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Review

Coding and decoding of oscillatory Ca^{2+} signals

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ABSTRACT

About 30 years after their first observation, Ca^{2+} oscillations are now recognised as a universal mechanism of signal transduction. These oscillations are driven by periodic cycles of release and uptake of Ca^{2+} between the cytoplasm and the endoplasmic reticulum. Their frequency often increases with the level of stimulation, which can be decoded by some molecules. However, it is becoming increasingly evident that the widespread core oscillatory mechanism is modulated in many ways, depending on the cell type and on the physiological conditions. Interplay with inositol 1,4,5-trisphosphate metabolism and with other Ca^{2+} stores as the extracellular medium or mitochondria can much affect the properties of these oscillations. In many cases, these finely tuned characteristics of Ca^{2+} oscillations impact the physiological response that is triggered by the signal. Moreover, oscillations are intrinsically irregular. This randomness can also be exploited by the cell. In this review, we discuss evidences of these additional manifestations of the versatility of Ca^{2+} signalling.

1. Introduction

Ca^{2+} is a very effective signalling ion, as it binds to many proteins with high affinity and can thereby initiate a variety of physiological responses. However, this ion is also an inducer of apoptosis and Ca^{2+} signals most often arise in the form of repetitive spikes to avoid prolonged increases in cellular Ca^{2+}, which are toxic for the cell. These spikes are generated by the opening of channels bridging the cytoplasm with the main Ca^{2+} pools, the endoplasmic reticulum (ER) and the extracellular medium. Because the Ca^{2+} gradients between the cytosol and these Ca^{2+} pools are huge (the ratio of concentrations is $\sim 10^4$), short openings are able to drastically change the Ca^{2+} concentration inside the cytosol. To avoid Ca^{2+} overloading, a variety of Ca^{2+} removing processes are rapidly turned on as soon as cytosolic Ca^{2+} concentration starts to rise. Ca^{2+} concentration thus goes down nearly as fast as it had gone up. In the continuous presence of the stimulus, this spike is the first one of a train of Ca^{2+} spikes regularly spaced in the course of time. This series is called "Ca^{2+} oscillations" [1].

In most cell types, these Ca^{2+} oscillations are initiated by the binding of an external agonist to its receptor, which first triggers the activation of receptor-associated G-proteins. This in turn stimulates a phospholipase C (PLC) that catalyses the hydrolysis of membrane-bound phosphatidylinositol 4,5-bisphosphate (PIP_2) to form inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 diffuses in the cytosol and binds to IP_3 receptors (IP_3R) on the membrane of the endoplasmic or sarcoplasmic reticulum (ER/SR). The IP_3R is indeed a tetrameric Ca^{2+} channel that opens when the four IP_3-binding sites are occupied [2]. The Ca^{2+} releasing activity of the IP_3R is moreover regulated by Ca^{2+}: low concentrations stimulate release, while high concentrations tend to close the IP_3R Ca^{2+} channel. Thus, after a sharp rise in surrounding Ca^{2+} due to Ca^{2+}-induced Ca^{2+} release (CICR), the channel closes. Ca^{2+} release from the ER can be further amplified by a similar Ca^{2+}-induced Ca^{2+} release from ryanodine receptors (RyR), mostly expressed in excitable cells. On the other hand, Ca^{2+} ATPases (SERCA, Sarco- or Endoplasmic Reticulum Ca^{2+} ATPases) pump Ca^{2+} back into the ER. Once Ca^{2+} concentration gets back to its basal level, another Ca^{2+} peak can emerge. The interval between two successive spikes, i.e. the period of oscillations, is mainly fixed by the time it takes to build up the threshold cytosolic Ca^{2+} concentration leading to IP_3R activation. The interplay between these IP_3R and the SERCA pumps thus constitutes the core oscillator responsible for repetitive Ca^{2+} spikes [3].

This classical description of Ca^{2+} oscillations, schematised in Fig. 1, is now well established. It provides a very useful tool to get a global and qualitative understanding of the mechanism of oscillations, of their possible appearance/disappearance when changing the level of stimulation, or of the increase in frequency with the concentration of IP_3. This oscillatory mechanism shares many properties with that driving

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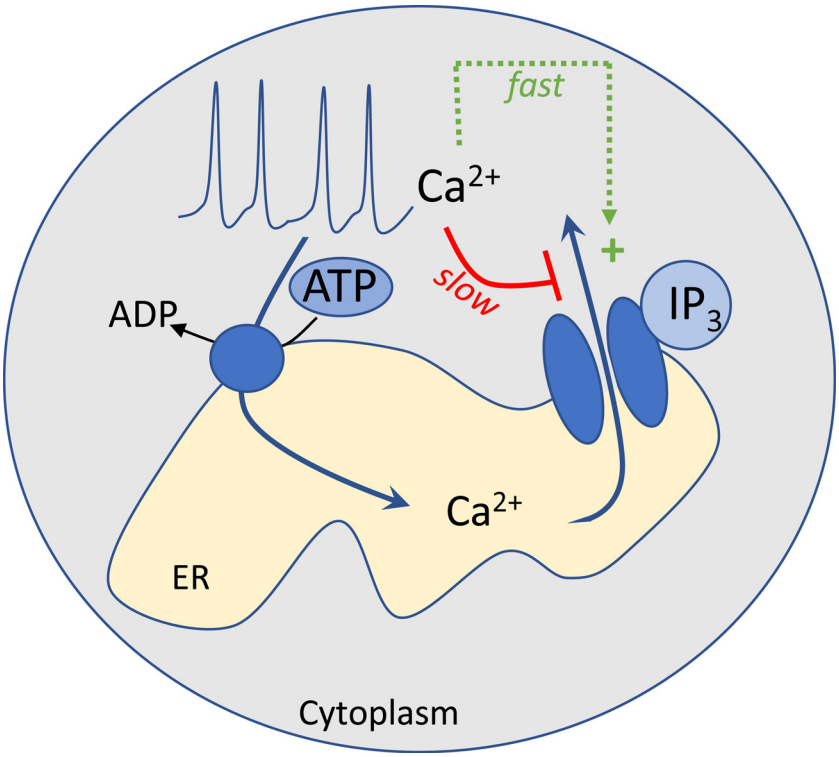

Fig. 1. Schematic representation of the core oscillatory mechanism of Ca^{2+} oscillations. Ca^{2+} is released from the ER through the IP_3 receptor. This release is activated by Ca^{2+}, and more slowly inhibited by higher Ca^{2+} concentrations. Ca^{2+} is pumped back in the ER via the SERCA pumps.

regenerative electrical activity in neurons, since CICR is mechanistically similar to the positive feedback between Na^+ entry and plasma membrane depolarisation. Thus, many characteristics about repetitive spiking and frequency decoding can be transposed from neurophysiology to calcium signalling [3]. Changes in frequency can in turn be decoded by the Ca^{2+}-sensitive targets playing a role in the control of gene expression, secretion, contraction, etc. Understanding the regulation of the kinetics of intracellular Ca^{2+} changes is thus highly relevant from a physiological point of view.

