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Instability and blowup phenomena induced by diffusion in some reaction-diffusion-OED systems

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1 Introduction

Diffusion-driven instability (DDI) is a phenomenon in mathematical biology, which has been often used to explain *de novo* pattern formation. The ideas on DDI have inspired development of a vast number of mathematical models since the seminal paper of Turing [14], providing some explanations on symmetry breaking and *de novo* pattern formation during development, explaining shape of animal coat markings, and predicting oscillating chemical reactions.

In particular, the following reaction-diffusion system

$$u_t = \varepsilon^2 \Delta u + f(u, v), \qquad v_t = D\Delta v + g(u, v),$$

has been proposed as a mathematical model describing DDI. Here, the unknown functions $u = u(x, t)$ and $v = v(x, t)$ are sometimes called an *activator* and an *inhibitor*, respectively, and it is assumed that $0 < \varepsilon \ll D$. DDI is a bifurcation that arises in a reaction-diffusion system, when there exists a spatially homogeneous solution, which is asymptotically stable with respect to spatially homogeneous perturbations, but unstable to spatially heterogeneous perturbations. Models with DDI describe then a process of a destabilization of stationary spatially homogeneous steady states and evolution of spatially heterogeneous structures towards spatially heterogeneous steady states.

There are some mathematical models of a pattern formation arising in processes described by a system of a single reaction-diffusion equation coupled with an ordinary differential equation (reaction-diffusion-ODE system). Such models arise when studying coupling of the diffusive processes with processes which are localized in space, such as, for example, growth processes [9, 10, 11, 13] or intracellular signaling [2, 3, 4, 15]. In the latter case, macroscopic reaction-diffusion-ODE models have been derived as a homogenization limit of the models describing coupling of cell-localized processes with cell-to-cell communication through diffusion in a cell assembly [12, 5]. The dynamics of such models appear to be very different from that of classical reaction-diffusion models. The systems coupling a single reaction-diffusion equation with ODEs may exhibit DDI. However, in this case all Turing patterns are unstable, *i.e.* the same mechanism which destabilizes constant solutions, destabilizes also all continuous spatially heterogenous stationary solutions [7, 8]. Simulations of different models of this form indicate formation of dynamical, multimodal and apparently irregular structures, the shape of which depends strongly on initial conditions [1, 10, 11, 13]. Therefore, the existence and stability of spatially heterogeneous patterns arising in models exhibiting diffusion-driven instability, but consisting of only one reaction-diffusion equation is an interesting issue.

Our aim of this work is to give a systematic study on the dynamics of general reaction-diffusion-ODE systems with a single diffusion operator. We would like to understand what is DDI in the system, how DDI influences the dynamics of the system, and so on. In this paper, first we shall discuss the instability of inhomogeneous stationary solutions. It will be shown that a certain natural (autocatalysis) property of a system leads to instability of all inhomogeneous stationary solutions. Next, we shall discuss a possible large time behavior of solutions. To understand mechanisms of pattern formation in reaction-diffusion equations, it is worth studying the limiting versions of the model dynamics, for example by letting small or large diffusion coefficient tend to zero or infinity, respectively, so that the reduced model is an approximation of the original dynamics and, in particular, the phenomenon of pattern formation is preserved. Thus, as a first step, we focus on a nonlocal problem related to a reaction-diffusion-ODE model, and we will see that space inhomogeneous solutions of the problem become unbounded in either finite or infinite time, even if space homogeneous solutions are bounded uniformly in time.

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2 Instability of stationary solutions

We focus on the following two-equation system:

$$u_t = f(u,v), \qquad \text{for} \quad x \in \overline{\Omega}, \quad t > 0, \tag{2.1}$$

$$v_t = D\Delta v + g(u,v) \qquad \text{for} \quad x \in \Omega, \quad t > 0 \tag{2.2}$$

in a bounded domain $\Omega \subset \mathbb{R}^N$ for $N \geq 1$, with a sufficiently regular boundary $\partial\Omega$, supplemented with the Neumann boundary condition for v:

$$\partial_\nu v = 0 \qquad \text{for} \quad x \in \partial\Omega, \quad t > 0, \tag{2.3}$$

where $\partial_\nu = \partial/\partial\nu$ and ν denotes the unit outer normal vector to $\partial\Omega$, and initial data

$$u(x,0) = u_0(x), \qquad v(x,0) = v_0(x). \tag{2.4}$$

A constant $D > 0$ is the diffusion coefficient, and the nonlinearities $f = f(u,v)$ and $g = g(u,v)$ are arbitrary C^2-functions that satisfy certain natural (biologically motivated) assumptions.

