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Homogenization results for the calcium dynamics in living cells

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Abstract

Via the periodic unfolding method, the effective behavior of a nonlinear system of coupled reaction–diffusion equations arising in the modeling of the dynamics of calcium ions in living cells is analyzed. We deal, at the microscale, with two reaction–diffusion equations governing the concentration of calcium ions in the endoplasmic reticulum and, respectively, in the cytosol, coupled through an interfacial exchange term. Depending on the magnitude of this term, various models arise at the macroscale. In particular, we obtain, at the limit, a bidomain model. Such a model is widely used for studying the dynamics of the calcium ions, which are recognized to be important intracellular messengers between the endoplasmic reticulum and the cytosol inside the biological cells.

Keywords: Homogenization; Calcium dynamics; The bidomain model; The periodic unfolding method

1. Introduction

Calcium is a very important second messenger in a living cell, participating in many cellular processes, such as protein synthesis, muscle contraction, cell cycle, metabolism or apoptosis (see, for instance, [8]). Intracellular free calcium concentrations must be very well regulated and many buffer proteins, pumps or carriers of calcium take part in this complicated process. The finely structured endoplasmic reticulum, which is surrounded by the cytosol, is an important multifunctional intracellular organelle involved in calcium homeostasis and many of its functions depend on the calcium dynamics. The endoplasmic reticulum plays an important role in the metabolism of human cells. It performs diverse functions, such as protein synthesis, translocation across the membrane and folding. This complex and highly heterogeneous cellular structure spreads throughout the cytoplasm, generating various zones with diverse morphology and functions. The study of the dynamics of calcium ions, acting as messengers between the endoplasmic reticulum and the cytosol inside living cells, represents a topic of huge interest, which still requires special attention. Many biological mechanisms involving the functions of the cytosol and of the endoplasmic reticulum are not yet perfectly understood.

Our goal in this paper is to rigorously analyze, using the periodic unfolding method, the macroscopic behavior of a nonlinear system of coupled reaction–diffusion equations arising in the modeling of calcium dynamics in living cells.

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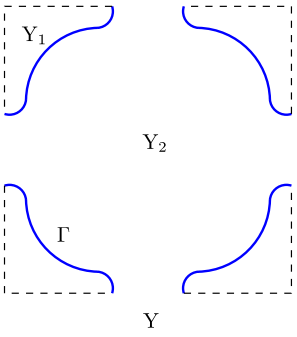

Fig. 1. The reference cell Y.

We consider, at the microscale, two equations governing the concentration of calcium ions in the cytosol and, respectively, in the endoplasmic reticulum, coupled through an interfacial exchange term. Depending on the magnitude of this term, different models arise at the limit. In a particular case, we obtain, at the macroscale, a bidomain model, which is largely used for studying the dynamics of the calcium ions in human cells. The calcium bidomain system consists of two reaction–diffusion equations, one for the concentration of calcium ions in the cytosol and one for the concentration of calcium ions in the endoplasmic reticulum, coupled through a reaction term. For details about the physiological background of such a model, the reader is referred to [17]. Bidomain models arise also in other contexts, such as the modeling of diffusion processes in partially fissured media (see [4,11] and [12]) or the modeling of the electrical activity of the heart (see [3,2] and [19]).

Our models can serve as a tool for biophysicists to analyze the complex mechanisms involved in the calcium dynamics in living cells, justifying in a rigorous manner some biological points of view concerning such processes.

The problem of obtaining the calcium bidomain equations using homogenization techniques was addressed by a formal approach in [13] and by a rigorous one, based on the use of the two-scale convergence method, in [14]. Our results constitute a generalization of some of the results contained in [13] and [14]. The proper scaling of the interfacial exchange term has an important influence on the limit problem and, using some techniques from [10], we extend the analysis from [14] to the case in which the parameter γ arising in the exchange term belongs to $\mathbb{R}$. Also, the tool we use for obtaining the above mentioned macroscopic models, namely the periodic unfolding method, allows us to treat a large class of heterogeneous media.

The layout of this paper is as follows: Section 2 is devoted to the setting of the microscopic problem. In Section 3, we present the main convergence results, which are proven in the last section.

2. Setting of the microscopic problem

Let Ω be a bounded domain in $\mathbb{R}^n (n \geq 3)$, having a Lipschitz boundary $\partial\Omega$ formed by a finite number of connected components. The domain Ω is supposed to be a periodic structure made up of two connected parts, Ω_1^ε and Ω_2^ε, separated by an interface Γ^ε. We assume that only the phase Ω_1^ε reaches the outer fixed boundary $\partial\Omega$. Here, ε is considered to be a small positive real parameter related to the characteristic dimension of our two regions. For modeling the dynamics of the concentration of calcium ions in a biological cell, the phase Ω_1^ε represents the cytosol, while the phase Ω_2^ε is the endoplasmic reticulum. Let Y_1 be an open connected Lipschitz subset of the elementary cell $Y = (0, 1)^n$ and $Y_2 = Y \setminus \overline{Y_1}$ (see Fig. 1). We consider that the boundary Γ of Y_2 is locally Lipschitz and that its intersections with the boundary of Y are reproduced identically on the opposite faces of the elementary cell. Moreover, if we repeat Y in a periodic manner, the union of all the sets $\overline{Y_1}$ is a connected set, with a locally C^2 boundary. Also, we consider that the origin of the coordinate system lies in a ball contained in the above mentioned union (see [12]).

For any $\varepsilon \in (0, 1)$, let

$$Z_\varepsilon = \{k \in \mathbb{Z}^n \mid \varepsilon k + \varepsilon Y \subseteq \Omega\},$$
$$K_\varepsilon = \{k \in Z_\varepsilon \mid \varepsilon k \pm \varepsilon e_i + \varepsilon Y \subseteq \Omega,\ \forall i = 1, \ldots, n\},$$