Calcium Oscillations

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Calcium signaling results from a complex interplay between activation and inactivation of intracellular and extracellular calcium permeable channels. This complexity is obvious from the pattern of calcium signals observed with modest, physiological concentrations of calcium-mobilizing agonists, which typically present as sequential regenerative discharges of stored calcium, a process referred to as calcium oscillations. In this review, we discuss recent advances in understanding the underlying mechanism of calcium oscillations through the power of mathematical modeling. We also summarize recent findings on the role of calcium entry through store-operated channels in sustaining calcium oscillations and in the mechanism by which calcium oscillations couple to downstream effectors.

Calcium ions participate in a multiplicity of physiological and pathological functions. Among the most intensely studied, and the major focus of this article, is the role of Ca^{2+} as a cellular signal. Elevations in cytoplasmic Ca^{2+} mediate a plethora of cellular responses, ranging from extremely rapid events (muscle contraction, neurosecretion), to slower more subtle responses (cell division, differentiation, apoptosis). In contrast to most cellular signals, it is a relatively simple matter to observe changes in cytoplasmic Ca^{2+} in real time in living cells. As a result, the truly complex nature of Ca^{2+} signaling pathways has been revealed. The challenge is to understand what regulates these

signals and what the biological significance of their complexity is.

In the majority of laboratory experiments examining effects of various stimulants on Ca^{2+} signaling, supramaximal concentrations of activating agonists are employed resulting in rapid, robust, and often sustained increases in cytoplasmic Ca^{2+} . It has long been appreciated that these signals result from a coordinated release of intracellular stores and increased Ca^{2+} influx across the plasma membrane (Bohr, 1973; Putney et al. 1981). The intracellular release of Ca^{2+} most commonly results from the Ca^{2+} releasing action of the phospholipase C-derived second messenger, inositol 1,4,5-trisphosphate

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(InsP₃) (Streb et al. 1983), whereas the entry of Ca²⁺ is because of the activation of store-operated channels in the plasma membrane (Putney 1986). However, it is becoming increasingly clear that these large sustained elevations seldom occur with physiological levels of stimulants. Rather the more common pattern of Ca²⁺ signaling, in both excitable and nonexcitable cells is a pattern of periodic discharges and/or entry of Ca²⁺. In excitable cells, such as the heart for example, these may be comprised of, or initiated by regenerative all-or-none plasma membrane channel activation, the Ca²⁺ action potential (Tsien et al. 1986) with amplification by intracellular Ca²⁺ release (Fabiato 1983). In nonexcitable cells, these spikes of cytoplasmic Ca²⁺ arise from regenerative discharge of stored Ca²⁺, a process generally termed Ca²⁺ oscillations (Prince and Berridge 1973; Woods et al. 1986). Like Ca²⁺ action potentials, these all-or-none discharges of Ca²⁺ represent a form of excitable behavior of the intracellular Ca²⁺ release signaling mechanism. However, because it is not possible to easily monitor and control the transmembrane chemical and biophysical parameters, as is the case for excitable plasma membrane behavior, it has been more difficult to fully understand the basic mechanisms by which these Ca²⁺ oscillations arise. Thus, although the question has been exhaustively studied for well over twenty years, there is still uncertainty and controversy over the underlying processes that give rise to Ca²⁺ oscillations. A number of reviews have discussed these issues at some length (Berridge and Galione 1988; Rink and Jacob 1989; Berridge 1990; Petersen and Wakui 1990; Berridge 1991; Cuthbertson and Cobbold 1991; Meyer and Stryer 1991; Hellman et al. 1992; Tepikin and Petersen 1992; Thomas et al. 1992; Dupont and Goldbeter 1993; Keizer 1993; Sneyd et al. 1994; Li et al. 1995; Thomas et al. 1996; Shuttleworth 1999; Lewis 2003; Dupont et al. 2007). In the current treatment, we have chosen to focus on two important aspects of Ca²⁺ oscillations. First, we review the available evidence for various computational models of Ca²⁺ oscillations that employ a quantitative approach to validate or repudiate specific mechanisms. Second, we consider the

interrelationship between Ca²⁺ oscillations and plasma membrane Ca²⁺ influx mechanisms, with the view that we may learn more of the physiological function that these intracellular discharges of Ca²⁺ provide.

COMPUTATIONAL MODELS FOR Ca²⁺ OSCILLATIONS

Since the first observations of Ca²⁺ oscillations, the experimental investigation of their molecular mechanism has been accompanied by numerous modeling approaches. One of the reasons for this is that rhythmic phenomena are known to rely on specific, nonlinear feedback processes that cannot readily be fully approached by intuitive and qualitative reasoning. Likewise, cAMP oscillations, circadian rhythms, cell cycle-related variations of the activity of cyclin associated kinases or the tumor-associated p53/mdm2 loop are other oscillatory phenomena in biology whose investigation largely benefits from a modeling approach (Goldbeter 2008). In the field of Ca²⁺ dynamics, modeling was also promoted by the fact that cytosolic Ca²⁺ was initially the only measurable variable of the system. This also prompted investigators to use modeling to identify the main messenger responsible for intra- or intercellular wave propagation when those spatially organized phenomena were reported in a variety of cell types (Thomas et al. 1996; Dupont et al. 2007). More recently, sub-cellular Ca²⁺ increases because of the opening of a small number of Ca²⁺ channels have also been simulated computationally. In this case, models offer the possibility to make the link between properties of the channels measured with electrophysiology and their behavior in the cytoplasm. In addition, simulations are required to understand how the regularity that is observed at the whole cell level (oscillations and waves) can emerge from the random behavior inherent to any ion channel.

One of the most attractive features about models is their ability to make experimentally testable predictions. That Ca²⁺ oscillations can occur in the presence of a constant level of InsP₃ and that the self-amplification of Ca²⁺ release from the ER into the cytoplasm lies at

the basis of Ca^{2+} oscillations was for example first predicted theoretically (Goldbeter et al. 1990). This regulation is known as Ca^{2+} -induced Ca^{2+} release (CICR). However, this early model assumed that Ca^{2+} oscillations require the existence of 2 types of pools, some sensitive to InsP_3 and others possessing RyR and thereby sensitive to Ca^{2+} . This turned out not to be necessary as the InsP_3R is itself sensitive to both Ca^{2+} and InsP_3 .

In the past 20 years, many computational models have been developed. They differ by the precise oscillations that they aim to describe, as determined both by the cell type and by the agonist. Models also vary according to the level of description, from microscopic (in which case stochastic modeling must be used) to macroscopic (corresponding to a deterministic description). Another, somewhat intermediate level of description allowing one to take easily spatial and stochastic aspects into account is known as “threshold models” (see below). In each case, several models differing by the specific underlying assumptions have been proposed. Such a classification is presented in Table 1, together with some typical models in each category. Although in this review we focus on InsP_3 -regulated Ca^{2+} oscillations, we have also indicated in Table 1 models for Ca^{2+} oscillations because of plasma-membrane voltage-gated Ca^{2+} channels or ryanodine receptors. Such models should be kept in mind when investigating InsP_3 -induced Ca^{2+} increases, especially in view of the fact that they could provide a secondary oscillatory mechanism in some cell types. For example, in pancreatic acinar cells (Ventura and Sneyd 2006) or airway smooth muscle cells (Wang et al. 2008); the interplay between InsP_3R and RyR plays a major physiological role.

Models for Ca^{2+} Oscillations With or Without InsP_3 Oscillations

As the InsP_3R is biphasically regulated by Ca^{2+} (Bezprozvanny et al. 1991; Finch et al. 1991), models that describe the changes of states of this receptor can on their own account for Ca^{2+} oscillations. Such InsP_3R -based models

are numerous and mainly differ by their level of details, the most detailed being useful to dissect the quantitative effect of possible changes in kinetic constants and affinities. The simplest ones allow for a better understanding of the essence of the observed phenomena, as exemplified by the early CICR model mentioned above (Goldbeter et al. 1990). As another example, simplified models point to the fact that for oscillations to occur, activation by Ca^{2+} has to be much faster than inhibition. Some of these InsP_3R -based models are indicated in Table 1 (class: InsP_3R , constant InsP_3) and readers should turn to (Sneyd and Falcke 2005) for a more comprehensive review of this type of model. All of these models face a common problem: the period of Ca^{2+} oscillations is imposed by the time taken by the receptor to recover from Ca^{2+} -induced inhibition. However, this rate constant has been estimated experimentally to be of the order of approximately 10 seconds in vitro (Finch et al. 1991; Combettes et al. 1994) and of a few seconds in vivo (Fraiman et al. 2006). These time delays are significantly shorter than the observed periods of Ca^{2+} oscillations that frequently exceed 1 minute. Thus, modeling here brings to light a clearly important limitation in our understanding of the mechanism of Ca^{2+} oscillations.

Such a discrepancy could either be explained by the existence of an additional control of the InsP_3R activity, such as agonist-induced PKA-dependent phosphorylation (LeBeau et al. 1999) or InsP_3 -induced inactivation (Hajnóczky and Thomas 1994), or suggest that although CICR at the level of the InsP_3R has the potential to generate oscillations, it is not the main oscillatory mechanism in vivo. Periodic variations in the concentration of InsP_3 could indeed also drive Ca^{2+} oscillations, in which case the period would be imposed by the rates of InsP_3 metabolism (right column in Table 1). This assumption was in fact at the basis of some early models for agonist-induced Ca^{2+} oscillations (Meyer and Stryer 1988; Cuthbertson and Chay 1991). In both models, cytosolic Ca^{2+} and InsP_3 act as cross-catalytic messengers because InsP_3 triggers Ca^{2+} release from the ER, which in turn activates InsP_3 synthesis because

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Table 1. Schematic classification of the main types of computational models for intracellular Ca^{2+} oscillations.

