Journal of Theoretical Biology 349 (2014) 92–99

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/yjtbi

Linear noise approximation for stochastic oscillations of intracellular calcium

Laura Cantini [a], Claudia Cianci [b], Duccio Fanelli [c,*], Emma Massi [a], Luigi Barletti [a]

[a] Dipartimento di Matematica e Informatica "U. Dini", University of Florence, Viale Morgagni 67/A, 50139 Florence, Italy
[b] Dipartimento di Sistemi e Informatica and INFN, University of Florence, Via S. Marta 3, 50139 Florence, Italy
[c] Dipartimento di Fisica e Astronomia, University of Florence and INFN, Via Sansone 1, 50019 Sesto Fiorentino, Florence, Italy

HIGHLIGHTS

- A stochastic model of intracellular calcium oscillations is analytically studied.
- By using the linear noise approximation, a closed prediction for the power spectrum of fluctuations is derived.
- Stochastic, noise induced oscillations which extend outside the region of deterministic limit cycle are predicted to occur.
- Comparison with stochastic simulations confirms the adequacy of the theory.

ARTICLE INFO

Article history:
Received 11 July 2013
Received in revised form
7 January 2014
Accepted 24 January 2014
Available online 3 February 2014

Keywords:
Calcium oscillations
Goldbeter model
Stochastic processes
Intrinsic noise

ABSTRACT

A stochastic model of intracellular calcium oscillations is analytically studied. The governing master equation is expanded under the linear noise approximation and a closed prediction for the power spectrum of fluctuations analytically derived. A peak in the obtained power spectrum profile signals the presence of stochastic, noise induced oscillations which extend also outside the region where a deterministic limit cycle is predicted to occur.

1. Introduction

Calcium Ca^{2+} oscillations prove fundamental in many different life processes, including, among the others, muscle contraction, neural activity and fertilization (Lodish, 2002). At rest conditions, the calcium in the cell cytoplasm is kept at a low concentration, while it is present at a much higher concentration outside the cell, or inside small intracellular compartments as the endoplasmic reticulum, the sarcoplasmic reticulum and the mitochondria. Large gradients can indeed induce a sudden increase in the concentration of calcium dispersed inside the cellular *milieau*, by either releasing it from the internal stores or importing it from the outside environment, through specific channels.

In non-excitable cells, binding of an agonist, hormone or neurotransmitter to cell-surface receptors initiates a cascade of reactions which promotes the production of the second messenger inositol trisphosphate (IP3). This latter diffuses through the cytoplasm and eventually binds to the IP3 receptors, positioned on the membrane of the endoplasmatic reticulum. The IP3 receptors act also as channels: upon binding of the IP3, the channels open and let the Ca^{2+} flow from the endoplasmatic reticulum into the cell cytoplasm. Importantly, the release of calcium as mediated by the IP3 receptors can occasionally stimulate an additional release of Ca^{2+} from the endoplasmic reticulum. This is an autocatalytic process, usually termed calcium-induced calcium release (CICR) (Tsien and Tsien, 1990).

Different models have been developed in the past to describe the self-consistent generation of calcium oscillations. According to the pioneering model (Meyer and Stryer, 1988) sustained oscillations of cytosolic Ca^{2+} develop as mediated by the rise in IP3, triggered by external stimulation. This rise elicits the release of Ca^{2+} from an IP3-sensitive intracellular store, a process which in turn activates a further release of calcium from a second, independent compartment insensitive to IP3. Building on this formulation Goldbeter and collaborators (Goldbeter, 1996; Dupont and Goldbeter, 1989) have then elaborated a simplified scheme, particularly interesting for pedagogical reasons, where two distinct

* Corresponding author.

http://dx.doi.org/10.1016/j.jtbi.2014.01.035
0022-5193

species, the cytosolic calcium and the calcium stored inside a IP3 sensitive compartments, are solely assumed to mutually interact. Working in this simplified setting, it was observed (Goldbeter et al., 1990) that repetitive calcium spikes, evoked by external stimuli, are not necessarily linked to concomitant IP3 oscillations. The models mentioned above are deterministic in nature and, as such, assume the system to be ideally described in terms of continuum concentration amounts.

As opposed to this vision, one can favour an individual based description, which effectively accounts for the intrinsic discreteness of the scrutinized system. Stochastic effects are therefore present and stem from the finite size of the population of elementary constituents. Such stochastic contributions, endogenous to the system, can amplify via a resonant mechanism and so yield macroscopic oscillations in the discrete concentration in a region of the parameters for which a stable fixed point is predicted, as follows the deterministic linear stability analysis (McKane and Newman, 2005; Dauxois et al., 2009). Similar conclusions apply to spatially extended systems (Lugo and McKane, 2008; de Anna et al., 2010; Butler and Goldenfeld, 2011; Biancalani et al., 2010).