However, many observations related to Ca^{2+} signalling do not fit in the simple description of the oscillatory mechanism given just above. For example, Ca^{2+} handling by other Ca^{2+} pools than the ER or by Ca^{2+} buffers can drastically affect cytosolic Ca^{2+} dynamics (Fig. 2). It was also shown that IP_3 concentration does not always remain constant since its metabolism is Ca^{2+}-sensitive, or that cytosolic Ca^{2+} microdomains can develop and influence Ca^{2+} signals at the whole cellular level. In many cases, Ca^{2+} oscillations are moreover quite irregular, which questions the picture of a clock-like oscillator as the one just described. As a last example, in some cell types, the frequency of Ca^{2+} oscillations does not increase with the level of stimulation. These observations, and many others, indicate that an additional level of complexity needs to be incorporated in the classical IP_3R/SERCA-based description of Ca^{2+} oscillations. In this review, we aim at putting forward the idea that Ca^{2+} oscillations are differently regulated and decoded, depending on the cell type, the agonist used or the actual conditions of the cell. Despite their universal character, oscillatory Ca^{2+} signals exhibit a large number of fine-tuning possibilities, which is a supplementary manifestation of their versatility [1].

2. IP_3 oscillations

The aforementioned biphasic regulation of the IP_3R is the most widespread mechanism responsible for Ca^{2+} oscillations (Fig. 1). In this framework, Ca^{2+} oscillations can occur in the presence of a constant level of IP_3, which controls the rate at which Ca^{2+} is released between two successive spikes, and hence the oscillation frequency. In some cases, however, Ca^{2+} oscillations rely on periodic variations in IP_3 concentration. IP_3 oscillations have for example been observed in Madin-Darby canine kidney epithelial cells [4] or in HSY cells, a human salivary duct cell line [5]. Concomitant oscillations of IP_3 and Ca^{2+} are also observed in cell lines expressing the metabotropic glutamate receptor 5 (mGluR5). These oscillations, observed over a wide range of glutamate concentrations, have unusual characteristics. Instead of depending on the glutamate concentration, the frequency of these oscillations is sensitive to the level of receptor expression [6]. As a result, receptor trafficking on the cell surface can retune the Ca^{2+} signature induced by glutamate delivery [7].

IP_3 oscillations can arise from several mechanisms. One of these is the regulation of protein kinase C (PKC), a Ca^{2+} and/or DAG-dependent kinase, which exerts a negative feedback on the receptor/G-protein complex [8,9]. IP_3 oscillations can also be produced when Ca^{2+} directly feedbacks on the activity of the IP_3 synthesising enzyme, PLC. This occurs *in vivo* when PLC activity is stimulated by Ca^{2+} levels corresponding to those encountered during Ca^{2+} oscillations (~50 nM –1 μM). Two specific isoforms are clearly regulated at these Ca^{2+} concentrations: PLCδ [10] and PLCζ [11]. The latter is sperm-specific and is responsible for the Ca^{2+} oscillations during fertilisation. In agreement with this, IP_3 oscillations were recently reported in fertilised mouse eggs [12]. Interestingly, these IP_3 oscillations were not observed directly, but inferred from an experiment of photorelease of caged IP_3. As predicted by mathematical modelling [13], such an addition of exogenous IP_3 provokes a phase resetting of Ca^{2+} oscillations if these are caused by IP_3 oscillations. In other words, the pulse induces a transient disappearance of Ca^{2+} oscillations. When they re-appear, they do so with the same period as before the pulse. This is exactly what is observed in fertilised mouse eggs [12]. In contrast, if Ca^{2+} oscillations relied on successive cycles of activation/inhibition of the IP_3R as depicted in Fig. 1, the addition of IP_3 during Ca^{2+} oscillations would provoke a transient rise in the frequency of oscillations, with a progressive return to the original frequency. This is the case in airway