	Channels-based models				InsP ₃ metabolism-based models
	Voltage-gated	RyR	InsP ₃ R		Active InsP ₃ oscillations
			Constant InsP ₃	Passive InsP ₃ oscillations	
Deterministic	Fioretti et al. 2005; Zeng et al. 2009	Keizer and Levine 1996; Tang and Othmer 1994	De Young and Keizer 1992; Li and Rinzel 1994; Atri et al. 1993; Dupont and Swillens 1996; Tang et al. 1996; Bezprozvanny 1994	Dupont and Erneux 1997	Meyer and Stryer 1988; Cuthbertson and Chay 1991
Threshold				De Pitta et al. 2009; Kummer et al. 2000; Höfer et al. 2002	
Stochastic		Zahradnikova and Zahradnik 1996	Dawson et al. 1999; Coombes et al. 2004; Thul et al. 2008	Falcke 2004; Shuai et al. 2009; Williams et al. 2008	Kummer et al. 2005

In each category, only representative examples are indicated. Models indicated in the frame overlapping two columns are based on two distinct oscillatory mechanisms, one based on the InsP₃R and one based on InsP₃ metabolism.

PLC is assumed to be stimulated by physiological levels of Ca^{2+} . This regulation of PLC activity by Ca^{2+} in the 0.1–1 μM range has been observed for the δ (Allen et al. 1997) and ζ isoforms (Kouchi et al. 2004) but not for the β (Renard et al. 1987), which is the isoform coupled to the G-protein pathway that is most frequently associated with hormone stimulation. However, these models differ in their assumptions about the nature of the negative feedback process required to switch off the Ca^{2+} rise. Meyer and Stryer (Meyer and Stryer 1988) assumed that Ca^{2+} started to decrease in the cytoplasm because of rapid pumping into the mitochondria, whereas Cuthbertson and Chay (Cuthbertson and Chay 1991) presumed that Ca^{2+} -activated PKC would down-regulate the G-proteins transducing receptor stimulation to PLC activation. Models for Ca^{2+} oscillations

induced by InsP₃ oscillations fell somewhat into disfavor when the biphasic Ca^{2+} sensitivity of the InsP₃R was discovered. Still, some models drew attention to the fact that oscillations in InsP₃ could occur because of the activation of InsP₃ catabolism by Ca^{2+} . As one of the InsP₃-metabolizing enzymes, the inositol 1,4,5-trisphosphate 3-kinase, is stimulated by the Ca^{2+} /calmodulin complex, each peak in Ca^{2+} induces a decrease in InsP₃ (Dupont and Erneux 1997). Models taking this regulation into account predict the concomitant occurrence of InsP₃ and Ca^{2+} oscillations. Interestingly, they also predict that these passive InsP₃ oscillations do not significantly affect the timing of the Ca^{2+} spikes (Dupont and Erneux 1997; Dupont et al. 2003; Tanimura et al. 2009). InsP₃ oscillations were reported in some cell types by monitoring the translocation of green

fluorescent protein (GFP) tagged to the pleckstrin homology (PH) domain of PLC, thus reawakening interest for models based on oscillatory production of InsP_3 (Taylor and Thorn 2001). Interestingly, concomitant oscillations of both InsP_3 and Ca^{2+} have been mostly observed in cell lines expressing the mGluR5 receptor. These glutamate-induced Ca^{2+} oscillations have unusual characteristics: most importantly, oscillations occur over a wide range of agonist concentration, their frequency is practically insensitive to the level of stimulation, and they are inhibited by PKC inhibitors. It is thus plausible that depending on the receptor type, different oscillatory mechanisms would prevail. In recent models for such types of oscillations, both oscillatory mechanisms (i.e., InsP_3R -based and InsP_3 metabolism-based) are considered at the same time (Kummer et al. 2000; Hofer et al. 2002; De Pitta M. et al. 2009). This allows the period of InsP_3R -based Ca^{2+} oscillations to be controlled by the rate of InsP_3 synthesis, through the regulation of either PLC or PKC by Ca^{2+} .

Modeling has also been used to define experimental tests that could discriminate between an InsP_3R -based and an InsP_3 metabolism-based

mechanism. Sneyd et al. (2006) proposed to perturb agonist-induced Ca^{2+} oscillations by the direct, artificial release of InsP_3 in the cytoplasm (flash photolysis of caged InsP_3). As shown in Figure 1, the pattern of the Ca^{2+} rise after such a spike very much depends on the underlying oscillatory mechanism. In a model where InsP_3 metabolism is at the basis of Ca^{2+} oscillations, this sudden increase in InsP_3 will provoke a delay in the occurrence of the next Ca^{2+} spike, which corresponds to the time required for the level of InsP_3 to go back to its normal range of concentrations during oscillatory cycles. Once this is done, the situation is similar to the prepulse one and no change in frequency is observed as clearly shown in the left panel of Figure 1. The situation is drastically different for Ca^{2+} oscillations occurring with a constant level of InsP_3 because of the sequential activation and inhibition of the InsP_3R . In the framework of such a mechanism, the frequency of Ca^{2+} oscillations directly depends on the (constant) level of InsP_3 . Thus, a sudden increase in InsP_3 during agonist-induced Ca^{2+} oscillations provokes a transient rise in frequency (Fig. 1, right panel). The interspike interval then progressively decreases to the period of the unperturbed

Figure 1. Schematic representation of the protocol proposed by Sneyd et al. (2006) to discriminate between an InsP_3R -based or an InsP_3 metabolism-based mechanism for Ca^{2+} oscillations. If phospholipase C (PLC) activity is stimulated by Ca^{2+} (left panel), oscillations in InsP_3 must accompany Ca^{2+} oscillations. If some InsP_3 is exogenously added during Ca^{2+} oscillations, it will delay the next Ca^{2+} spikes, without significant change in the frequency of Ca^{2+} oscillations. In contrast (right panel), if Ca^{2+} oscillations rely on successive cycles of activation/inhibition of the InsP_3R , Ca^{2+} oscillations can occur with a constant level of InsP_3 . In this case, the addition of InsP_3 during oscillations will provoke a transient rise in the frequency of Ca^{2+} oscillations, with a progressive return to the original frequency. See text and Sneyd et al. (2006) for details.

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system. The number of spikes necessary to the resettlement of the prepulse periodicity increases with the amount of InsP_3 released into the cell (Sneyd et al. [2006]; see also Chatton et al. [1998]).

To test this hypothesis, InsP_3 was released by flash photolysis in methacholine-stimulated pancreatic acinar cells and in carbachol-stimulated smooth muscle cells. In pancreatic acinar cells, liberation of InsP_3 during agonist-induced Ca^{2+} oscillations provoked a delay similar to the one shown in the left panel of Figure 1, suggesting that PLC activation by Ca^{2+} plays a predominant role in the oscillatory mechanism in this cell type. In contrast, the release of InsP_3 during methacholine-induced Ca^{2+} oscillations in airway smooth muscle cells provokes a transient acceleration of Ca^{2+} oscillations, as that seen in the right panel of Figure 1. It is thus concluded that in this cell type, Ca^{2+} oscillations rely on the InsP_3R dynamics. More recently, Swann and Yu (Swann and Yu 2008) have applied the same testing protocol to fertilization-induced Ca^{2+} oscillations in mouse eggs. As in panel A of Figure 1, the InsP_3 pulse induced an immediate Ca^{2+} spike followed by a delay longer than the period of oscillations before the next one. The return to the prepulse periodicity was straightforward. This is compatible with a mechanism whereby InsP_3 metabolism drives Ca^{2+} oscillation, in agreement with the fact that $\text{PLC}\zeta$, the PLC isoform triggering Ca^{2+} oscillations in mammalian eggs, is activated by physiological Ca^{2+} levels (Saunders et al. 2002; Dupont and Dumollard 2004).

A second indirect method to assess the involvement of InsP_3 dynamics in the core oscillatory mechanism has been tested in CHO cells (Politi et al. 2006). This method is based on the slowing down of InsP_3 dynamics with an InsP_3 -binding protein that acts as an “ InsP_3 buffer.” As buffers change the kinetics but not the steady states, this compound would only affect Ca^{2+} oscillations relying on InsP_3 metabolism (as InsP_3R -based oscillations occur with a constant level of InsP_3). Moreover, the slowing-down of InsP_3 variations is assumed to affect intracellular dynamics only if InsP_3 oscillations rely on activation of InsP_3 synthesis by Ca^{2+}

(PLC) and not stimulation of InsP_3 catabolism by Ca^{2+} (3-kinase). This protocol was applied in ATP-stimulated CHO cells transfected with an InsP_3 -binding protein. These cells showed a dose-dependent quenching of Ca^{2+} oscillations, suggesting a PLC-based oscillatory mechanism in this cell type.

Models for Ca^{2+} Oscillations Taking Stochastic Aspects Into Account

All of the models discussed in the previous section are deterministic. This means that the effects of fluctuations (because of internal noise and microscopic inhomogeneities) are neglected. This is the common approach in modeling biochemical and chemical systems when the numbers of molecules involved in the process under interest are sufficiently large. In this case, stochastic fluctuations do not affect the average behavior of the ensemble, mainly because they statistically cancel each other out. For example, in electrophysiology, it is well known that the behavior of a few channels is random, but that the dynamics of neurons are very well described by deterministic equations of the Hodgkin-Huxley type.