Indeed stochastic effects in intracellular calcium signalling have been thoroughly studied in the recent past. In Marchant and Parker (2001) the hierarchy of spatiotemporal patterns was experimentally characterized for Xenopus oocytes and a variability in the wave period demonstrated, which ultimately stems from the probabilistic nature of the stochastic events which initiate the process. A model that accounts for the stochastic binding and dissociation of Ca^{2+} to binding sites on a single subunit of the IP3 receptor channel was then proposed (Falcke, 2003a). The collective oscillations, as triggered by local stochastic events, were found in good agreement with the experimental observation. A campaign of comprehensive measurements of interspike interval series in different cell types, complemented by dedicated statistical analysis, further reinforced the idea that global oscillations result from a sequence of randomly occurring spikes (Skupin, 2008; Skupin and Falcke, 2010). Deterministic and stochastic approaches to the problem of intracellular calcium dynamics are discussed by Falcke (2003b). Particularly interesting is the analysis presented in Thul and Falcke (2006) where the random dynamics of the so-called Ca^{2+} puffs is mapped into an escape process. Different approximations of the governing master equation are discussed to characterize the initiation of the Ca^{2+} puffs.

Li et al. (2005) have proposed a discrete version of the a-spatial Goldbeter model, showing that the inherent demographic noise can possibly drive stochastic oscillations, even when the underlying deterministic system is in a non-oscillatory state. The original analysis carried out in Li et al. (2005) relies on numerical simulations. The effect of the internal noise, as revealed numerically, has been later on explained analytically by the same authors (Hou et al., 2006; Xiao et al., 2007; Ma et al., 2008), by developing a stochastic normal form theory in the vicinity of the Hopf bifurcation.

In this paper we shall work along these lines, by establishing a formal bridge between the internal noise coherent resonance phenomenon, as identified by Li and collaborators, and the concept of *quasi-cycles* discussed in e.g. McKane and Newman (2005). We will in particular perform a complete analytical treatment of the stochastic model (Li et al., 2005), recover Goldbeter's scheme in the mean field limit and characterize the distribution of stochastic fluctuations in terms of a Fokker–Planck equation, derived under the linear noise approximation. In doing so, we will obtain a close prediction for the power spectrum of stochastic fluctuations and characterize the resonant frequency as a function of the parameters of the model. Importantly, a linear Langevin equation is eventually recovered and shown to provide an adequate description of the inspected stochastic dynamics. This is at variance with the approach discussed in Hou et al. (2006), Xiao et al. (2007), and Ma et al. (2008), where a Chemical Langevin equation (Gillespie, 2000) with multiplicative noise is instead analysed.

The paper is organized as follows. In the next section we will introduce the stochastic model, inspired by Li et al. (2005) and constructed so as to converge to the Goldbeter scheme (Goldbeter, 1996; Dupont and Goldbeter, 1989) in the deterministic limit. In Section 2.1 we will then turn to study the governing master equation, under the linear noise approximation and elaborate on the role of stochastic fluctuations. We will in particular obtain a close prediction for the power spectrum of fluctuations that we will benchmark to direct simulations. An approximate expression for the resonant frequency is also derived and proved to be adequate. Finally, in Section 4 we will sum up and draw our conclusions.

2. Stochastic model and the master equation

We will hereafter introduce a stochastic model for intracellular calcium oscillations that we shall study throughout the paper. The model describes the process of calcium-induced calcium release (CICR), a biological process whereby calcium promotes calcium release from intracellular stores. As we shall discuss in the following the model is inspired[1] by the formulation (Li et al., 2005) and set up so as to make contact, in the mean field, with the celebrated model proposed by Goldbeter and collaborators (Dupont and Goldbeter, 1989). We will in particular consider two species that we shall denote Z and Y. Z stands for the calcium ions Ca^{2+} which are populating the cytosol, the liquid found inside cells. Y is meant to label the Ca^{2+} which are stored inside a specific compartment, insensitive to the IP3 and termed $\mathcal{Y}$. We will indicate with s the number of ions of type Z, i.e. dispersed in the cytoplasmic matrix. The integer q quantifies instead the abundance of species Y, the ions sequestered in the compartment.

To progress in the model definition, we assume that the stochastic dynamics, which ultimately governs the evolution of the intracellular calcium, is a homogeneous Markov process. We will moreover label with V the volume of the cell. V defines in turn the characteristic size of the system. As we shall make clear in the following, the continuum deterministic limit is recovered by taking $V \to \infty$.

A Ca^{2+} ion can for instance migrate outside the cell, passing through specific channels which are hosted on the membrane walls. In terms of chemical equation, one can ideally represent this event as

$$Z \xrightarrow{k} 0,$$

where the parameter k stands for the reaction rate associated to the hypothesized transformation. Conversely, calcium ions can reach the cytosol, coming from a second IP3 sensitive compartment, called $\mathcal{X}$. Following the CICR paradigm, this latter process is autocatalytic and can be represented as

$$Z \xrightarrow{\nu_1 \beta V/s} Z+Z.$$

[1] Indeed we assume here exactly the same chemical equations of Li et al. (2005) and recast in an equivalent form the associated transition rates, so as to make the perturbative analysis more transparent. To speculate on the validity of the model and/or propose further extension of it beyond the original setting of Li et al. (2005) is not the purpose of the present paper. Given the model, we are in fact interested in the emerging oscillation as driven by the noise internal to the system and in the possibility of providing a quantitative explanation, alternative to the one presented in Hou et al. (2006), Xiao et al. (2007), and Ma et al. (2008), of such a phenomenon.