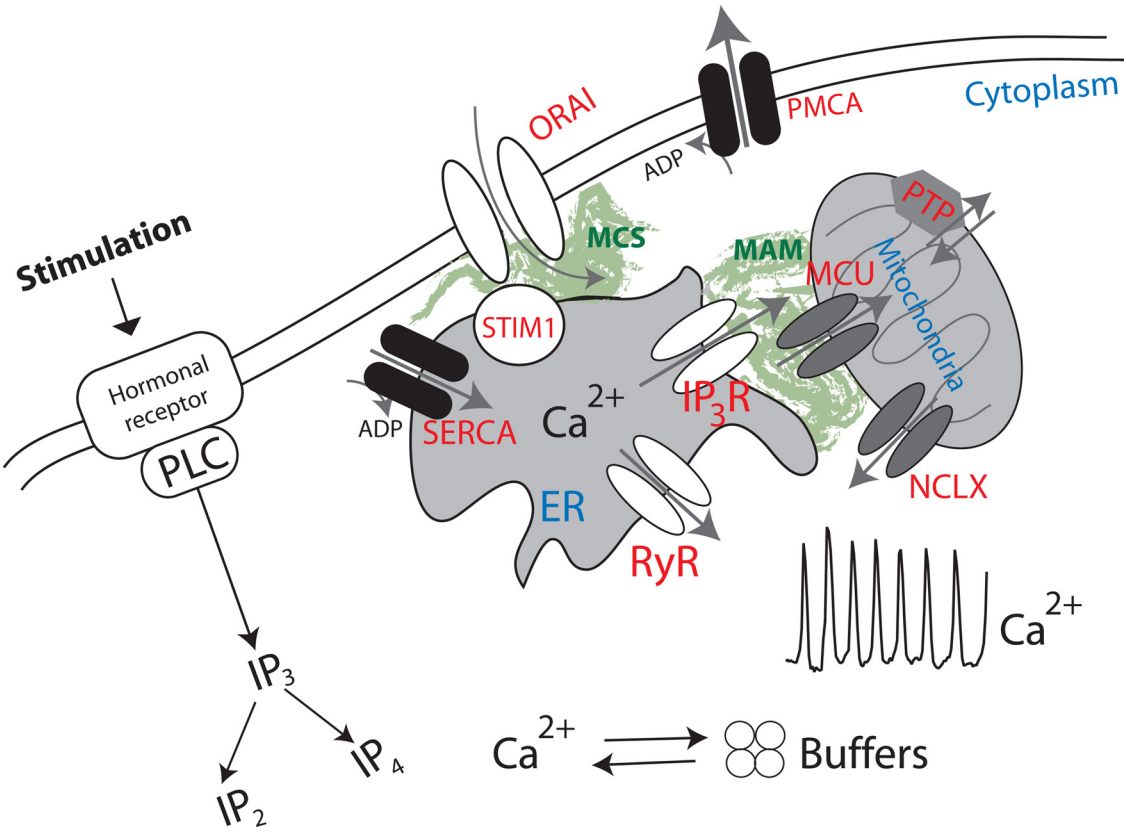

Fig. 2. Schematic representation of the main processes involved in Ca^{2+} signalling. Depending on the cell type and the agonist, the level of activity of each process can be highly variable. They are described throughout the text.

smooth muscle cells [13].

The analysis of Ca^{2+} dynamics in the presence of IP_3 buffers [14,15] led to the conclusion that the Ca^{2+}-stimulation of PLC also plays a key role in hepatocytes and COS cells, although these cells mostly express PLCβ. A genetically encoded IP_3 buffer indeed transforms an oscillatory Ca^{2+} response into a single, broad $[Ca^{2+}]$ transient with a much slower rising phase. It also decreases the rate of propagation of the Ca^{2+} wave. As the presence of an IP_3 buffer does not decrease the steady state level of IP_3, the authors concluded that Ca^{2+} spikes are prevented by the slowing down of IP_3 dynamics. These dynamics thus play a causal role in generating Ca^{2+} oscillations. Computational modelling moreover suggested that only a positive feedback by Ca^{2+} on IP_3 synthesis can account for the experimental observations [15].

Finally, IP_3 can also oscillate because its transformation into IP_4 by an IP_3 3-kinase is stimulated by Ca^{2+} [16]. If this kinase is significantly active, each Ca^{2+} spike is followed by a transient decrease in IP_3. In this scenario, the peak in Ca^{2+} precedes the peak in IP_3, which results in IP_3 oscillations with a phase relation differing from the one presented above. These IP_3 oscillations can thus not drive Ca^{2+} oscillations but could reduce their frequency by decreasing the amount of IP_3 and hence the IP_3R activity between the spikes. However, as IP_3 metabolism is mostly performed by the Ca^{2+}-insensitive IP_3 5-phosphatase in most cell types, IP_3 oscillations due to Ca^{2+} feedback on IP_3 metabolism mostly appear as a side effect that does not affect Ca^{2+} signalling [17,18].

3. Ca^{2+} entry

At each Ca^{2+} spike, some Ca^{2+} is expelled from the cell through plasma-membrane Ca^{2+} ATPases (PMCA). In the absence of extracellular Ca^{2+}, the ER is not fully replenished after a spike and oscillations become damped before finally disappearing. The rate of damping is highly dependent on the cell type [19]. At physiological extracellular Ca^{2+} concentrations (~1 mM), a tightly regulated mechanism of Ca^{2+} entry maintains a constant total Ca^{2+} level, which ensures that oscillations remain unchanged as long as the stimulus is present. The main mechanism of Ca^{2+} entry is known as SOCE, for store-operated Ca^{2+} entry, and is extensively described in another chapter of this special issue [20]. SOCE involves the stromal interaction molecule (STIM) and the Orai protein, localised inside the ER and in the plasma membrane, respectively [21]. A decrease of the $[Ca^{2+}]$ in the ER ($[Ca^{2+}]_{ER}$) below ~~200 μM leads to STIM1 aggregation, followed by their migration to ER-plasma membrane (PM) junctions. The resulting local close apposition between the two membranes constitutes membrane contact sites (MCS). There, STIM1 oligomers bind and activate Orai1, forming a channel that allows the entry of external Ca^{2+} into the cytoplasm (Fig. 2). Activation of SOCE is a steep decreasing function of $[Ca^{2+}]_{ER}$. As the depth of the MCS is in the order of 10–40 nm, $[Ca^{2+}]$ rapidly rises in MCS [22]. This local Ca^{2+} rise inactivates SOCE through Ca^{2+}-induced inactivation (CDI), a process that is necessary to avoid Ca^{2+} overload in the cell [23]. It should be kept in mind that inside MCS, Ca^{2+} not only controls SOCE termination, but also regulates many physiological processes, such as muscle contraction and depolarisation or lipid trafficking [24,25].

From a perspective point of view, one could question the physiological advantage of a stimulation of Ca^{2+} entry by a decrease in the level of ER Ca^{2+} and not directly by an increase in cytosolic Ca^{2+}. One possible answer to this question could be linked to the large spatial heterogeneity of cytosolic Ca^{2+} inside the cytoplasm. The existence of microdomains with large cytosolic Ca^{2+} concentration in an elsewhere resting cytoplasm could lead to contradictory signals in the activation of Ca^{2+} entry if it was regulated by cytosolic Ca^{2+} only. In contrast, homogenisation of the Ca^{2+} level within the ER is a rapid process [26], which could lead to a more coherent signal controlling Ca^{2+} entry.