An impressive number of studies have been devoted to the imaging of the Ca^{2+} releasing activity of a small number of InsP_3 receptors in vivo. These can occur either spontaneously or at submaximal InsP_3 concentrations. As expected, these events appear to be inherently stochastic. Their amplitude and the interval among them vary significantly under the same conditions, allowing only for a statistical description. The smallest observed events, called blips, involve a rise in cytosolic Ca^{2+} of about 40 nM and last in average 70 ms. These blips are believed to correspond to successive openings of a single InsP_3 receptor in the cytoplasm. This is possible because of the poor diffusing properties of Ca^{2+} in the cytoplasm allowing for rapid rebinding of Ca^{2+} on the channel activating sites, as indicated by quantitative models (Swillens et al. 1998). Alternatively, openings of one InsP_3R may trigger other InsP_3Rs within a cluster to generate slightly larger Ca^{2+} increases known as Ca^{2+} puffs. The rise in Ca^{2+} is then

about 200 nM and lasts approximately 300 ms. Blips and puffs have been extensively studied in HeLa cells (Thomas et al. 2000; Bootman et al. 2002) and *Xenopus* oocytes (Marchant et al. 1999; Smith and Parker 2009). These elementary events have been modeled using a stochastic description of the dynamics of the InsP_3R (Swillens et al. 1999; Williams et al. 2008; Smith et al. 2009). These have for example allowed prediction of the approximate number of InsP_3Rs present in a cluster site (Swillens et al. 1999). As we will see below, this notion of clustering of InsP_3 receptors, necessary to explain the existence of puffs, has important implications in our understanding of global Ca^{2+} signals at the cell level.

In experiments, a rise in the level of InsP_3 transforms stochastic, elementary Ca^{2+} increases into regular, periodic Ca^{2+} increases propagating as waves in the cytoplasm. This transition would correspond to the fact that the rise in InsP_3 leads to an increase in the number of channels participating in the Ca^{2+} dynamics. Thus, the effect of fluctuations would become rather small, allowing the transition into a deterministic regime (i.e., a regime in which the behavior of the system can be predicted, as opposed to random processes). To test this hypothesis, we have performed a statistical analysis of the regularity of Ca^{2+} oscillations in noradrenaline-stimulated hepatocytes and found that the coefficient of variation of the period lies between 10% and 15%. Stochastic simulations taking into account realistic numbers of InsP_3Rs (about 6000 in a typical hepatocyte) accounted for such variability, if the receptors are assumed to be grouped in clusters of a few tens of channels (Dupont et al. 2008; Dupont and Combettes 2009). This supports the idea that repetitive Ca^{2+} spiking can be described as a deterministic oscillator. However, as the number of clusters is rather low, this oscillator is perturbed by noise leading to the 10-15% variation in the period. In agreement with this view, this coefficient of variation decreases with increasing levels of InsP_3 , as the number of active channels increases. That this is the case both in the model and in hepatocytes is shown in Figure 2.

It has also been proposed that even at the cellular level, Ca^{2+} dynamics are intrinsically stochastic. The reason for that would lie in the spatial arrangement of the InsP_3Rs in clusters spaced from each other by a few microns. As Ca^{2+} is a poorly diffusible messenger in the cytoplasm, the Ca^{2+} rise occurring at one puff site would be unable to activate release from adjacent sites. This absence of communication would prevent global signaling. Thus, Ca^{2+} waves could be initiated only if, by chance, a sufficient number of clusters of InsP_3Rs become active at the same time. This process, called nucleation, would lead to a Ca^{2+} increase that is large enough to activate all the InsP_3 -bound InsP_3Rs and generate a Ca^{2+} spike. In this type of modeling, the variation of the period is of the order of the period itself (Falcke 2004; Skupin et al. 2008). Interestingly, in this framework, spike initiation that corresponds to the time required for the concomitant opening of a few adjacent cluster sites can take very long as it is a random event. This would provide a possible explanation to the long periodicity of Ca^{2+} oscillations as compared with the characteristic kinetic parameters of InsP_3R dynamics (see above).

Stochastic simulations taking spatial aspects into account are computationally extremely expensive, and, in fact, can only be performed when assuming drastic simplifications. In this framework, “threshold” models can easily be used to simulate spatial propagation of Ca^{2+} waves while taking stochastic effects into account. Threshold models, sometimes referred to “fire-diffuse-fire” models (Dawson et al. 1999; Thul et al. 2008) are based on the concept of excitability. The idea is that the cell consists on a set of Ca^{2+} releasing sites spaced by region of the cytoplasm where Ca^{2+} can only be diffused or be pumped back in the ER. At each releasing site, release will occur when Ca^{2+} exceeds a threshold. These simulations lead to saltatory waves that much resemble experimental observations. Interestingly, the value of the threshold may be chosen to fluctuate to approximate the stochastic gating of receptors (Coombes et al. 2004). These studies allowed investigation of how noise can shape the dynamics of intracellular Ca^{2+} waves.

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Figure 2. Comparison among Ca^{2+} oscillations observed in hepatocytes stimulated by noradrenaline (*upper panels*) and simulated by a stochastic Gillespie's algorithm taking into account realistic numbers of clusters of InsP_3 receptors (*lower panels*). The model is based on the assumption that Ca^{2+} dynamics occur in a deterministic regime, in which fluctuations are visible because of the rather low number of clusters. Both in the model and in experiments, the variability decreases when the frequency increases. See Dupont et al. (2008) for details.

Perspectives in Modeling Ca^{2+} Oscillations

The detailed characteristics of Ca^{2+} oscillations vary considerably from one cell type to another. In view of the large number of physiological responses mediated by Ca^{2+} , these changes may have significant implications. Modeling can be used to capture some detailed and quantitative understanding of this cell-to-cell variability. As an important factor, cells differ in their levels of expression of the three isoforms of the InsP_3R . This can be considered in models by simulating three distinct populations of channels, differing in their regulatory properties by Ca^{2+} and InsP_3 . Simulations then point to the fact that modest changes in the regulatory properties of the InsP_3R can lead to significantly

different oscillatory patterns, even if the bell-shaped dependence of the open probability on the level of Ca^{2+} are only slightly altered (Dupont and Combettes 2006). In particular, the model shows that the robustness of Ca^{2+} oscillations is clearly isoform-dependent, with type 2 being the most robust. This agrees with experiments wherein the levels of expression of the various InsP_3R subtypes have been genetically modified in DT40, HeLa, and COS-7 cells (Miyakawa et al. 1999; Hattori et al. 2004).

Surprisingly, many factors that are known to alter Ca^{2+} oscillations have not yet been extensively considered in models. For example, despite the large number of experimental studies devoted to the mechanism of Ca^{2+} entry (Putney and Bird 2008), most models for

Ca^{2+} oscillations in nonexcitable cells consider a closed system where Ca^{2+} exchanges are limited to fluxes between the cytoplasm and the ER. Mitochondrial Ca^{2+} handling is also known to alter cellular Ca^{2+} signals in the cytoplasm (Halestrap 2009). Although some models have been developed to explain the pumping and releasing properties of suspensions of mitochondria (Selivanov et al. 1998), their implication in intact cells have rarely been investigated theoretically (Marhl et al. 1998; Fall and Keizer 2001). As a last example, much remains to be performed in the field of intercellular Ca^{2+} wave propagation in which the oscillatory signal is coordinated at the organ level. Although quite well understood at the level of the communication among a few cells (Sneyd et al. 1995; Dupont et al. 2000; Hofer et al. 2002; Gracheva and Gunton 2003), signal transmission on large populations of cells remains puzzling. Such communication has vital implications as in the case of liver regeneration (Nicou et al. 2007) or in the brain (Haas et al. 2006).

INTERPLAY BETWEEN Ca^{2+} ENTRY AND Ca^{2+} RELEASE DURING Ca^{2+} OSCILLATIONS

The release of Ca^{2+} from intracellular stores, whether by maximal or submaximal concentrations of agonists, is generally accompanied by an

increased influx of Ca^{2+} across the plasma membrane (Putney et al. 1981). Ca^{2+} oscillations run down in the absence of extracellular Ca^{2+} , suggesting a requirement for Ca^{2+} influx for their maintenance. However, at least in some nonexcitable cells, Ca^{2+} influx does not appear to be required to drive the oscillations. This can be shown by use of a technique that we have termed “lanthanide insulation” (Bird and Putney 2005). Relatively high concentrations (mM) of lanthanides (Gd^{3+} , La^{3+}) effectively inhibit both Ca^{2+} influx and Ca^{2+} extrusion at the plasma membrane (Van Breemen et al. 1972). Thus, in the presence of these high lanthanide concentrations, $[\text{Ca}^{2+}]_i$ signals are sustained, even in the absence of extracellular Ca^{2+} (Kwan et al. 1990; Bird and Putney 2005). This is also true for Ca^{2+} oscillations; lanthanide insulation permits sustained oscillations in the absence of extracellular Ca^{2+} (Sneyd et al. 2004; Bird and Putney 2005; Di Capite et al. 2009) (Fig. 3). This will be important in considering arguments about the physiological function of Ca^{2+} oscillations in a subsequent section.