By a standard theory, the boundary value problem (2.1)-(2.4) has a unique local-in-time solution *e.g.* for every $u_0, v_0 \in L^\infty(\Omega)$.

2.1 Constant steady states

Theorem 2.1. *Assume that the constant vector $(\bar{u},\bar{v})$ is a (stationary) solution of the initial-boundary value problem for the reaction-diffusion-ODE system* (2.1)-(2.4). *If*

$$f_u(\bar{u},\bar{v}) > 0,$$

then $(\bar{u},\bar{v})$ is an unstable solution of this problem.

If $(\bar{u},\bar{v})$ is stable solution of the corresponding ordinary differential equation, then Theorem 2.1 provides a simple criterion for the diffusion-driven instability.

2.2 Non-constant stationary solutions

We consider *regular stationary solutions* (U, V) of problem (2.1)-(2.3), namely, we assume that there exists a solution (not necessarily unique) of the equation $f\big(U(x), V(x)\big) = 0$ that is given by the relation $U(x) = k(V(x))$ for all $x \in \Omega$ with a C^1-function $k = k(V)$. Thus, every regular stationary solution (U, V) of the boundary value problem

$$f(U,V) = 0 \qquad \text{for} \quad x \in \overline{\Omega}, \tag{2.5}$$

$$D\Delta V + g(U,V) = 0 \qquad \text{for} \quad x \in \Omega, \tag{2.6}$$

$$\partial_\nu V = 0 \qquad \text{for} \quad x \in \partial\Omega \tag{2.7}$$

satisfies the elliptic problem

$$D\Delta V + h(V) = 0 \qquad \text{for} \quad x \in \Omega, \tag{2.8}$$

$$\partial_\nu V = 0 \qquad \text{for} \quad x \in \partial\Omega, \tag{2.9}$$

where

$$h(V) = g\big(k(V), V\big) \qquad \text{and} \qquad U(x) = k(V(x)). \tag{2.10}$$

Each constant solution $(\bar{u}, \bar{v}) \in \mathbb{R}^2$ of problem (2.1)-(2.4) is a particular case of regular solutions.

The following theorem shows that regular stationary solutions appear to be unstable solutions to problem (2.1)-(2.4) under a simple assumption imposed on the first equation.

Theorem 2.2 (Instability of regular solutions). *Let (U, V) be a regular solution of problem* (3.5)-(2.7) *satisfying the following "autocatalysis condition":*

$$f_u\big(U(x), V(x)\big) > 0 \quad \textit{for all } x \in \overline{\Omega}. \tag{2.11}$$

Then, (U, V) is an unstable solution the initial-boundary value problem (2.1)-(2.4).

Inequality (2.11) can be interpreted as an autocatalysis in the dynamics of u at the steady state (U, V). In a system of reaction-diffusion equations with a constant solution having the DDI property, one expects stable patterns to appear around that constant steady state. For the initial-boundary value problem for reaction-diffusion-ODE system with a single diffusion equation (2.1)-(2.4), stationary solutions can be constructed in the case of several interesting models. However, the DDI mechanism which destabilizes constant solutions of such models, destabilizes also non-constant solutions.

2.3 Model examples

In some concrete models, the autocatalysis consisiton (2.11) can be checked easily. Therefore, we obtain that all positive regular stationary solutions to the following systems are unstable.

2.3.1 Resource-consumer system

We consider positive solutions of the following system:

$$u_t = -u + u^2 v \qquad \text{for} \quad x \in \overline{\Omega},\ t > 0, \tag{2.12}$$

$$v_t = D\Delta v - v - ku^2 v + B \qquad \text{for} \quad x \in \Omega,\ t > 0, \tag{2.13}$$

where D, B and k are positive constants, with the zero-flux boundary condition for v. Here, every regular positive stationary solution (U, V) of (2.12)-(2.13) has to satisfy the relation $U(x) = 1/V(x)$, and the function $f_u(U(x), V(x))$ satisfies

$$f_u(U(x), V(x)) = -1 + 2U(x)V(x) = 1 > 0. \qquad \text{for all} \quad x \in \Omega.$$