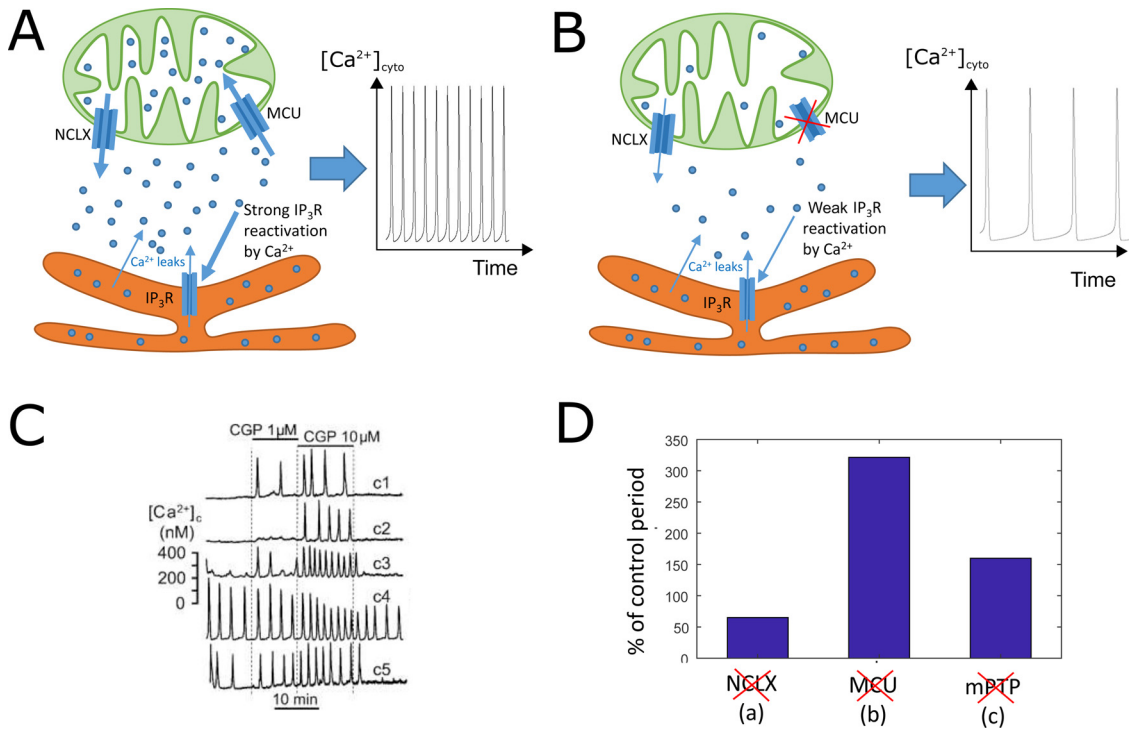

Fig. 3. Impact of the mitochondrial Ca^{2+} fluxes on the frequency of cytosolic Ca^{2+} oscillations.In the control case (A), mitochondria are able to accumulate Ca^{2+} during a spike, and to slowly release their Ca^{2+} content to trigger a new spike through CICR. If the MCU is inhibited (B), mitochondria do not release Ca^{2+}. The onset of a new spike is thus delayed. In (A) and (B), time series are schematic representations of the oscillatory behaviour in HeLa cells. (C) Experiments showing spontaneous cytosolic Ca^{2+} oscillations in fibroblasts. The addition of the NCLX inhibitor CGP37157 decreases the period of the oscillations. Data from [42]. See text for details. (D) Quantitative impact of mitochondrial Ca^{2+} transporters on the frequency of cytosolic Ca^{2+}oscillations. Affecting the activity of three different transport mechanisms of Ca^{2+} across the mitochondrial membrane has a significant effect on the frequency of Ca^{2+} oscillations. In each case, 100% corresponds to the control case in the absence of the blocking agent. a) Inhibition of the NCLX in fibroblasts with 1 µM CGP37157. Data from [42]. b) Inhibition of the MCU in HeLa cells stimulated by 5 µM Histamine, with si-RNA against MCU. Data from [47]. c) Inhibition of the PTP in Hela cells stimulated by 10 µM histamine, with 1 µM CSA. Data from [47].

What drives rapid homogenisation of Ca^{2+} in the ER is not fully understood since diffusion of Ca^{2+} in this compartment is *a priori* expected to be slow. The ER is indeed made of an interconnected network of flattened, convoluted membranes. Ca^{2+} diffusion inside this organelle may thus be hindered by geometrical constraints. In addition, Ca^{2+} is heavily buffered in the ER, which also significantly reduces the mobility of the ion. Diffusion coefficients of the order of 20 µm^2/s [27], *i.e.* slightly smaller than in the cytosol, are generally reported. The paradox of a slow diffusion and fast homogenisation of free Ca^{2+} in the ER may be related to the abundance and rapidity of the ER Ca^{2+} buffers. Simulations indeed predict that local depletion would be rapidly compensated by Ca^{2+} dissociation from the buffers, thus avoiding the formation of significant gradients of Ca^{2+} concentration in this organelle [28]. This theoretical prediction may explain the rapid equilibration of Ca^{2+} concentration in the lumen of pancreatic acinar cells after Ca^{2+} uncaging [26]. Deciphering the spatio-temporal Ca^{2+} dynamics inside the ER is needed not only to understand the activation of SOCE that is triggered by ER Ca^{2+} depletion, but also to establish the molecular bases of the process of "Ca^{2+} tunnelling" allowing the release of Ca^{2+} taken up by the SOCE mechanism through IP_3R located at distal sites [29].

Depending on the cell type, other modes of Ca^{2+} entry participate to Ca^{2+} homeostasis and signalling. For example, arachidonate-regulated Ca^{2+} channels (ARC) open in response to agonist binding to the extracellular receptor. This pathway is mediated by arachidonic acid, which is synthesised from DAG that is produced together with IP_3. The interplay with SOCE is complex, as ARC channels are formed by a combination of specific Orai isoforms, and are regulated by STIM proteins present in the plasma membrane. These channels may contribute to Ca^{2+} entry during Ca^{2+} oscillations at low concentrations of agonist, while SOCE would be predominant at high concentrations [30]. Finally, the Ca^{2+} entry in the cytosol can also be mediated by connexin (Cx) hemichannels. These hemichannels are also known to enhance, in some cases, the occurrence of Ca^{2+} oscillations. More precisely, they amplify Ca^{2+} signalling by enabling the release of ATP into the extracellular medium, which further activates purinergic signalling in an auto- or paracrine manner [31,32].