In most cell types, especially in nonexcitable cells, release of store Ca^{2+} activates influx through store-operated Ca^{2+} (SOC) channels (Putney 1986; Parekh and Putney 2005). The most extensively studied and characterized

Figure 3. Lanthanide insulation renders Ca^{2+} oscillations independent of extracellular Ca^{2+} . (A) 5 μM methacholine (MCh) induces sustained oscillations in a HEK293 cell. (B) In the absence of extracellular Ca^{2+} , oscillations are not sustained. (C) In the presence of 1 mM Gd^{3+} , oscillations are sustained, even in the absence of extracellular Ca^{2+} . These panels illustrate responses of single cells. The statistical evaluation of multiple cells analyzed with this procedure is summarized in Bird and Putney (2005).

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SOC current is the calcium-release-activated-calcium current (I_{crac}) (Hoth and Penner 1992; Parekh and Putney 2005). The channels underlying I_{crac} have thus been referred to as CRAC channels, which may represent a specific type of SOC channel. The properties of CRAC channels include high Ca^{2+} selectivity and very low single channel conductance (Parekh and Putney 2005). However, both store-operated Ca^{2+} fluxes (generally measured by use of fluorescent Ca^{2+} indicators) as well as I_{crac} have been most commonly investigated utilizing strategies that produce extensive, nearly complete depletion of endoplasmic Ca^{2+} stores, rather than under conditions of modest depletion as expected during Ca^{2+} oscillations. Indeed, the nature of the Ca^{2+} influx mechanism that supports Ca^{2+} oscillations has been the subject of some debate. Shuttleworth suggested that, rather than store operated channels, channels activated by arachidonic acid is necessary to maintain oscillations (Shuttleworth 1999). Such channels clearly exist and the Ca^{2+} -selective current underlying arachidonic acid-activated entry, termed I_{arc} , has been well characterized (Shuttleworth et al. 2004). The physiological function of these channels is less clear, however. The idea that ARC channels are involved in Ca^{2+} entry was based largely on pharmacological evidence utilizing a phospholipase A_2 inhibitor of questionable specificity (Bird and Putney 2005). On the other hand, use of Gd^{3+} (at low μM concentrations) and 2-aminoethyldiphenyl borate (2APB), two known inhibitors of SOC channels, caused rundown of muscarinic receptor-induced Ca^{2+} oscillations in HEK293 cells in a manner indistinguishable from that seen by simple omission of extracellular Ca^{2+} (Bird and Putney 2005).

Store-Operated Ca^{2+} Channels

The major molecular components of the SOC entry pathway are STIM (STIM1 and 2) and Orai (Orai1, 2, and 3) (Frischauf et al. 2008). STIM1 and 2 reside in the endoplasmic reticulum where they function as sensors of endoplasmic reticulum Ca^{2+} content. Both proteins have a Ca^{2+} -binding EF-hand motif in the N-

terminus, directed toward the lumen of the endoplasmic reticulum (Dziadek and Johnstone 2007). A drop in endoplasmic reticulum Ca^{2+} content causes Ca^{2+} to dissociate from STIM1. This results in a conformational change (Zheng et al. 2008) that permits self-association of STIM molecules (Liou et al. 2007). In this poorly defined aggregated state, STIM localizes to near plasma membrane junctions (Orci et al. 2009) where it appears to be capable of directly interacting with Orai subunits of the store-operated channels (Park et al. 2009). There are also a number of publications implicating members of the TRPC (canonical transient receptor potential) cation channel family as candidate SOC channels (Birnbaumer et al. 2000; Rosado and Sage 2000; Abeele et al. 2003; Albert and Large 2003; Beech 2005; Ambudkar 2006; Huang et al. 2006). However, some of the published findings implicating TRPCs as SOC channels could not be reproduced (DeHaven et al. 2009). Nonetheless, it is clear that activation of phospholipase C activates Ca^{2+} -permeable TRPC channels (Vazquez et al. 2004) and it is thus possible that they will play a role in Ca^{2+} oscillations. In the HEK293 cell model, and consistent with the pharmacological data, knockdown by RNAi of either STIM1 or Orai1 in HEK293 essentially completely abrogated Ca^{2+} oscillations (Wedel et al. 2007). However, these proteins are also thought to play a role in the arachidonic acid pathway (Shuttleworth et al. 2007; Mignen et al. 2008). The role of STIM1 in ARC channel activation is quite different from that for SOC channels. ARC channels require STIM1 in the plasma membrane (Shuttleworth et al. 2004), whereas for the SOC channels, STIM1 is only necessary in the endoplasmic reticulum (Mercer et al. 2006). Thus, it is significant that loss of sustained oscillations following RNAi knockdown of STIM1 could be reversed by expression of a STIM1 construct modified to preclude its translocation to the plasma membrane (Wedel et al. 2007). In aggregate, the evidence convincingly supports the view that in the HEK293 cell model, the Ca^{2+} entry underlying Ca^{2+} oscillations is store-operated Ca^{2+} entry (Putney and Bird 2008).

During the process of Ca^{2+} oscillations, the quantity of Ca^{2+} discharged with each spike can be quite small (Bird and Putney 2005). Thus, it is presumed that when even a small amount of Ca^{2+} is lost from the endoplasmic reticulum, STIM is activated and causes Orai channels to open sufficiently to maintain intracellular Ca^{2+} stores. In this context, it is important to consider the sensitivities of the two STIM proteins, STIM1 and STIM2, to Ca^{2+} store depletion. When stores are gradually depleted of Ca^{2+} , STIM2 begins to move to the plasma membrane before STIM1 (Brandman et al. 2007; Bird et al. 2009). In addition, overexpression of STIM2, but not STIM1, results in constitutive Ca^{2+} entry (Soboloff et al. 2006b; Brandman et al. 2007; Parvez et al. 2008; Bird et al. 2009). These findings suggest that STIM2 is responsive to a very small degree of Ca^{2+} store depletion and is apparently partially active under resting conditions. STIM1 on the other hand, appears to require a substantial degree of Ca^{2+} store depletion before it can be activated. It was thus somewhat surprising that when the relative roles of STIM1 and STIM2 in Ca^{2+} oscillations were assessed, it was STIM1 rather than STIM2 that was required (Bird et al. 2009).

In the HEK293 cell model used for these studies, Western analysis clearly showed the presence of STIM2 in quantities similar to those for STIM1 (Bird et al. 2009). Why then did the STIM2 play no significant role in supporting the Ca^{2+} oscillations? The answer is probably that STIM2 is a very inefficient activator of Orai channels. When both STIM2 and STIM1 are overexpressed in cells, STIM2 appears to act as an inhibitor of STIM1 (Soboloff et al. 2006a), as would be expected if its interaction with Orai channels is relatively ineffective. This should not be surprising if in fact STIM2 is already partially active under basal conditions. Nonetheless, when STIM2 is overexpressed in cells, along with overexpressed Orai1, large STIM2-dependent Ca^{2+} influx signals can be observed (Parvez et al. 2008). However, the stoichiometry of STIM2 and Orai1 is unknown in this condition, such that the relative efficiency of STIM2 as an activator of Orai1 cannot be evaluated. To compare the

efficiency of STIM1 and STIM2 under conditions of similar stoichiometry with Orai1, the EF-hand mutants of STIM1 and STIM2 were transiently transfected into HEK293 cells, but without transfecting the cells with additional Orai1 (Bird et al. 2009). In this condition, STIM1 or STIM2 is presumed to be in considerable excess relative to the native Orai1. The EF-hand mutants of STIM1 and 2 are constitutively active, precluding the need for store depletion and thereby eliminating any contribution from endogenous STIM proteins. The result of this experiment was a robust constitutive entry of Ca^{2+} in the cells expressing the EF-hand mutant of STIM1, but no constitutive entry in cells expressing the EF-hand mutant of STIM2, consistent with the idea that STIM2 is a much poorer activator of Orai1 channels (Bird et al. 2009).

Thus, at least in HEK293 cells, the Ca^{2+} entry that supports Ca^{2+} oscillations is triggered by STIM1 interacting with and activating plasma membrane Orai1 channels. This suggests that during the oscillations, the endoplasmic reticulum Ca^{2+} concentration falls into the range in which STIM1 is activated. This presumably occurs in a small domain of the endoplasmic reticulum situated in close proximity to the plasma membrane, and this is consistent with earlier suggestions that there is a subcompartment of the endoplasmic reticulum that is specifically involved in regulating plasma membrane SOC channels (Ribeiro and Putney 1996; Parekh et al. 1997; Orci et al. 2009).

Physiological Relevance of SOC Channels for Cellular Signaling

The aforementioned scenario is relevant to a long standing question in the Ca^{2+} signaling field: what is the functional significance of Ca^{2+} oscillations? The generally accepted answer to this question is that Ca^{2+} oscillations provide a digital signal to downstream effectors and this is advantageous at low levels of signaling because of the high signal-to-noise discrimination of digital information encoding (Meyer et al. 1992; Thomas et al. 1996; Berridge 1997; Dolmetsch et al. 1998). Implicit in this

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conclusion is that the effectors downstream of the Ca^{2+} oscillations must have at least moderately elevated thresholds for responding, providing high signal-to-noise and preventing any ambiguity in distinguishing a true signal from random fluctuations. One well established target of Ca^{2+} released from the endoplasmic reticulum through InsP_3 receptors is the mitochondria (Rizzuto et al. 1992; Hajnóczky et al. 1995; Rizzuto et al. 1998; Rizzuto and Pozzan 2006). The mitochondrial uniporter, responsible for accumulation of Ca^{2+} , has a sensitivity to Ca^{2+} well above the physiological range of global Ca^{2+} changes (Blaustein et al. 1977; Burgess et al. 1983). Yet, the positioning of uptake sites close to sites of release, provides a kind of intracellular synapse assuring that bursts of local Ca^{2+} release are read by mitochondria, resulting in the activation of important Ca^{2+} -regulated mitochondrial enzymes (Csordas et al. 2006).

