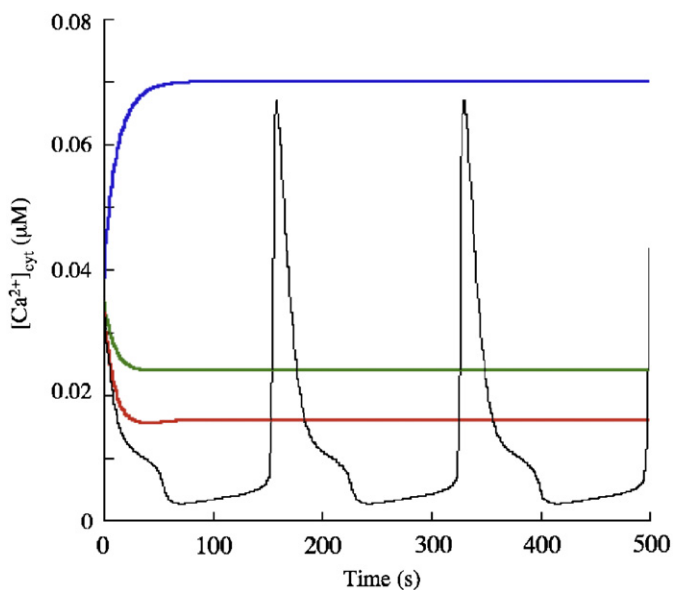

Fig. 4. With an increase in v_{in}, which mimics the increasing inhibition of PKC, the behavior changes from oscillatory to steady state. As v_{in}, continues to increase, the steady-state concentration also increases relative to the baseline concentration seen in the oscillatory state. Oscillation: (black) v_{in} is equal to 0.06 μm/s. Steady states in increasing concentration order: (red) v_{in} is equal to 0.08 μm/s, (green) v_{in} is equal to 0.12 μm/s, and (blue) v_{in} is equal to 0.35 μm/s.

activation and inhibition of the sarco(endo)plasmic reticulum ATPase (SERCA) pump, a primary route by which Ca^{2+} is returned to the ER, has profound effects on the behavior of the calcium ions. By decreasing the value of v_{M2}, the parameter controlling the maximum flow rate through the SERCA pump, the flow of Ca^{2+} ions into the ER is lowered and the inhibition of the pump is mimicked. Simulations show that when this flow rate is lowered, the ability to form multiple high amplitude spikes is reduced (Fig. 5). Similarly, experimental inhibition of the SERCA pump by cyclopiazonic acid leads to large reduction in the number of cells undergoing the spontaneous behavior, and for those cells that did exhibit concentration changes the typical result was a short initial increase in cytoplasmic calcium, and then a slow return to baseline levels after a few minutes (Nett et al., 2002; Parri and Crunelli, 2003; Parri et al., 2001). Further observations of the inhibition of the SERCA pump by thapsigargin found that there was a decrease in both the amplitude and frequency of the $[Ca^{2+}]_{cyt}$ oscillations (Aguado et al., 2002; Tashiro et al., 2002). In the simulations, the frequency of the oscillations increases in contrast to experiment. However, similar to experiment, by reducing the flow rate into the ER, our simulations show that the oscillatory amplitude was reduced and would eventually go to steady state (Fig. 6). This is brought about by the increase in the baseline concentration of cytosolic Ca^{2+} that feeds into increasing the rate of IP_3 production and degradation; ultimately this increases the frequency, but shortens the duration of the open phase of the IP_3R.

In terms of the release of Ca^{2+} from the ER, the IP_3 receptor is a central player. To simulate the inhibition of this receptor, the value of v_{M3} was lowered. As the flow of calcium ions through the IP_3R was reduced the results (Fig. 7) show that oscillations cease. Similar dynamics are seen experimentally when heparin or 2-aminoethoxydiphenylborate (2-APB) interact with this receptor (Nett et al., 2002; Parri and Crunelli, 2003).