4. Interplay with mitochondria

Ca^{2+} oscillates not only in the cytosol and the ER, but also inside mitochondria. Indeed, the inner membrane of these organelles holds Ca^{2+} transporters that uptake and extrude Ca^{2+}, and hence transfer cytosolic Ca^{2+} oscillations into mitochondria. The Ca^{2+} entry is mainly ensured by the Mitochondrial Calcium Uniporter (MCU) whereas its extrusion is mediated by other channels such as the Na^+/Ca^{2+} exchanger (NCLX), which is a main exchanger in electrically non-excitable cells. The former one imports Ca^{2+} with a low affinity in a cooperative way that notably depends on the MICU1 regulator. In particular, different MICU1/MCU ratios explain the variable thresholds and cooperativities observed in different cell types such as liver or heart cells [33]. The latter one exports Ca^{2+} by importing Na^+, although the exact stoichiometry of this exchange still remains unclear [34].

Intramitochondrial Ca^{2+} signals regulate cell bioenergetics by activating some key-enzymes of the Krebs cycle [35]. An oscillatory level of Ca^{2+} in mitochondria consequently leads to oscillations in metabolic intermediates such as NADH [36]. ATP production in mitochondria also follows cytosolic Ca^{2+} changes [37]. Modelling of the interplay between intracellular Ca^{2+} oscillations and Ca^{2+}-stimulated mitochondrial metabolism suggests that the physiological properties of the

cytosolic oscillations (frequency and amplitude) result in an optimised ATP production [38]. The fine tuning of mitochondrial Ca^{2+} is moreover suggested by the fact that mitochondrial Ca^{2+} overload can trigger the opening of the mitochondrial Permeability Transition Pore (mPTP) and thus acts as a death signal [39].

Cytosolic Ca^{2+} oscillations thus affect mitochondrial Ca^{2+} and metabolism, but conversely, mitochondria are likely to modify Ca^{2+} oscillations in the cytosol. Besides, most mitochondrial Ca^{2+} transporters are voltage-dependent, and are influenced by the proton gradient established by mitochondrial metabolism. To unravel the impact of mitochondria on cytosolic oscillations, the phase relationship between peaks in the different compartments has been studied both by experimental and modelling approaches. It appears that at the dawn of a new cytosolic spike, the ER Ca^{2+} stock is still refilling, while mitochondria are emptying. It means that mitochondria are able to affect the emergence of a new spike by slowly releasing the Ca^{2+}that they have stored [38,40,41]. This is supported by experiments showing the impact of blocking mitochondrial Ca^{2+} transporters on the frequency of cytosolic oscillations (Fig. 3D). In HeLa cells stimulated by histamine, a si-RNA against the MCU increases the period by 223% [38]. A plausible interpretation of this observation is that the lack of Ca^{2+} entry in mitochondria during a cytosolic Ca^{2+} spike prevents the release of Ca^{2+} between spikes, and thus delays the activation of the IP_3R (Fig. 3A and B). In agreement with this assumption, in HeLa cells, the addition of the NCLX inhibitor CGP37157 slows down the oscillations, because the Ca^{2+}that has been stored during the spike is not released sufficiently fast to reactivate the IP_3R [42]. However, this effect seems to be cell-dependent, as the NCLX inhibitor decreases the period of the spontaneous oscillations in fibroblasts by 35% (Fig. 3C and D). Modelling approaches suggest that this cell-specificity could rely on different levels of expression of the transporters. The behaviour observed in fibroblasts can indeed be explained by a higher expression of the NCLX, which leads to a significant Ca^{2+} extrusion during the cytosolic spike, even before IP_3R can be reactivated. In this case, the Ca^{2+} released by the NCLX prolongs the time during which the IP_3R remains inhibited. Consequently, in this cell type, reducing NCLX activity triggers faster oscillations. Actually, there are other examples of opposite consequences of the inhibition of one mitochondrial Ca^{2+} transporter on Ca^{2+} oscillations, which likely reflects the variety of Ca^{2+} flux rates of the different components [43–45].

Accumulating evidence highlights the importance of local aspects of Ca^{2+} signalling, notably in the microdomains delimited by mitochondria and the ER, called MAM (Mitochondria-Associated Membranes). These areas are rich in Ca^{2+} channels such as IP_3R. During Ca^{2+} release, the signal first remains confined inside the MAM, leading to locally high Ca^{2+} concentrations [46]. As MCU have a low Ca^{2+} affinity, the accumulation of Ca^{2+} in MAM is important to allow a significant uptake by mitochondria. A way to pinpoint the importance of these MAM in the Ca^{2+} dynamics is to observe the different rates of Ca^{2+} entry in mitochondria in intact cells or in suspensions [47]. The absence of MAM in suspensions of isolated mitochondria indeed much slows down Ca^{2+} entry into these organelles at low levels of extra-mitochondrial Ca^{2+}. In agreement with this observation, the kinetics of Ca^{2+} entry into mitochondria is also controlled by the distance between the membranes, which is finely regulated and fixed by different tethering proteins (FATE1, PERK, Mfn2). The distance between membranes indeed controls the level of Ca^{2+} reached in the MAM. The spatial and temporal scales of such Ca^{2+} microdomains prevent any precise experimental determination of the inter-organelle distance that optimises Ca^{2+} entry in mitochondria. A computational model suggests a distance within the 30–85 nm range [48]. This distance modifies the shape and the frequency of Ca^{2+} oscillations. Experimentally, the importance of an optimal distance between the IP_3R and the mitochondrial membrane is illustrated for example, in myocytes deficient in Mfn2, which have a lower efficiency of Ca^{2+} uptake, and show impaired bioenergetics responses [49]. A weaker expression of FATE1 reduces the distance between the ER and the mitochondria, leading to cells that are more sensitive to apoptotic stimuli [50]. Alterations of the size of MAM and of the Ca^{2+} dynamics in these microdomains are thus involved in numerous diseases such as neurodegenerative disorders, obesity, or cancers [51].