But in addition to mitochondrial function, Ca^{2+} signaling, most commonly through some kind of oscillatory mechanism, regulates a large variety of downstream effectors. There is evidence that some of these are tightly coupled to Ca^{2+} entering through SOC channels. One of the most extensively documented and investigated examples is the requirement for Ca^{2+} influx through CRAC channels for activation of calcineurin/NFAT signaling in T-lymphocytes (Oh-Hora 2009). Because activation of this pathway is known to require Ca^{2+} elevation for hours, it is implicitly understood that Ca^{2+} influx is necessary to maintain signaling over such a prolonged period. And it is clear that signaling fails in the absence of Ca^{2+} influx through CRAC channels (Feske et al. 2006). However, it is not clear whether Ca^{2+} entry provides the Ca^{2+} directly responsible for activation of calcineurin/NFAT signaling, or rather serves to maintain intracellular stores such that continued release through InsP_3 receptors can activate the pathway. There are a few studies that have experimentally shown the specific requirement of Ca^{2+} entering through SOC channels. Perhaps the first such Ca^{2+} -sensitive effectors found to be closely coupled to SOC entry were some of the Ca^{2+} -regulated adenylyl

cyclases (Cooper et al. 1994). Another example elegantly showed in a study from Parekh's laboratory is cytoplasmic phospholipase A2 (cPLA2) (Chang et al. 2006), an important Ca^{2+} -regulated effector in many cells in the immune system and elsewhere. In the mast cell line RBL-1, Ca^{2+} store depletion activates plasma membrane CRAC channels, which leads to cPLA2 activation. The activation of cPLA2 was mediated by extracellular signal regulated kinases (ERKs). The ERKs are apparently activated by protein kinase C α , which is the likely target of Ca^{2+} entering through the CRAC channels (Chang et al. 2006). In this same study, it was shown that activation of the early gene, *c-fos*, was also closely coupled to Ca^{2+} entering through CRAC channels but was not dependent on ERK activation. The dependence of these responses specifically on Ca^{2+} entry was shown by use of the "lanthanide insulation" technique described above (Bird and Putney 2006). Thus, in the absence of extracellular Ca^{2+} but in the presence of high concentrations of lanthanides, depletion of Ca^{2+} stores with thapsigargin induced large sustained elevations of cytoplasmic Ca^{2+} , yet cPLA2 was not induced (Chang et al. 2008). This result indicated that the global rise in intracellular Ca^{2+} was not important for activation of gene expression, rather it was the Ca^{2+} specifically entering through the plasma membrane CRAC channels.

The above-discussed examples all used supramaximal stimuli to produce large, sustained increases in Ca^{2+} influx. In one study, the role of Ca^{2+} influx in activating gene expression during Ca^{2+} oscillations was investigated. Di Capite et al. (2009), following on the earlier demonstration of *c-fos* induction by SOC entry, examined the activation of *c-fos* expression in response to Ca^{2+} oscillations induced by modest concentrations of leukotriene C4 applied to RBL-1 cells. By use of the "lanthanide insulation" technique, oscillations were obtained in the absence of extracellular Ca^{2+} , but in the presence of high lanthanum and these oscillations were sustained and indistinguishable from those in the presence of extracellular Ca^{2+} . However, *c-fos* was only induced in the presence of extracellular Ca^{2+} when Ca^{2+} influx

could occur through the CRAC channels. Thus, it may be concluded that in this instance the global rise in Ca^{2+} associated with Ca^{2+} oscillations is irrelevant for activation of the pathway that leads to *c-fos* activation. Rather, Ca^{2+} entering through the plasma membrane CRAC channels couples specifically to the initial steps in this signaling pathway (Di Capite et al. 2009).

The generality of this scenario remains to be shown. Indeed, gene expression can clearly be turned on in some experimental situations by elevations in global Ca^{2+} (Dolmetsch et al. 1998). Also, it is clear that Ca^{2+} released by IP_3Rs can also be coupled to specific signaling pathways. The clearest such example is the regulation of carbohydrate and energy metabolism through close IP_3R -mitochondrial coupling (Rizzuto and Pozzan 2006). Nonetheless, a specialized signaling function of SOC channels fits nicely with the previously related story of Ca^{2+} entry signaling by STIM1 during oscillations. If in fact Ca^{2+} entering through SOC channels can provide the key signal for downstream pathways, then it is not so surprising that STIM1 and not STIM2, provides the link between the oscillations and the SOC channels. It has for some time been supposed that the digital nature of cytoplasmic Ca^{2+} oscillations provides a high signal-to-noise signal input to downstream Ca^{2+} -regulated effectors, obviating the possibility of small unintentional signaling fluctuations. Because STIM1 requires a threshold of Ca^{2+} store depletion for activation, this then means that a Ca^{2+} oscillation, producing a transient but apparently substantial drop in ER luminal Ca^{2+} , will produce a transient activation of STIM1 and an incremental activation of the SOC channel. Small fluctuations in ER Ca^{2+} will not affect STIM1, preventing unintentional activation of SOC channels. However, small fluctuations in ER Ca^{2+} can activate STIM2 which will produce small activation of SOC channels sufficient to keep stores filled, but insufficient to activate downstream effectors. With this reasoning, the rise in cytoplasmic Ca^{2+} that is experimentally observed during Ca^{2+} oscillations is not directly relevant to the signaling pathway, except insofar as it reflects the digital drop in ER Ca^{2+} and

subsequent activation of SOC channels. By similar reasoning, one would speculate that in some cell types, or in response to specific stimuli, SOC channels do not function to maintain intracellular stores so that InsP_3 -induced release can activate downstream signaling; rather one might conclude that during Ca^{2+} oscillations, InsP_3 -induced release functions to drive ER Ca^{2+} into the STIM1 sensing range, resulting in SOC channel opening and activation of downstream signaling. This would require not only spatial organization of the immediate downstream Ca^{2+} sensor, but also some degree of localized endoplasmic reticulum depletion because during a single Ca^{2+} oscillation, the extent of global endoplasmic reticulum depletion is quite small.

CONCLUSIONS

In this review, we have analyzed two major aspects of Ca^{2+} oscillations. First, we show how the use of computational models of Ca^{2+} oscillations can lead to a number of important conclusions about mechanisms of generation of oscillations. Models indeed allow us to conceptualize and quantify intuitive reasoning, which is particularly useful for oscillatory phenomena. We also emphasize the need for specific modeling approaches depending on the cell type, the stimulus and the specific aspect of Ca^{2+} signaling of interest. Second, we review recent findings indicating an important role for store-operated Ca^{2+} entry in Ca^{2+} oscillations and particularly in the physiological mechanism by which the digital information contained in the oscillations is linked to downstream effectors. Hopefully, continued research in these two areas will further increase our understanding of the mechanisms and meaning of the fascinating phenomena, Ca^{2+} oscillations.

