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Transitions and heteroclinic cycles in the general Gierer–Meinhardt equation and cardiovascular calcification model

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ABSTRACT

The article is concerned with transitions and pattern selection analysis of the inhibitor–activator system proposed in connection with recent studies of cardiovascular calcification patterns. Explicit criteria are derived to enable us to distinguish between stable and metastable patterns. By deriving a reduced system of equations, the existence of certain complicated structures is discussed; in particular, heteroclinic cycles are identified and their properties are studied. It is also discussed that the change of boundary conditions can affect the transitions of the system. In this connection, we will also study asymptotic behavior of patterns after transitions and will compare the results with numerical simulations.

1. Introduction

The formation of calcified patterns in blood vessels seems to be a reoccurrence of an earlier embryonic process of bone formation caused by vascular mesenchymal cells (VMCs) [1,2]. It is observed experimentally that a uniform monolayer of VMSC culture is capable of self-organizing and displaying spontaneous patterns [3]. This process of pattern formation is thought to be the result of the simultaneous interaction of two chemical substances, morphogens, namely, bone morphogenetic protein 2 acting as an activator and matrix GLA protein acting as an inhibitor. Motivated by this idea, a variant of the Gierer–Meinhardt (GM) model [4] has been suggested to describe the essential features of the calcification mechanism [5]. The model reads

$$\begin{aligned} \frac{\partial a}{\partial t} &= D_a \Delta a + \rho_a \frac{a^2 h^{-1}}{1 + q^2 a^2} - \mu_a a + A, \\ \frac{\partial h}{\partial t} &= D_h \Delta h + \rho_h a^2 - \mu_h h + H, \end{aligned} \tag{1.1}$$

where a and h represent concentrations of the two morphogens. D_a and D_h are diffusion rates, ρ_a and ρ_h are cross-reaction coefficients, μ_a and μ_h are degradation rates, q is the saturation constant, and A and H are source terms, respectively.

Different forms of the Gierer–Meinhardt model [4,6] have been studied analytically and numerically; see among others [7–10]. The present study is motivated by recent studies on system (1.1) and its applications [11,12]. However, we focus on a rather general form of system (1.1); later, the results are applied to system (1.1) and are compared with numerical simulations.

A key factor in understanding the pattern selection process is the distinction between transient, long-term stable, and metastable states. By a transient state, it is meant a pattern arising spontaneously and directly from a previously stable homogeneous condition (a pre-pattern). Such states has been studied on confined domains (see [13,14], and Murray's

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monograph [15] and references therein). The existence of invariant regions for reaction–diffusion systems [16] often justifies the finite amplitude property of such states. But it is not generally known if such transient patterns will persist in the long term. Moreover, the patterns that are typically observed are at large deviations from the critical conditions, and also on timescales far from the initial instability. We will show that the behavior of such states can be tracked in the long run by the calculation of certain transition numbers; we will take advantage of the phase transition scheme proposed in [17] to classify them.

Coherent states form another fundamental aspect of the behavior of excitable media. The present approach aims to study such phenomena in reaction–diffusion (RD) systems. By a numerical approach [11], it is shown that phenomena, such as *pining*, can exist in RD systems; but a unifying rigorous theory seems to be still missing in this connection [18]. In fact, to study any state beyond the so-called Turing instabilities, one needs to employ strictly nonlinear approaches. The center manifold reduction method suits the needs of this work [19,15]. Other approaches based on unbounded domain methods can act in a restricted manner when dealing with similar problems on confined domains, often due to symmetry considerations, while, for the center manifold approaches, symmetries have a simplifying effect only [20,21]. By using a new approach to the center manifold reduction method, the existence and properties of heteroclinic cycles for the generalized one-dimensional (1D) Gierer–Meinhardt equation are established in this work; heteroclinic cycles for 2D RD systems have been studied in [22]. The methods and proofs presented here can be well extended to similar cases in other RD systems. It is hoped that certain connections, such as the role of boundary conditions in transitions, can also be potentially interesting from an experimental point of view.

The paper is organized as follows. In Section 2, we establish the general analysis framework for the one-dimensional model. Next, in Section 3, the bifurcation and stability of simple patterns are discussed. In Section 4, we calculate the reduced equations to prepare the ground for studying the phase transitions and asymptotic behavior of more complicated patterns; in this section, we discuss the existence of heteroclinc cycles and study their properties. In Section 5, system (1.1) is elaborated; we also compare some numerical simulations with our analytical results in this section.

2. Functional setting of the problem

We consider a quite general form of the system of equations (1.1) in its dimensionless form,

$$\begin{aligned} \frac{\mathrm{d}U}{\mathrm{d}t} &= D\Delta U + f(U,V),\\ \frac{\mathrm{d}V}{\mathrm{d}t} &= \Delta V + PU^2 - EV + S, \end{aligned} \tag{2.1}$$

on $\Omega = (\ell_0, \ell_1)$ with D, P, E being positive constants; D is the diffusion ratio, P represents the generalized cross-reaction rates ratio, E is the degradation ratio, and S is the generalized inhibitor source term. We will assume that the system is subject to periodic or Neumann boundary conditions and a typical initial condition. In the rest of this work, we let $P = 1$ and $g(U,V) = U^2 - EV + S$. Assume that (u_*, v_*) is a positive uniform steady-state solution of (2.1). The system (2.1) can be recast in the form

$$\begin{aligned} u_t &= f_u u + f_v v + f_{nl}(u,v) + D\Delta u,\\ v_t &= g_u u + g_v v + g_{nl}(u,v) + \Delta v, \end{aligned} \tag{2.2}$$

where

$$u = U - u_*, \qquad v = V - v_*,$$

with $f_u = f_u(u_*, v_*)$, etc., and f_{nl} and g_{nl} are purely nonlinear terms of Taylor expansions of f and g respectively.

The system of equations (2.2) can be conveniently expressed in a functional setting and as a single vector from equation

$$w_t = \mathcal{L}_\lambda(w) + \mathcal{H}_\lambda(w) \tag{2.3}$$

for a vector

$$w(x,\cdot) = \begin{pmatrix} u(x,\cdot)\\ v(x,\cdot)\end{pmatrix}, \tag{2.4}$$

where $\mathcal{L}_\lambda$ and $\mathcal{H}_\lambda$ represent the linear and nonlinear operators, respectively, and λ is the control parameter of the system, $\lambda = (S, E, D)$. The operators are defined as $\mathcal{L}_\lambda$ and $\mathcal{H}_\lambda : H_1 \longrightarrow H$ with $H = (\dot{L}^2(\Omega))^2$, where the dot $\dot{}$ represents the zero-average condition,

$$\dot{L}^2(\Omega) = \left\{ u \in L^2(\Omega) \mid \int_\Omega u = 0 \right\}, \tag{2.5}$$

and

$$H_1 = \{ w \in (\dot{H}^2(\Omega))^2 : n \cdot \nabla w = 0 \text{ on } \partial\Omega \}, \tag{2.6}$$