Another element intimately related to cytosolic Ca^{2+} oscillations is the mPTP. The mPTP is associated with the permeabilisation of the mitochondrial membranes. The molecular identity of the pore has been recently identified as the F_1F_o ATPase, and the nature of the Ca^{2+} binding site responsible for pore opening has been established. However, the opening mechanism still needs to be investigated [52]. The mPTP can open in two conductance modes. The first one is transitory and stochastic. In this mode, the mPTP is permeable to small ions such as Ca^{2+}, H^+ or K^+ [39]. These fluxes could have a role inside microdomains, as suggested by observations on Ca^{2+} effluxes in Ca^{2+} microdomains in astrocytes. It has been proposed that Ca^{2+} release through the low conductance mode regulates Ca^{2+} homeostasis and prevents mitochondrial overload, without impairing the bioenergetics of the cell. However, the exact consequences of this low conducting mode still have to be elucidated [53,54]. As the NCLX and the MCU, the mPTP is likely to alter cytosolic Ca^{2+} oscillations, as suggested by observations on the frequency of oscillations in HeLa cells (Fig. 3D) in the presence of CsA, a mPTP inhibitor [38]. In stressful or pathological conditions, the mPTP can open in its high conductance mode and become permeable to larger molecules (< 1.5 kDa). The opening in the high conductance mode is physiologically irreversible, leads to the dissipation of the mitochondrial membrane potential and triggers cellular apoptosis. This signal can be induced by a wide range of compounds such as Ca^{2+} overload, inorganic phosphate, or reactive oxygen species [39].

5. Oscillations or random spikes?

Recent observations both at single channel and cellular levels have suggested that noise could play a predominant role in Ca^{2+} signalling. First, data on single channels indicate that the open probability of the IP_3R fluctuates at constant IP_3 and Ca^{2+} concentrations. More specifically, this channel exhibits different *modes*, each with a different open probability. Switching from one mode to the other occurs spontaneously, but at a slower frequency than channel gating. The number of modes is variously claimed to be two [55] or three [56,57]. The physiological implications of these observations in intact cells remain to be clarified, but certainly point to the need for taking randomness into account to describe the dynamics of opening and closing of the IP_3R as changes in the opening probabilities are not fixed for a given set of ligand concentrations.

At the level of the intact cells, IP_3R are moreover gathered in clusters where Ca^{2+} can reach very high concentrations [58]. Such clusters most of the time behave as individual entities, due to their reduced coupling through Ca^{2+} diffusion, and generate local signals called “puffs”. These signals are characterised by a high degree of stochasticity, which directly results from the random dynamics of individual channels within the cluster just described. The time interval between two successive puffs at a given cluster (interpuff time interval or IPI) lasts a few seconds at most and is compatible with the recovery period from Ca^{2+} inhibition of IP_3R [59]. At higher stimulus intensities, successive puffs can trigger a global elevation of Ca^{2+} thanks to the activation of more IP_3R, leading to a global spike. However, the inhibition and activation timescales of IP_3R are much shorter than the average interspike time interval (ISI), which is hence believed to result from a more global recovery mechanism than the local inhibition by Ca^{2+}. Such a global feedback could rely on IP_3 metabolism [14] or on variations in the sensitivity of IP_3R to Ca^{2+} or IP_3 [56,57]. The global and repetitive Ca^{2+} increases are often called “spikes” instead of “Ca^{2+} oscillations” to highlight their stochastic character, in contrast to classical biological oscillators, such as the cell cycle or the electrical activity

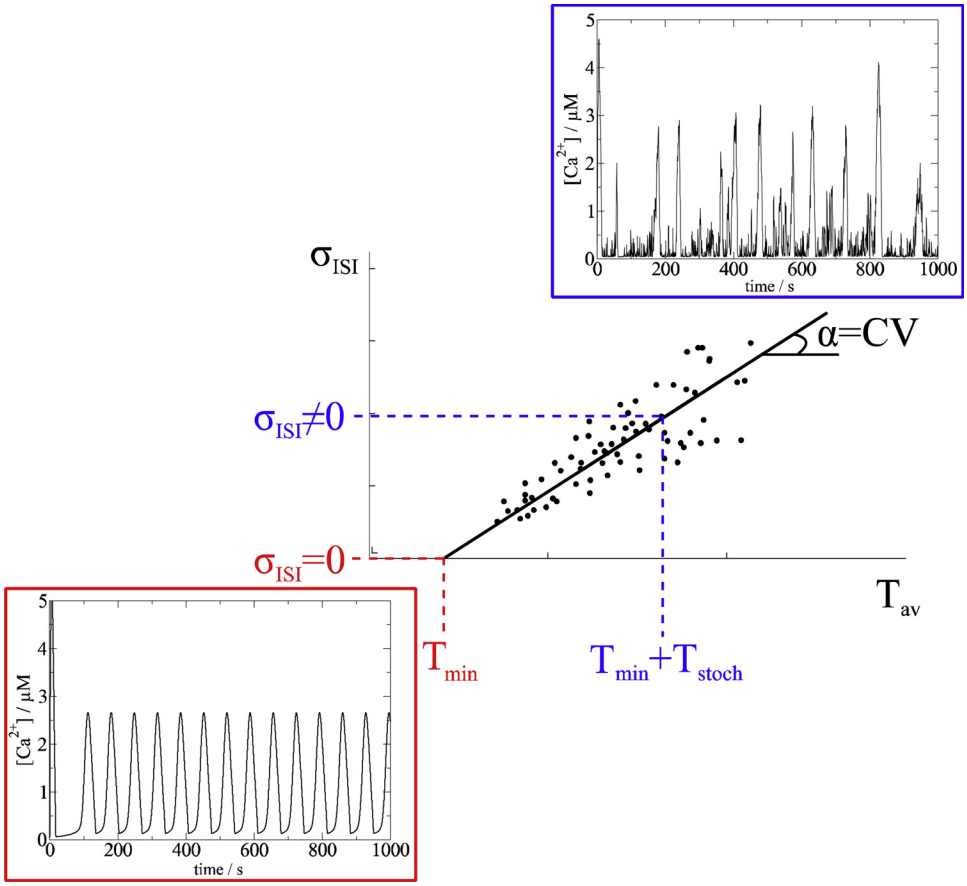

Fig. 4. Random character of Ca^{2+} oscillations. The central panel schematises the linear relationship between the standard deviation on the interspike interval and the average interspike (T_{av}) that is observed in many cell types [60]. Minimal standard deviations correspond to high frequencies (small T_{av}), in which case oscillations are regular. For large T_{av}, the standard deviation is comparable to the interspike interval, and oscillations appear very noisy. In both cases, oscillations correspond to numerical simulations using a fully stochastic simulation scheme based on [62].

of pacemaker neurons.