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REFERENCES

- Abeele FV, Shuba Y, Roudbaraki M, Lemonnier L, Vanoverberghe K, Mariot P, Skryma R, Prevarskaya N. 2003. Store-operated Ca^{2+} channels in prostate cancer epithelial cells: function, regulation, and role in carcinogenesis. *Cell Calcium* **33**: 357–373.
- Albert AP, Large WA. 2003. Store-operated Ca^{2+} -permeable non-selective cation channels in smooth muscle cells. *Cell Calcium* **33**: 345–356.
- Allen V, Swigart P, Cheung R, Cockcroft S, Katan M. 1997. Regulation of inositol lipid-specific phospholipase $\text{c}\delta$ by changes in Ca^{2+} ion concentrations. *Biochem J* **327**: 545–552.
- Ambudkar IS. 2006. Ca^{2+} signaling microdomains: Platforms for the assembly and regulation of TRPC channels. *Trends Pharmacol Sci* **27**: 25–32.
- Atri A, Amundson J, Clapham D, Sneyd J. 1993. A single-pool model for intracellular calcium oscillations and waves in the *Xenopus laevis* oocyte. *Biophys J* **65**: 1727–1739.
- Beech DJ. 2005. Emerging functions of 10 types of TRP cationic channel in vascular smooth muscle. *Clin Exp Pharmacol Physiol* **32**: 597–603.
- Berridge MJ. 1990. Calcium oscillations. *J Biol Chem* **265**: 9583–9586.
- Berridge MJ. 1991. Cytoplasmic calcium oscillations: A two pool model. *Cell Calcium* **12**: 63–72.
- Berridge MJ. 1997. Elementary and global aspects of calcium signalling. *J Physiol (Lond)* **499**: 291–306.
- Berridge MJ, Galione A. 1988. Cytosolic calcium oscillators. *FASEB J* **2**: 3074–3082.
- Bezprozvanny I. 1994. Theoretical analysis of calcium wave propagation based on inositol (1,4,5)-trisphosphate (InsP_3) receptor functional properties. *Cell Calcium* **16**: 151–166.
- Bezprozvanny I, Watras J, Ehrlich BE. 1991. Bell-shaped calcium-response curves of $\text{Ins}(1,4,5)\text{P}_3$ and calcium-gated channels from endoplasmic reticulum of cerebellum. *Nature* **351**: 751–754.
- Bird GS, Putney JW. 2005. Capacitative calcium entry supports calcium oscillations in human embryonic kidney cells. *J Physiol* **562**: 697–706.
- Bird GS, Putney JW. 2006. Fluorescent indicators—facts and artifacts. In *Calcium Signaling* (ed. JW Putney), pp. 51–84. CRC Press, Boca Raton.
- Bird GS, Hwang SY, Smyth JT, Fukushima M, Boyles RR, Putney JW Jr. 2009. STIM1 is a calcium sensor specialized for digital signaling. *Curr Biol* **19**: 1724–1729.
- Birnbaumer L, Boulay G, Brown D, Jiang M, Dietrich A, Mikoshiba K, Zhu X, Qin N. 2000. Mechanism of capacitative Ca^{2+} entry (CCE): interaction between IP_3 receptor and TRP links the internal calcium storage compartment to plasma membrane CCE channels. *Recent Prog Horm Res* **55**: 127–161.
- Blaustein MP, Kendrick NC, Fried RC, Ratzlaff RW. 1977. Calcium metabolism at the mammalian presynaptic nerve terminal: Lessons from the synaptosome. In *Society for Neuroscience Symposia, Vol. II. Approaches to the Cell Biology of Neurons* (ed. MW Cowan, JA Ferrendelli), pp. 172–194. Society for Neuroscience, Bethesda, MD.
- Bohr DF. 1973. Vascular smooth muscle updated. *Circ Res* **32**: 665–672.
- Bootman MD, Berridge MJ, Roderick HL. 2002. Calcium signalling: more messengers, more channels, more complexity. *Curr Biol* **12**: R563–R565.
- Brandman O, Liou J, Park WS, Meyer T. 2007. STIM2 is a feedback regulator that stabilizes basal cytosolic and endoplasmic reticulum Ca^{2+} levels. *Cell* **131**: 1327–1339.
- Burgess GM, McKinney JS, Fabiato A, Leslie BA, Putney JW. 1983. Calcium pools in saponin-permeabilized guinea-pig hepatocytes. *J Biol Chem* **258**: 15336–15345.
- Chang WC, Capite JDi, Singaravelu K, Nelson C, Halse V, Parekh AB. 2008. Local Ca^{2+} Influx through Ca^{2+} Release-activated Ca^{2+} (CRAC) Channels Stimulates Production of an Intracellular Messenger and an Intercellular Pro-inflammatory Signal. *J Biol Chem* **283**: 4622–4631.
- Chang WC, Nelson C, Parekh AB. 2006. Ca^{2+} influx through CRAC channels activates cytosolic phospholipase A2, leukotriene C4 secretion, and expression of c-fos through ERK-dependent and -independent pathways in mast cells. *FASEB J* **20**: 2381–2383.
- Chatton JY, Cao Y, Stucki JW. 1998. Perturbation of myo-inositol-1,4,5-trisphosphate levels during agonist-induced Ca^{2+} oscillations. *Biophys J* **74**: 523–531.
- Combettes LHannaert-Merah Z, Coquil J-F, Rousseau C, Claret M, Swillens S, Champeil P. 1994. Rapid filtration studies of the effect of cytosolic Ca^{2+} on inositol 1,4,5-trisphosphate-induced $^{45}\text{Ca}^{2+}$ release from cerebellar microsomes. *J Biol Chem* **269**: 17561–17571.
- Coombs S, Hinch R, Timofeeva Y. 2004. Receptors, sparks, and waves in a fire-diffuse-fire framework for calcium release. *Prog Biophys Mol Biol* **85**: 197–216.
- Cooper DMF, Yoshimura M, Zhang Y, Chiono M, Mahey R. 1994. Capacitative Ca^{2+} entry regulates Ca^{2+} -sensitive adenylyl cyclases. *Biochem J* **297**: 437–440.
- Csordas G, Renken C, Varnai P, Walter L, Weaver D, Buttler KE, Balla T, Mannella CA, Hajnoczky G. 2006. Structural and functional features and significance of the physical linkage between ER and mitochondria. *J Cell Biol* **174**: 915–921.

- Cuthbertson KS, Chay TR. 1991. Modeling receptor-controlled intracellular calcium oscillators. *Cell Calcium* **12**: 97–109.
- Cuthbertson KSR, Cobbold PH. 1991. Oscillations in cell calcium (Collected papers and reviews). *Cell Calcium* **12**: 61–268.
- Dawson SP, Keizer J, Pearson JE. 1999. Fire-diffuse-fire model of dynamics of intracellular calcium waves. *Proc Natl Acad Sci* **96**: 6060–6063.
- DeHaven WI, Jones BF, Petranka JG, Smyth JT, Tomita T, Bird GS, Putney JW. 2009. TRPC channels function independently of STIM1 and Orai1. *J Physiol* **587**: 2275–2298.
- De Pitta M, Goldberg M, Volman V, Berry H, Ben-Jacob E. 2009. Glutamate regulation of calcium and IP(3) oscillating and pulsating dynamics in astrocytes. *J Biol Phys* **35**: 383–411.
- De Young GW, Keizer J. 1992. A single-pool inositol 1,4,5-trisphosphate-receptor-based model for agonist-stimulated oscillations in Ca^{2+} concentration. *Proc Nat Acad Sci* **89**: 9895–9899.
- DiCapite J, Ng SW, Parekh AB. 2009. Decoding of cytoplasmic Ca^{2+} oscillations through the spatial signature drives gene expression. *Curr Biol* **19**: 853–858.
- Dolmetsch RE, Xu KL, Lewis RS. 1998. Calcium oscillations increase the efficiency and specificity of gene expression. *Nature* **392**: 933–936.
- Dupont G, Goldbeter A. 1993. One-pool model for Ca^{2+} oscillations involving Ca^{2+} and inositol 1,4,5-trisphosphate as co-agonists for Ca^{2+} release. *Cell Calcium* **14**: 311–322.
- Dupont G, Swillens S. 1996. Quantal release, incremental detection, and long-period Ca^{2+} oscillations in a model based on regulatory Ca^{2+} -binding sites along the permeation pathway. *Biophys J* **71**: 1714–1722.
- Dupont G, Erneux C. 1997. Simulations of the effects of inositol 1,4,5-trisphosphate 3-kinase and 5-phosphatase activities on Ca^{2+} oscillations. *Cell Calcium* **22**: 321–331.
- Dupont G, Dumollard R. 2004. Simulation of calcium waves in ascidian eggs: insights into the origin of the pacemaker sites and the possible nature of the sperm factor. *J Cell Sci* **117**: 4313–4323.
- Dupont G, Combettes L. 2006. Modeling the effect of specific inositol 1,4,5-trisphosphate receptor isoforms on cellular Ca^{2+} signals. *Biol Cell* **98**: 171–182.
- Dupont G, Combettes L. 2009. What can we learn from the irregularity of Ca^{2+} oscillations?. *Chaos* **19**: 037112.
- Dupont G, Combettes L, Leybaert L. 2007. Calcium dynamics: spatio-temporal organization from the subcellular to the organ level. *Int Rev Cytol* **261**: 193–245.
- Dupont G, Bou-Lovergne A, Combettes L. 2008. Stochastic Aspects of Oscillatory Ca^{2+} Dynamics in Hepatocytes. *Biophys J* **95**: 2193–2202.
- Dupont G, Koukoui O, Clair C, Erneux C, Swillens S, Combettes L. 2003. Ca^{2+} oscillations in hepatocytes do not require the modulation of InsP_3 3-kinase activity by Ca^{2+} . *FEBS Lett* **534**: 101–105.
- Dupont G, Tordjmann T, Clair C, Swillens S, Claret M, Combettes L. 2000. Mechanism of receptor-oriented intercellular calcium wave propagation in hepatocytes. *FASEB J* **14**: 279–289.
- Dziadek MA, Johnstone LS. 2007. Biochemical properties and cellular localisation of STIM proteins. *Cell Calcium* **42**: 123–132.
- Fabiato A. 1983. Calcium-induced release of calcium from the cardiac sarcoplasmic reticulum. *Am J Physiol* **245**: C1–C4.
- Falcke M. 2004. Reading the patterns in living cells—the physics of Ca^{2+} signaling. *Adv Physics* **53**: 255–440.
- Fall CB, Keizer JE. 2001. Mitochondrial modulation of intracellular Ca^{2+} signaling. *J Theor Biol* **210**: 151–165.
- Feske S, Gwack Y, Prakriya M, Srikanth S, Puppel SH, Tanasa B, Hogan PG, Lewis RS, Daly M, Rao A. 2006. A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. *Nature* **441**: 179–185.
- Finch EA, Turner TJ, Goldin SM. 1991. Calcium as a co-agonist of inositol 1,4,5-trisphosphate-induced calcium release. *Science* **252**: 443–446.
- Fioretti B, Franciolini F, Catacuzzeno L. 2005. A model of intracellular Ca^{2+} oscillations based on the activity of the intermediate-conductance Ca^{2+} -activated K^+ channels. *Biophys Chem* **113**: 17–23.
- Fraiman D, Pando B, Dargan S, Parker I, Dawson SP. 2006. Analysis of puff dynamics in oocytes: interdependence of puff amplitude and interpuff interval. *Biophys J* **90**: 3897–3907.
- Frischauf I, Schindl R, Derler I, Bergsmann J, Fahrner M, Romanin C. 2008. The STIM/Orai coupling machinery. *Channels (Austin)* **2**: 261–268.
- Goldbeter A. 2008. Biological rhythms: clocks for all times. *Curr Biol* **18**: R751–R753.
- Goldbeter A, Dupont G, Berridge MJ. 1990. Minimal model for signal-induced Ca^{2+} oscillations and for their frequency encoding through protein phosphorylation. *Proc Nat Acad Sci* **87**: 1461–1465.
- Gracheva ME, Gunton JD. 2003. Intercellular communication via intracellular calcium oscillations. *J Theor Biol* **221**: 513–518.
- Haas B, Schipke CG, Peters O, Sohl G, Willecke K, Kettenmann H. 2006. Activity-dependent ATP-waves in the mouse neocortex are independent from astrocytic calcium waves. *Cereb Cortex* **16**: 237–246.
- Hajnóczky G, Thomas AP. 1994. The inositol trisphosphate calcium channel is inactivated by inositol trisphosphate. *Nature* **370**: 474–477.
- Hajnóczky G, Robb-Gaspers LD, Seitz MB, Thomas AP. 1995. Decoding of cytosolic calcium oscillations in the mitochondria. *Cell* **82**: 415–424.
- Halestrap AP. 2009. Mitochondrial calcium in health and disease. *Biochim Biophys Acta* **1787**: 1289–1290.
- Hattori M, Suzuki AZ, Higo T, Miyauchi H, Michikawa T, Nakamura T, Inoue T, Mikoshiba K. 2004. Distinct roles of inositol 1,4,5-trisphosphate receptor types 1 and 3 in Ca^{2+} signaling. *J Biol Chem* **279**: 11967–11975.
- Hellman B, Gylfe E, Grapengiesser E, Lund P-E, Berts A. 1992. Cytoplasmic Ca^{2+} oscillations in pancreatic b-cells. *Biochim Biophys Acta* **1113**: 295–305.
- Hofer T, Venance L, Giaume C. 2002. Control and plasticity of intercellular calcium waves in astrocytes: A modeling approach. *J Neurosci* **22**: 4850–4859.