Although most experimental work shows spike sequences similar to period-1 behavior, there are often small variations in frequency. For the parameter values tested no variation such as this were encountered, but it should be noted that this model is deterministic and treats the leak of Ca^{2+} from the extracellular matrix to the cytosol as a constant. Under normal cellular conditions it would be expected that the inward flux varies stochastically and that could result in small frequency variation. Other studies show more complex behavior (Aguado et al., 2002; Nett et al., 2002; Tashiro et al., 2002). This model, with small changes in parameter values, can also be shown to go through more complex oscillations such as a period adding regime to chaos (Fig. 8). These simulations result from a higher value for k_{CaA} and k_{CaI}, and a lower k_p value than given in Fig. 2, and an example of the oscillatory profile is shown in Fig. 9. In comparison to the simulations above, physically these changes would mean that the PLCδ1 dynamics have a faster response to Ca^{2+}, the rate of release
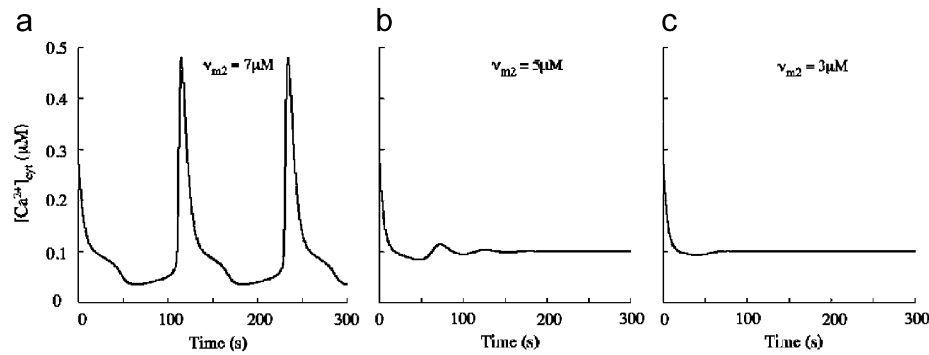
Fig. 5. Decreased flow rate through the SERCA pump leads to a damping of oscillatory behavior. The increasing inhibition of the SERCA pump is modeled by decreasing v_{M2}, the maximum flow rate through the SERCA pump. As v_{M2} is lowered (a–c) the ability to form sustained high-amplitude oscillations is diminished.
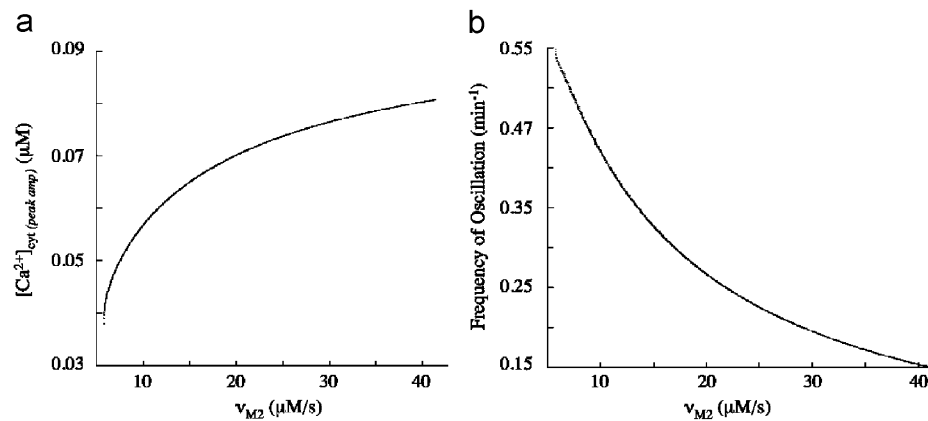

Fig. 6. Changes in SERCA pump flow rate cause changes in oscillatory amplitude and frequency: (a) within the oscillatory range, as v_{M2} is decreased (indicating greater inhibition of the SERCA pump) the peak amplitude decreases; (b) however, the periodicity increases.
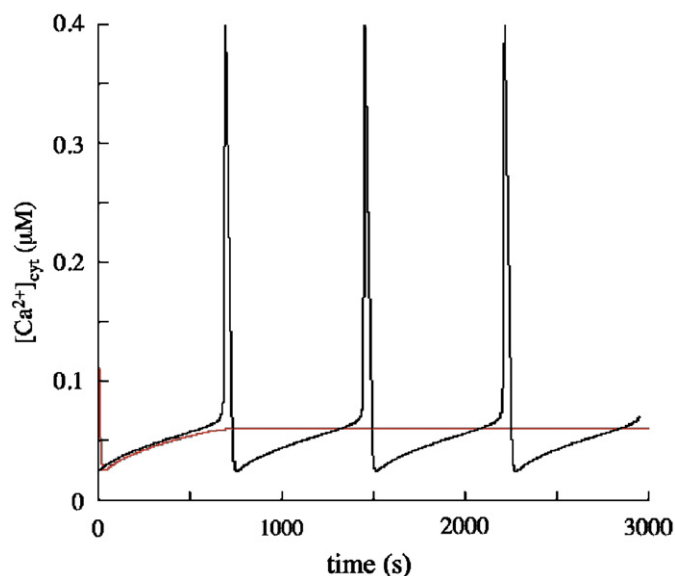

Fig. 7. Decreased flow rate through IP$_3$R leads to loss of oscillatory behavior. The parameter v_{M3}, which guides the maximal flow rate through the IP$_3$R, was decreased from $40\,\mathrm{s}^{-1}$ (black line) to $10\,\mathrm{s}^{-1}$ (red line) the behavior changes from period-1 oscillations to steady state.

of Ca^{2+} via the IP$_3$R occurs at a higher concentration of cytosolic Ca^{2+} and this rate would not drop off as quickly. Within the experimental work, no linkage was made as why the different modes of behavior arose; however, based on our work it could be hypothesized that small changes in the efficiency of the mechanistic steps due to developmental stage, injury, etc., could cause a significant change in the oscillatory response of the cytosolic Ca^{2+}.