The relative regularity of Ca^{2+} spike sequences contrasts with the randomness of puffs. There is also a large difference of timescales between local and global signals, as the interpuff intervals are of the order of a few seconds, while the average ISI is at least 10 times larger. As the same Ca^{2+} channels underlie Ca^{2+} puffs and waves, such properties are puzzling and the hierarchical organisation of Ca^{2+} signals is at the core of ongoing theoretical research [60]. Extensive analyses of experimental spike sequences have highlighted that the average ISI is subjected to a significant variability, both at the single cell level and among a population of cells exposed to the same stimulus [61]. The average ISI (T_{av}) and the standard deviation of the ISI (σ_{ISI}) are even of the same order of magnitude, which again points to the random character of global spikes in a single cell. Moreover, experiments run on populations of cells have further shown that T_{av} is linearly related to σ_{ISI} by $\sigma_{ISI} = \alpha(T_{av} - T_{min})$, where the ISI is decomposed into a fixed part (T_{min}) and a stochastic part ($T_{stoch} = T_{av} - T_{min}$) responsible for the variability. If spikes were not random, the ISI would be simply given by T_{min}, which represents the spike duration and the absolute, global recovery period following a spike (Fig. 4).

Experiments indicate that the slope (α) of the aforementioned linear relation between σ_{ISI} and T_{av} typically ranges between 0 and 1 and gives the population averaged coefficient of variation or the invert of the signal-to-noise ratio (α^{-1}). When decreasing the dose of stimulus, T_{av} decreases and the cell shifts from frequent, regular oscillations to highly irregular, less frequent Ca^{2+} spikes [63]. This provides another type of information coding, supplementing the frequency encoding of Ca^{2+} oscillations (see below). Moreover, while α is robust against stimulus intensity and pharmacological perturbations, it displays much more sensitivity to the cell type and the agonist used to stimulate the cell [61]. In other words, Ca^{2+} spiking with a specific T_{av} can result from different signalling pathways, but the different α and σ_{ISI} give rise to a different signal-to-noise ratio, which could be decoded by the cell as a stimulus of different nature [63]. In other words, cells are able to decode the information conveyed in stochastic signals through properties differing from frequency, amplitude or half-width, which usually characterise oscillations.

6. Some spatial considerations

During a Ca^{2+} spike, $[Ca^{2+}]$ does not rise simultaneously in the whole cytoplasm. Indeed, as detailed just above, Ca^{2+} spikes arise through the release of Ca^{2+} through discretely distributed groups of IP_3R named clusters. Because of the relatively large distance between the clusters –less than 1 μm to about 10 μm depending on the cell type– synchronised opening would require fast diffusion of Ca^{2+} between the clusters. As Ca^{2+} is heavily buffered in the cytoplasm, its diffusion coefficient is ~25 times lower than in water [57]. This slow diffusion enhances the occurrence of Ca^{2+} microdomains. Microdomain formation is much favoured at membrane contact sites, mostly between the membranes of the ER and the plasma membrane, and between those of the ER and the mitochondria [20,65].

In contrast, IP_3 was long considered as a long-range messenger until recently, because its diffusion coefficient had been estimated to ~280 $\mu m^2/s$ in cytosolic extracts [64]. When photoreleasing caged IP_3 in SH-SY5Y cells, Dickinson et al. (2016) found that the delay of appearance of Ca^{2+} puffs at various distances from the flash location did not match the delay estimated on the base of a 280 $\mu m^2/s$ diffusion coefficient [66]. From this indirect measurement, the IP_3 diffusion was estimated to ~10 $\mu m^2/s$. One of the factors that could partially explain this difference is that the amount of photoreleased IP_3 could have been too low to activate all puff sites [67]. The authors also speculated that not all IP_3R are able to release Ca^{2+} and that the inactive ones slow down IP_3 diffusion by binding it, thus acting as buffers. Another important

consideration to explain their observation is the fact that IP_3R require binding of IP_3 to their four subunits to release Ca^{2+} [2]. Thus, not fully occupied IP_3R would also bind IP_3 and slow down its diffusion. Indeed, because the concentration of IP_3 binding sites is similar to the affinity of IP_3R for IP_3 (both close to 100 nM), a significant proportion of IP_3 molecules could be bound to IP_3R without leading to IP_3R activity [68]. The precise implications of this IP_3 buffering process at higher IP_3 concentrations leading to oscillations still remain to be investigated.

7. Cellular decoding of Ca^{2+} signalling

The current idea is that the precise time and space control of Ca^{2+} signalling allows the selective activation of the diversity of cellular processes controlled by Ca^{2+}, thus allowing this simple ion to regulate a wide spectrum of cellular processes. Samanta and Parekh (2017) have recently reviewed how the spatial profiling of the Ca^{2+} oscillations impacts the signalling power of Ca^{2+} [69], which will thus not be discussed here. Concerning the importance of the temporal characteristics of Ca^{2+} oscillations on the nature and extent of the target cellular responses, it was early proposed that cells are able to decode the frequency of Ca^{2+} oscillations [70,71]. This assumption first relied on the observation that the level of external stimulation is most often *encoded* in the frequency of Ca^{2+} oscillations. As the extent of the cellular response mediated by Ca^{2+} also increases with the level of stimulation, it was thought that cells are able to *decode* the frequency of the oscillations in the concentration of this second messenger. This is an attractive concept, given the well-known robustness of frequency-controlled responses, which are much less sensitive to noise than amplitude-controlled ones.