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- Hoth M, Penner R. 1992. Depletion of intracellular calcium stores activates a calcium current in mast cells. *Nature* **355**: 353–355.
- Huang GN, Zeng W, Kim JY, Yuan JP, Han L, Muallem S, Worley PF. 2006. STIM1 carboxyl-terminus activates native SOC, Icrac and TRPC1 channels. *Nat Cell Biol* **8**: 1003–1010.
- Keizer J, Levine L. 1996. Ryanodine receptor adaptation and Ca^{2+} -induced Ca^{2+} release-dependent Ca^{2+} oscillations. *Biophys J* **71**: 3477–3487.
- Keizer J. 1993. Calcium oscillations and waves: Is the IP_3R Ca^{2+} channel the culprit? *Biophys J* **65**: 1359–1361.
- Kouchi Z, Fukami K, Shikano T, Oda S, Nakamura Y, Takenawa T, Miyazaki S. 2004. Recombinant phospholipase C ζ has high Ca^{2+} sensitivity and induces Ca^{2+} oscillations in mouse eggs. *J Biol Chem* **279**: 10408–10412.
- Kummer U, Olsen LE, Dixon CJ, Green AK, Bornberg-Bauer E, Baier G. 2000. Switching from simple to complex oscillations in calcium signaling. *Biophys J* **79**: 1188–1195.
- Kummer U, Krajnc B, Pahle J, Green AK, Dixon CJ, Marhl M. 2005. Transition from stochastic to deterministic behavior in calcium oscillations. *Biophys J* **89**: 1603–1611.
- Kwan CY, Takemura H, Obie JE, Thastrup O, Putney JW. 1990. Effects of methacholine, thapsigargin and La^{3+} on plasmalemmal and intracellular Ca^{2+} transport in lacrimal acinar cells. *Am J Physiol* **258**: C1006–C1015.
- LeBeau AP, Yule DI, Groblewski GE, Sneyd J. 1999. Agonist-dependent phosphorylation of the inositol 1,4,5-trisphosphate receptor. A possible mechanism for agonist-specific calcium oscillations in pancreatic acinar cells. *J Gen Physiol* **113**: 851–871.
- Lewis RS. 2003. Calcium oscillations in T-cells: Mechanisms and consequences for gene expression. *Biochem Soc Trans* **31**: 925–929.
- Li YX, Rinzel J. 1994. Equations for IP_3 receptor-mediated $[\text{Ca}^{2+}]_i$ oscillations derived from a detailed kinetic model: a Hodgkin-Huxley like formalism. *J Theor Biol* **166**: 461–473.
- Li Y-X, Keizer J, Stojilkovic SS, Rinzel J. 1995. Ca^{2+} excitability of the ER membrane: an explanation for IP_3 -induced Ca^{2+} oscillations. *Am J Physiol* **269**: C1079–C1092.
- Liou J, Fivaz M, Inoue T, Meyer T. 2007. Live-cell imaging reveals sequential oligomerization and local plasma membrane targeting of stromal interaction molecule 1 after Ca^{2+} store depletion. *Proc Natl Acad Sci* **104**: 9301–9306.
- Marchant J, Callamaras N, Parker I. 1999. Initiation of IP_3 -mediated Ca^{2+} waves in *Xenopus* oocytes. *EMBO J* **18**: 5285–5299.
- Marhl M, Schuster S, Brumen M. 1998. Mitochondria as an important factor in the maintenance of constant amplitudes of cytosolic calcium oscillations. *Biophys Chem* **71**: 125–132.
- Mercer JC, DeHaven WI, Smyth JT, Wedel B, Boyles RR, Bird GS, Putney JW. 2006. Large store-operated calcium-selected currents due to co-expression of orai1 or orai2 with the intracellular calcium sensor, stim1. *J Biol Chem* **281**: 24979–24990.
- Meyer T, Stryer L. 1988. Molecular model for receptor-stimulated calcium spiking. *Proc Nat Acad Sci* **85**: 5051–5055.
- Meyer T, Stryer L. 1991. Calcium spiking. *Annu Rev Biophys Biophys Chem* **20**: 153–174.
- Meyer T, Hanson PI, Stryer L, Schulman H. 1992. Calmodulin trapping by calcium-calmodulin-dependent protein kinase. *Science* **256**: 1199–1202.
- Mignen O, Thompson JL, Shuttlesworth TJ. 2008. Both Orai1 and Orai3 are essential components of the arachidonate-regulated Ca^{2+} -selective (ARC) channels. *J Physiol (Lond)* **586**: 185–195.
- Miyakawa T, Maeda A, Yamazawa T, Hirose K, Kurosaki T, Iino M. 1999. Encoding of Ca^{2+} signals by differential expression of IP_3 receptor subtypes. *EMBO J* **18**: 1303–1308.
- Nicou A, Serriere V, Hilly M, Prigent S, Combettes L, Guilhon G, Tordjmann T. 2007. Remodeling of calcium signaling during liver regeneration in the rat. *J Hepatol* **46**: 247–256.
- Oh-Hora M. 2009. Calcium signaling in the development and function of T-lineage cells. *Immunol Rev* **231**: 210–224.
- Orci L, Ravazzola M, Coadic MLe, Shen Ww, Demaurex N, Cosson P. 2009. STIM1-induced precortical and cortical subdomains of the endoplasmic reticulum. *Proc Natl Acad Sci* **106**: 19358–19362.
- Parekh AB, Putney JW. 2005. Store-operated calcium channels. *Physiol Rev* **85**: 757–810.
- Parekh AB, Fleig A, Penner R. 1997. The store-operated calcium current I_{CRAC} : Nonlinear activation by InsP_3 and dissociation from calcium release. *Cell* **89**: 973–980.
- Park CY, Hoover PJ, Mullins FM, Bachhawat P, Covington ED, Raunser S, Walz T, Garcia KC, Dolmetsch RE, Lewis RS. 2009. STIM1 clusters and activates CRAC channels via direct binding of a cytosolic domain to Orai1. *Cell* **136**: 876–890.
- Parvez S, Beck A, Peinelt C, Soboloff J, Lis A, Monteilh-Zoller M, Gill DL, Fleig A, Penner R. 2008. STIM2 protein mediates distinct store-dependent and store-independent modes of CRAC channel activation. *FASEB J* **22**: 752–761.
- Petersen OH, Wakui M. 1990. Oscillating intracellular Ca^{2+} signals evoked by activation of receptors linked to inositol lipid hydrolysis: Mechanism of generation. *J Membrane Biol* **118**: 93–105.
- Politi A, Gaspers LD, Thomas AP, Hofer T. 2006. Models of IP_3 and Ca^{2+} oscillations: Frequency encoding and identification of underlying feedbacks. *Biophys J* **90**: 3120–3133.
- Prince WT, Berridge MJ. 1973. The role of calcium in the action of 5-hydroxytryptamine and cyclic AMP on salivary glands. *J Exp Biol* **58**: 367–384.
- Putney JW. 1986. A model for receptor-regulated calcium entry. *Cell Calcium* **7**: 1–12.
- Putney JW, Bird GS. 2008. Cytoplasmic calcium oscillations and store-operated calcium influx. *J Physiol* **586**: 3055–3059.
- Putney JW, Poggioli J, Weiss SJ. 1981. Receptor regulation of calcium release and calcium permeability in parotid gland cells. *Phil Trans R Soc Lond B* **296**: 37–45.

