Journal of Computational and Applied Mathematics 289 (2015) 142–152

Contents lists available at ScienceDirect

Journal of Computational and Applied Mathematics

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

Turing-type instabilities in bulk–surface reaction–diffusion systems

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ARTICLE INFO

Article history:
Received 13 September 2014
Received in revised form 7 January 2015

MSC:
92C37
35K57
35Q92

Keywords:
Reaction–diffusion systems
PDE's on surfaces
Turing instability
Numerical simulations of reaction–diffusion systems

ABSTRACT

In this contribution we consider a coupled bulk–surface reaction–diffusion system and for infinitely fast bulk diffusion its formal reduction to a non-local surface PDE model. Thereby, we review results of linear stability analyses for both models showing that Turing-type instabilities can occur for equal lateral diffusion coefficients. The stability results are confirmed by new numerical results. As a specific application, we study a model for a spatial and reaction cycle of signalling molecules in a cell.

1. Introduction

Although the analytic results and numerical methods may apply to a broader class of applications, we describe the considered reaction–diffusion system by means of the specific application we have in mind as a standard example, the so-called GTPase cycle.

GTPase (GTP binding proteins) are signalling molecules appearing on the cell membrane in active and inactive state and play an important role for many cell processes such as cellular transport, cytoskeleton organization, and they also influence cell shape and movement [1,2]. In particular, localization of active GTPase precedes the budding of yeast [3].

On the membrane GTPase proteins cycle between an active and an inactive state. This cycle corresponds to enzyme reactions of inactive proteins into active proteins and vice versa. In addition to this reaction cycle on the membrane, there is a spatial cycle of inactive GTPase proteins between cytosolic (inside the membrane) state and membrane bound state, which leads to attachment/detachment processes at the cell membrane. In this scenario we are interested in the question whether a Turing-type mechanism (based on reaction and diffusion) can be responsible for localization of active proteins at the membrane.

The mathematical modelling of these processes leads us to a system of reaction–diffusion equations for the concentrations of membrane bound active and inactive GTPase molecules and of cytosolic inactive GTPase molecules [4]. This reaction–diffusion system is a bulk–surface system of PDE's due to the different dimensionalities of the involved quantities and it is related to a model in [5] with more chemical species under consideration and scaling factors accounting for the different dimensions of membrane and cytosolic cell volume.

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http://dx.doi.org/10.1016/j.cam.2015.02.050
0377-0427/

It is reported that active GTPase molecules (in complex with further proteins) serve as a further even more efficient catalyst for the activation reaction [6]. This positive feedback has to be included into the model for the reaction kinetics, in order to be able to observe a Turing-like instability in the reaction–diffusion system.

In addition to the above bulk–surface reaction–diffusion system we obtain in the formal limit of infinitely fast volume (cytosolic) diffusion a reduced non-local surface reaction–diffusion system, which is also topic of our investigations in this contribution.

In the subsequent modelling Section 2, we briefly introduce the mathematical models for the GTPase cycle proposed in [4]. In Section 3, we review the results of the analysis of the linear stability of spatially homogeneous stationary states for the above mentioned reduced non-local model [4,7] (see also [8]), and we find two scenarios for an instability [7]. While the first requires different diffusion constants for the two membrane bound species – which is common to classical Turing instabilities, but not a reasonable assumption in this application – the second is also possible for equal lateral diffusion coefficients due to the non-local nature of the model. In particular we find that the second scenario is different from a standard Turing-type instability as in this case the concentration of activated GTPase in a single spot (most typical in most examples of cell polarization) is always preferred independent of variations in the parameter values. For precise instability criteria for a specific choice of f and q we refer to [4]. Recently, another non-local reaction–diffusion model for the GTPase cycle has been introduced and analysed in [9].

The results of the linear stability analysis are confirmed by numerical investigations. As a first example we demonstrate the instability of the ODE system corresponding to the non-local model with respect to spatially heterogeneous perturbations, which is a particular property of the model. In the second example we apply the parametric finite element discretization of the non-local surface reaction–diffusion system introduced in [4] to numerically investigate an instability on a complicated surface, for which we take as an example a perturbed sphere.

The results from the linear stability analysis of the full coupled bulk–surface reaction–diffusion system presented in Section 4 are for sufficiently large cytosolic diffusion constant similar to the reduced non-local case. For the numerical treatment of this model, we use a diffuse-interface method as in [7]. As a numerical example, we consider two concentric spheres with the bulk phase in between. The results show that the concentration of active proteins becomes constant and maximal in the inner sphere, while afterwards additionally a pattern with one maximal spot of the concentration of active GTPase proteins on the outer sphere appears.

The above bulk–surface model has been extended to time dependent membranes and coupled to fluid flow outside and inside the membrane in [10]. The work [11] of Levine and Rappel is also closely related. There the authors study the linear stability of a two variable bulk–surface system consisting of a diffusion system in the cell and a reaction system on the membrane, which is numerically validated by a phase-field approach. Numerical approaches for coupled bulk–surface systems include finite element [12] and finite volume [13] techniques as well as diffuse-interface methods [11,14]. For the numerical treatment of reaction–diffusion systems on evolving surfaces we refer to [15,16] in the case of surface finite element methods and to [17] for a level set approach. Moreover, we would like to point a recent contribution on a level set method for reaction–advection–diffusion systems on time dependent surfaces [18].

2. Model description

In this work, we study a system of coupled bulk–surface reaction–diffusion equations introduced in [4] in order to mathematically describe a reaction cycle and a spatial cycle of signalling (GTPase) proteins. The mathematical model proposed in [4] encodes an improved coupling of processes with different dimensionalities. We consider the cytosolic volume $\Omega_1 \subset \mathbb{R}^3$ of the cell and assume that the domain Ω_1 is a bounded, connected, open set. The cell membrane is mathematically described by a smooth, closed surface $\Gamma := \partial\Omega_1$. Moreover, we denote by ν the outer unit normal of Ω_1 on Γ. Further, we consider smooth concentrations $V : \overline{\Omega}_1 \times I \to \mathbb{R}$, $u, v : \Gamma \times I \to \mathbb{R}$ of cytosolic inactive, membrane-bound active, and membrane-bound inactive GTPase, respectively, and we assume that u, v and V satisfy the non-dimensional coupled reaction–diffusion system

$$\partial_t V = D\Delta V \quad \text{in } \Omega_1 \times I, \tag{1}$$

$$\partial_t u = \Delta_\Gamma u + \gamma f(u, v) \quad \text{on } \Gamma \times I, \tag{2}$$

$$\partial_t v = d\Delta_\Gamma v + \gamma(-f(u, v) + q(u, v, V)) \quad \text{on } \Gamma \times I, \tag{3}$$

$$-D\nabla V \cdot \nu = \gamma q(u, v, V) \quad \text{on } \Gamma \times I, \tag{4}$$

where f describes the activation/inactivation reaction kinetics, and attachment/detachment kinetics at the membrane are specified by q. We present as a specific example the mathematical model for the GTPase cycle from [4] with explicit choices

$$q(u, v, V) = a_6 V(1 - (u + v))_+ - a_{-6} v, \tag{5}$$

$$f(u, v) = \left(a_1 + (a_3 - a_1)\frac{u}{a_2 + u}\right) v - a_4 \frac{u}{a_5 + u} \tag{6}$$

for f and q, where $a_1, \ldots, a_6, a_{-6}$ denote dimensionless kinetic coefficients.