However, it has to be admitted that some 30 years after the discovery of Ca^{2+} oscillations, the number of identified molecular decoders of Ca^{2+} oscillations remains rather limited: NFAT, NF-kB, CaMKII, PKC, MAPK, calpain (all reviewed in [72] or/and in [73]) and calcineurin [74]. There are moreover few clear examples of physiological responses to Ca^{2+} increases that are quantitatively controlled by the frequency of the Ca^{2+} oscillations. The fact that most Ca^{2+}-mediated cellular responses increase with the frequency of Ca^{2+} oscillations does not mean that these responses are frequency-encoded. Indeed, a higher frequency of Ca^{2+} oscillations always induces a larger average Ca^{2+} concentration, which may simply be the reason for a bigger response. However, changing the amplitude, the baseline or the duration of the oscillations may as well modulate the average Ca^{2+} level and hence, the cellular response. To be purely frequency-controlled, decoders must activate and de-activate at specific rates. If the ON rate of the target is much smaller than the rate of Ca^{2+} increase, the target will be insensitive to the Ca^{2+} changes. If the ON and OFF rates are larger than the rates of Ca^{2+} changes, the pattern of activation will directly follow the changes in Ca^{2+}. In this situation, the average level of target activation will be imposed by the average level of Ca^{2+}. A frequency decoder must have a fast ON rate and a slow OFF rate. In this situation, activity is building up at each Ca^{2+} spike and the decrease in activity is imposed by the time interval between the spikes. Thus, the higher the frequency, the smaller the decrease in activity between the spikes. For example, CaMKII is sensitive to the frequency of Ca^{2+} spikes if the time interval between two successive spikes lies in the [0.1 s, 2 s] interval, because the typical time for Ca^{2+}/CaM unbinding from a kinase subunit is of the order of 1 s [75,76]. In neurophysiology, such decoder is often referred to as “spike integrator” [77]. Of note, the decoder may not be one unique molecule but involve more enzymes, as, for example, a fast Ca^{2+}-sensitive kinase and a slower Ca^{2+}-insensitive phosphatase [78]. Mitochondrial dehydrogenases convert mitochondrial Ca^{2+} oscillations into an integrated metabolic output that depends on the whole Krebs cycle [36]. $[Ca^{2+}]_{ER}$-controlled Ca^{2+} entry through SOCE (see Section 3) also acts as a frequency decoder, as the formation and dissociation of the STIM-Orai complexes depend on the time interval between two successive cytosolic Ca^{2+} spikes [79].

Besides frequency, the shape of the spikes –i.e. their detailed time course– may play an important role. For example, spikes preceded by an important pacemaker-like Ca^{2+} increase could activate slow, low-threshold stimulated Ca^{2+} responses. In such a case, changing the frequency of the spikes would certainly *change* the response, but by no means *control* the response. Astrocytes provide an example where subtle changes in the shape of the spikes have an important effect on the cellular response. In this cell type indeed, knocking-down the Na^+/Ca^{2+} exchanger in mitochondrial membranes (NCLX) slightly affects cytosolic Ca^{2+} changes and, by doing so, significantly reduces glutamate release, wound closure and proliferation [80]. In many cell types, cell survival is sensitive to changes in the temporal patterns of cytosolic Ca^{2+} due to the interplay between the ER, cytoplasm, mitochondria and lysosomes [81]. As a last example, *Shigella* bacteria also finely tune the Ca^{2+} responses upon invasion of epithelial cells. While the wild-type strain induces smooth, low-amplitude Ca^{2+} changes in the host cell, a different strain induces more robust Ca^{2+} responses that are associated with lower survival rates of the host cells during the first hours of infection [82].

Actually, frequency encoding itself –i.e. the increase in frequency with the extent of stimulation– is not a universal feature of Ca^{2+} oscillations. It was shown in Ach-stimulated pancreatic acinar cells [83], methacholine-stimulated lacrimal cells [84], cell lines expressing the metabotropic glutamate receptor 5 [85] or fish hepatocytes [86] that an increase in stimulation does not modify the frequency of the resulting Ca^{2+} oscillations. The possible advantages of amplitude vs frequency coding have been recently investigated in fish hepatocytes [87]. Although transmission of information is easier in frequency-coded systems, amplitude coding is much more robust with respect to changing temperatures. By altering the rate constants, temperature indeed controls the frequency of Ca^{2+} oscillations while amplitude is mostly controlled by binding constants. Amplitude coding thus offers a sophisticated temperature compensation mechanism, most appropriate to fishes that undergo large variations in body temperature.

In the framework of a Ca^{2+} signal that would more resemble random spikes than oscillations (see Section 5 here above), the notion of frequency encoding is also quite puzzling. How could random sequences of spikes be responsible for the transfer of information? A combination of experimental observations and theoretical analyses suggests that cells are sensitive to changes in interspike intervals resulting from a change in the level of stimulation, rather than to the absolute frequency of the spikes [61]. A given change in stimulation level will always lead to the same relative change in average interspike interval, whatever the initial average interspike interval. As put forward by the authors of this study, cell information processing would be able to discard absolute values, in the same manner as our brain can recognise a melody as a sequence of relative changes of pitch, independently of the instrument that is playing it.

8. Concluding remarks

With the increasing number of observations on Ca^{2+} oscillations, the stereotypic character of these oscillations is becoming less evident. In contrast, it appears that depending on the cell type, the agonist, the metabolic state of the cells, etc., Ca^{2+} oscillations are differently regulated and have distinct time courses and properties. Although our main paradigm for the occurrence of oscillations is still based on the sequential activation/inhibition of the IP_3R, the understanding of their detailed properties requires the consideration of the interplay between this core oscillatory mechanism and the numerous modulating factors, such as the dynamics of IP_3 or the involvement of other Ca^{2+} pools. Similarly, this fine tuning of the oscillations, both at the temporal and the spatial levels, may have important consequences on the cellular responses of the cell to this highly sophisticated Ca^{2+} signals. Observations indeed indicate that Ca^{2+}-mediated responses are not always frequency-sensitive but are sometimes regulated by other factors

such as their basal level, amplitude, shape, or statistical properties.

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