- Renard D, Poggioli J, Berthon B, Claret M. 1987. How far does phospholipase C activity depend on the cell calcium concentration? A study in intact cells. *Biochem J* **243**: 391–398.
- Ribeiro CMP, Putney JW. 1996. Differential effects of protein kinase C activation on calcium storage and capacitative calcium entry in NIH 3T3 cells. *J Biol Chem* **271**: 21522–21528.
- Rink TJ, Jacob R. 1989. Calcium oscillations in non-excitable cells. *Trends Neurosci* **12**: 43–46.
- Rizzuto R, Pozzan T. 2006. Microdomains of intracellular Ca^{2+} : Molecular determinants and functional consequences. *Physiol Rev* **86**: 369–408.
- Rizzuto R, Pinton P, Carrington W, Fay FS, Fogarty KE, Lifshitz LM, Tuft RA, Pozzan T. 1998. Close contacts with the endoplasmic reticulum as determinants of mitochondrial Ca^{2+} responses. *Science* **280**: 1763–1766.
- Rizzuto R, Simpson AWM, Brini M, Pozzan T. 1992. Rapid changes of mitochondrial Ca^{2+} revealed by specifically targeted recombinant aequorin. *Nature* **358**: 325–327.
- Rosado JA, Sage SO. 2000. A role for the actin cytoskeleton in the initiation and maintenance of store-mediated calcium entry in human platelets. *Trends Cardiovasc Med* **10**: 327–332.
- Saunders CM, Larman MG, Parrington J, Cox LJ, Royse J, Blayney LM, Swann K, Lai FA. 2002. PLC zeta: A sperm-specific trigger of Ca^{2+} oscillations in eggs and embryo development. *Development* **129**: 3533–3544.
- Selivanov VA, Ichas F, Holmuhamedov EL, Jouaville LS, Evtodienko YV, Mazat JP. 1998. A model of mitochondrial Ca^{2+} -induced Ca^{2+} release simulating the Ca^{2+} oscillations and spikes generated by mitochondria. *Biophys Chem* **72**: 111–121.
- Shuai JW, Yang DP, Pearson JE, Rudiger S. 2009. An investigation of models of the IP_3R channel in *Xenopus* oocyte. *Chaos* **19**: 037105.
- Shuttleworth TJ. 1999. What drives calcium entry during $[\text{Ca}^{2+}]_i$ oscillations? - challenging the capacitative model. *Cell Calcium* **25**: 237–246.
- Shuttleworth TJ, Thompson JL, Mignen O. 2004. ARC channels: A novel pathway for receptor-activated calcium entry. *Physiology (Bethesda)* **19**: 355–361.
- Shuttleworth TJ, Thompson JL, Mignen O. 2007. STIM1 and the noncapacitative ARC channels. *Cell Calcium* **42**: 183–191.
- Skupin A, Kettenmann H, Winkler U, Wartenberg M, Sauer H, Tovey SC, Taylor CW, Falcke M. 2008. How does intracellular Ca^{2+} oscillate: By chance or by the clock? *Biophys J* **94**: 2404–2411.
- Smith IF, Parker I. 2009. Imaging the quantal substructure of single IP_3R channel activity during Ca^{2+} puffs in intact mammalian cells. *Proc Natl Acad Sci* **106**: 6404–6409.
- Smith IF, Wiltgen SM, Shuai J, Parker I. 2009. Ca^{2+} puffs originate from preestablished stable clusters of inositol trisphosphate receptors. *Sci Signal* **2**: ra77.
- Sneyd J, Falcke M. 2005. Models of the inositol trisphosphate receptor. *Prog Biophys Mol Biol* **89**: 207–245.
- Sneyd J, Charles AC, Sanderson MJ. 1994. A model for the propagation of intercellular calcium waves. *Am J Physiol* **266**: C293–C302.
- Sneyd J, Tsaneva-Atanasova K, Reznikov V, Bai Y, Sanderson MJ, Yule DI. 2006. A method for determining the dependence of calcium oscillations on inositol trisphosphate oscillations. *Proc Natl Acad Sci* **103**: 1675–1680.
- Sneyd J, Tsaneva-Atanasova K, Yule DI, Thompson JL, Shuttleworth TJ. 2004. Control of calcium oscillations by membrane fluxes. *Proc Natl Acad Sci* **101**: 1392–1396.
- Sneyd J, Wetton BT, Charles AC, Sanderson MJ. 1995. Intercellular calcium waves mediated by diffusion of inositol trisphosphate: A two-dimensional model. *Am J Physiol* **268**: C1537–C1545.
- Soboloff J, Spassova MA, Hewavitharana T, He LP, Xu W, Johnstone LS, Dziadek MA, Gill DL. 2006a. STIM2 is an inhibitor of STIM1-mediated store-operated Ca^{2+} entry. *Curr Biol* **16**: 1465–1470.
- Soboloff J, Spassova MA, Tang XD, Hewavitharana T, Xu W, Gill DL. 2006b. Orai1 and STIM reconstitute store-operated calcium channel function. *J Biol Chem* **281**: 20661–20665.
- Streb H, Irvine RF, Berridge MJ, Schulz I. 1983. Release of Ca^{2+} from a nonmitochondrial store in pancreatic cells by inositol-1,4,5-trisphosphate. *Nature* **306**: 67–68.
- Swann K, Yu Y. 2008. The dynamics of calcium oscillations that activate mammalian eggs. *Int J Dev Biol* **52**: 585–594.
- Swillens S, Champeil P, Combettes L, Dupont G. 1998. Stochastic simulation of a single inositol 1,4,5-trisphosphate-sensitive Ca^{2+} channel reveals repetitive openings during ‘blip-like’ Ca^{2+} transients. *Cell Calcium* **23**: 291–302.
- Swillens S, Dupont G, Combettes L, Champeil P. 1999. From calcium blips to calcium puffs: theoretical analysis of the requirements for interchannel communication. *Proc Natl Acad Sci* **96**: 13750–13755.
- Tang Y, Othmer HG. 1994. A model of calcium dynamics in cardiac myocytes based on the kinetics of ryanodine-sensitive calcium channels. *Biophys J* **67**: 2223–2235.
- Tang Y, Stephenson JL, Othmer HG. 1996. Simplification and analysis of models of calcium dynamics based on IP_3 -sensitive calcium channel kinetics. *Biophys J* **70**: 246–263.
- Tanimura A, Morita T, Nezu A, Shitara A, Hashimoto N, Tojyo Y. 2009. Use of fluorescence resonance energy transfer-based biosensors for the quantitative analysis of inositol 1,4,5-trisphosphate dynamics in calcium oscillations. *J Biol Chem* **284**: 8910–8917.
- Taylor CW, Thorn P. 2001. Calcium signalling: IP_3 rises again . . . and again. *Current Biol* **11**: R352–R355.
- Tepikin AV, Petersen OH. 1992. Mechanisms of cellular calcium oscillations in secretory cells. *Biochim Biophys Acta* **1137**: 197–207.
- Thomas AP, Renard DC, Rooney TA. 1992. Spatial organization of Ca^{2+} signaling and $\text{Ins}(1,4,5)\text{P}_3$ action. *Adv Second Messenger Phosphoprotein Res* **26**: 225–263.
- Thomas AP, Bird GSJ, Hajnóczky G, Robb-Gaspers LD, Putney JW. 1996. Spatial and temporal aspects of cellular calcium signalling. *FASEB J* **10**: 1505–1517.
- Thomas D, Lipp P, Tovey SC, Berridge MJ, Li W, Tsien RY, Bootman MD. 2000. Microscopic properties of elementary Ca^{2+} release sites in non-excitable cells. *Current Biol* **10**: 8–15.

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- Thul R, Smith GD, Coombes S. 2008. A bidomain threshold model of propagating calcium waves. *J Math Biol* **56**: 435–463.
- Tsien RW, Bean BP, Hess P, Lansman JB, Nilius B, Nowycky MC. 1986. Mechanisms of calcium channel modulation by β -adrenergic agents and dihydropyridine calcium agonists. *J Mol Cell Cardiol* **18**: 691–710.
- Van Breemen C, Farinas B, Gerba P, McNaughton ED. 1972. Excitation-contraction coupling in rabbit aorta studied by the lanthanum method for measuring cellular calcium influx. *Circ Res* **30**: 44–54.
- Vazquez G, Wedel BJ, Aziz O, Trebak M, Putney JW. 2004. The mammalian TRPC cation channels. *Biochim Biophys Acta* **1742**: 21–36.
- Ventura AC, Sneyd J. 2006. Calcium oscillations and waves generated by multiple release mechanisms in pancreatic acinar cells. *Bull Math Biol* **68**: 2205–2231.
- Wang I, Politi AZ, Tania N, Bai Y, Sanderson MJ, Sneyd J. 2008. A mathematical model of airway and pulmonary arteriole smooth muscle. *Biophys J* **94**: 2053–2064.
- Wedel B, Boyles RR, Putney JW, Bird GS. 2007. Role of the store-operated calcium entry proteins, Stim1 and Orai1, in muscarinic-cholinergic receptor stimulated calcium oscillations in human embryonic kidney cells. *J Physiol* **579**: 679–689.
- Williams GS, Molinelli EJ, Smith GD. 2008. Modeling local and global intracellular calcium responses mediated by diffusely distributed inositol 1,4,5-trisphosphate receptors. *J Theor Biol* **253**: 170–188.
- Woods NM, Cuthbertson KS, Cobbold PH. 1986. Repetitive transient rises in cytoplasmic free calcium in hormone-stimulated hepatocytes. *Nature* **319**: 600–602.
- Zahradnikova A, Zahradnik I. 1996. A minimal gating model for the cardiac calcium release channel. *Biophys J* **71**: 2996–3012.
- Zen S, Li B, Zeng S, Chen S. 2009. Simulation of spontaneous Ca^{2+} oscillations in astrocytes mediated by voltage-gated calcium channels. *Biophys J* **97**: 2429–2437.
- Zheng L, Stathopoulos PB, Li GY, Ikura M. 2008. Biophysical characterization of the EF-hand and SAM domain containing Ca^{2+} sensory region of STIM1 and STIM2. *Biochem Biophys Res Commun* **369**: 240–246.

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