The connection between the glia and neurological health has been postulated for the better part of a century; however, there was little evidence supporting this interaction until recently. From as early as 1927 it has been suspected that glia could be involved in neurological disease. The early studies by Penfield looked at the connection between glial scarring and post-traumatic epilepsy (Penfield, 1927). Recent studies have focused on the chemical interplay between neurons and glia and have more solidly implicated astrocytes, and the changes in their cytosolic Ca^{2+} concentration, as having an influence on some neurological and epileptic events (Fellin et al., 2006; Kang and Walker, 2005; Tian et al., 2005). Although their role has not been well defined, these observations
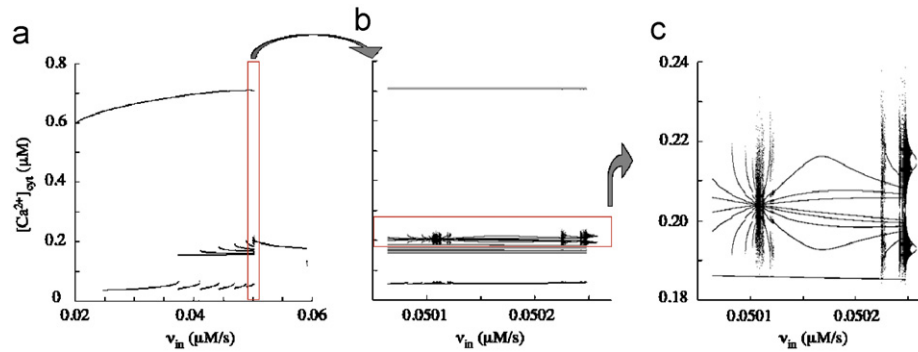
Fig. 8. Bifurcation diagrams showing more complex behavior can be generated by parameter changes. The period-adding behavior displayed above is seen when k_p is lowered, k_{CaA} and k_{CaI} are raised. In this case, $k_p = 0.164$, $k_{CaA} = 0.27$, and $k_{CaI} = 0.27$; all other parameters values are as noted in Fig. 2. (b) Enlargement of the bifurcation pattern found within the red box in (a) and (c) is an enlargement of the pattern found in the red box of (b).
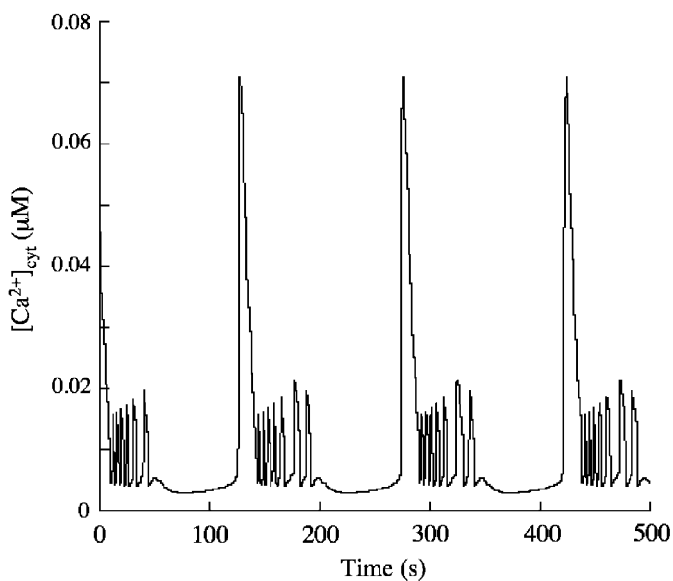

Fig. 9. Time series showing period-adding behavior with the simulation conditions noted in Fig. 8 and $v_{in} = 0.05 \, \mu m/s$.

underscore the importance of elucidating the mechanism behind the oscillatory behavior, as it appears to be not just a physiological curiosity, but also potentially an important link in neurological health.

5. Conclusion

Our model shows that spontaneous Ca^{2+} oscillations in the astrocyte can arise from a mechanism that involves interactions between IP_3 and pools of Ca^{2+} ions in the ER, cytosol and extracellular medium. Within the model, small changes in the rate in which Ca^{2+} enters the cell from the extracellular matrix can allow for the formation of IP_3 without an external signal and ultimately trigger a behavior change that is independent of the traditional signaling molecules. Using experimentally derived rate constants our model produces results that are qualitatively similar to that observed in the laboratory. Furthermore, as these constants are changed to mimic experimentally applied

stresses, with few exceptions our model's response is comparable to what is observed. These studies indicate that spontaneous oscillations can arise by a mechanism that does not require an extracellular signal, thus the astrocyte itself can initiate a process that could lead to neural signaling. At the same time, the formation and continuation of the oscillations is via the CICR and ICC mechanisms, elements common to models of receptor-mediated behavior. This may signify that the oscillatory regime has trigger points both internal and external to the cell; thus it is potentially able to process a variety of signal types and significantly influence its neighboring cells, including neurons. It may also mean that chemical networks that are, but slight deviations from normally established networks may influence certain pathological conditions.

Acknowledgement

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