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Global existence for a bulk/surface model for active-transport-induced polarisation in biological cells

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ABSTRACT

We consider a coupled bulk/surface model for advection and diffusion of interacting chemical species in biological cells. Specifically, we consider a signalling protein that can exist in both a cytosolic and a membrane-bound state, along with a variable that gives a coarse-grained description of the cytoskeleton. The main focus of our work is on the well-posedness of the model, whereby the coupling at the boundary is the main source of analytical difficulty. *A priori* L^p-estimates, together with classical Schauder theory, deliver global existence of classical solutions for small data on bounded, Lipschitz domains. For two physically reasonable regularised versions of the boundary coupling, we are able to prove global existence of solutions for *arbitrary* data. In addition, we prove the existence of a family of steady-state solutions of the main model which are parametrised by the total mass of the membrane-bound signal molecule.

1. Introduction

Cell-polarisation processes are the key to many biological functions, such as cell movement, differentiation and communication [23]. A prominent example is the budding of yeast, with the Rho GTPase protein Cdc42 as the main polarity marker [7]: preceding any mechanical deformation of the cell, one sees the emergence and maintenance of an inhomogeneous distribution of regulatory proteins at the cell membrane and in the inner cytosolic domain [26]. Various mechanisms have been identified that can contribute to this kind of symmetry breaking, whereby a distinction is commonly made between *driven* and *spontaneous* cell polarisation [11]. The former is induced by either extracellular chemical gradients (chemotaxis) or historical markers at the membrane, while the latter is, instead, a consequence of interactions between different

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regulatory proteins and/or other constituents of the cell. Turing-type interactions between short-range activators and long-range inhibitors are one scenario that may lead to spontaneous polarisation [10,28]. A distinct and well-documented mechanism [34,35,19] is a positive feedback between membrane-recruited signalling proteins and the cytoskeleton. The latter is built from actin monomers that polymerise to form long filaments: activated Cdc42 directs actin polymerisation at the membrane, and, in turn, Cdc42 is actively transported along the cytoskeleton filaments towards the membrane, leading to a positive feedback loop [25]. Such active transport relies on a permanent energy input from ATP hydrolysis, and hence constitutes an example of an *out-of-equilibrium* system.

In this paper we will analyse a mathematical model for the kind of actin-mediated spontaneous cell polarisation just described. The basis of our work is a modification of a model introduced by Hawkins et al. [11] that uses a coarse-grained description of the actin-filaments, and that leads to a coupled bulk/surface reaction–diffusion–advection model with a nonlinearity in the bulk of chemotaxis type. Our mathematical analysis will demonstrate the well-posedness of the associated initial-value problem under a smallness-condition on the initial data.

In order to introduce the model, consider a domain $B \subset \mathbb{R}^3$ with boundary $\Gamma = \partial B$, modelling the cell and, respectively, its outer cell-membrane. Consider further three chemical species (resp. their concentrations): the cytosolic concentration V of the biochemical messenger, the concentration u of the membrane-bound messenger, and the concentration, c, of actin filaments in the cell. While V and c live in the cell interior, B, the function u has its domain of definition on the cell membrane, Γ. We assume that V can diffuse in the cell interior, and that V and u are exchanged at the membrane. Moreover, u can diffuse throughout the membrane (i.e., tangentially), and acts as a boundary source for the (very) diffusible species c, generating an advective velocity field, ∇c, in B which tends to transport V towards the boundary. These model assumptions can be summarised as the following coupled system: consider a given time interval $(0,T)$, and look for positive functions $V, c : B \times (0,T) \to \mathbb{R}$, $u : \Gamma \times (0,T) \to \mathbb{R}$, such that

$$\partial_t V = D\Delta V - \nabla \cdot (V \nabla c), \tag{1}$$

$$0 = \Delta c - \alpha c \tag{2}$$

in $B \times (0,T)$, subject to the flux conditions

$$-\nu \cdot (D\nabla V - V\nabla c) = q(V,u), \tag{3}$$

$$\nu \cdot \nabla c = z(u) \tag{4}$$

on $\Gamma \times (0,T)$, such that u satisfies

$$\partial_t u = d\Delta_\Gamma u + q(V,u) \tag{5}$$

on $\Gamma \times (0,T)$, and such that the initial conditions

$$V(\cdot,0) = V_0, \quad u(\cdot,0) = u_0 \tag{6}$$

are satisfied, where $V_0 : B \to \mathbb{R}$ and $u_0 : \Gamma \to \mathbb{R}$ are given data. In (1)–(5) we denote by Δ_Γ the Laplace–Beltrami operator on the manifold $\Gamma = \partial B$, and we are assuming $\alpha > 0, d > 0$ and $D > 0$.

To close the system, we prescribe a constitutive law for the bulk–surface exchange term q, and for the boundary source z; in the present paper we will mainly consider simple linear laws,

$$q(V,u) := k_1 V - k_2 u, \quad k_1, k_2 > 0, \tag{7}$$

$$z(u) := \beta u, \quad \beta > 0, \tag{8}$$