2.3.2 Model of early carcinogenesis

The following system is a reduced two-equation model of a receptor-based model of cellular growth, which in turn was obtained rigorously in [8] based on a quasi-steady state approximation of a three-equation system:

$$u_t = \Big(\frac{auw}{d_b + d + uw} - d_c\Big)u \qquad \text{for } x \in \overline{\Omega},\ t > 0, \tag{2.14}$$

$$w_t = D\Delta w - d_g w - \frac{d_b}{d_b + d}u^2 w + \kappa_0 \qquad \text{for } x \in \Omega,\ t > 0. \tag{2.15}$$

Here, $a, d_c, d_b, d_g, d, D, \kappa_0$ denote positive constants. We see that every positive regular stationary solution satisfies the relation $U = \beta/W$, $\beta = d_c(d_b + d)/(a - d_c)$, and the autocatalysis condition (2.11) holds true because

$$f_u(U, W) = \frac{aUW}{d_b + d + UW} - d_c + \frac{a(d_b + d)UW}{(d_b + d + UW)^2} = \frac{a(d_b + d)\beta}{(d_b + d + \beta} > 0.$$

2.4 Spectrum of the linearized operator

The proof of Theorem 2.2 involves analysis of a continuous spectrum of a linear operator induced by the lack of diffusion in the destabilizing equation.

Let (U, V) be a regular stationary solution of problem (2.1)-(2.4). Substituting

$$u = U + \widetilde{u} \qquad \text{and} \qquad v = V + \widetilde{v}$$

into (2.1)-(2.2), we obtain the initial-boundary value problem for the perturbation $(\widetilde{u}, \widetilde{v})$:

$$\frac{\partial}{\partial t}\begin{pmatrix} \widetilde{u} \\ \widetilde{v} \end{pmatrix} = \mathcal{L}\begin{pmatrix} \widetilde{u} \\ \widetilde{v} \end{pmatrix} + \mathcal{N}\begin{pmatrix} \widetilde{u} \\ \widetilde{v} \end{pmatrix}$$

$$= \begin{pmatrix} 0 \\ D\Delta\widetilde{v} \end{pmatrix} + \begin{pmatrix} f_u(U,V) & f_v(U,V) \\ g_u(U,V) & g_v(U,V) \end{pmatrix}\begin{pmatrix} \widetilde{u} \\ \widetilde{v} \end{pmatrix} + \mathcal{N}\begin{pmatrix} \widetilde{u} \\ \widetilde{v} \end{pmatrix} \tag{2.16}$$

with the Neumann boundary condition, $\partial_\nu \widetilde{v} = 0$. In order to prove Theorem 2.2, it suffices to study the spectrum $\sigma(\mathcal{L})$ of the linear operator $\mathcal{L}$ with the domain $\mathcal{D}(\mathcal{L}) = L^2(\Omega) \times W^{2,2}(\Omega)$. Let us define the constants

$$\lambda_0 = \inf_{x \in \overline{\Omega}} f_u(U(x), V(x)) > 0 \qquad \text{and} \qquad \Lambda_0 = \sup_{x \in \overline{\Omega}} f_u(U(x), V(x)) > 0, \tag{2.17}$$

where the positivity of λ_0 is a consequence of the autocatalysis condition (2.11). We can prove that $\sigma(\mathcal{L}) \subset \mathbb{C}$ consists of all numbers from the interval $[\lambda_0, \Lambda_0]$ and of a set of (possibly complex) eigenvalues of $(\mathcal{L}, \mathcal{D}(\mathcal{L}))$ which are isolated points of $\mathbb{C}$ (See Figure 2.1).

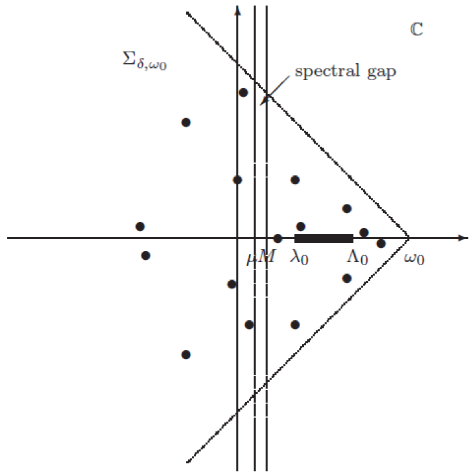

Figure 2.1: The spectrum $\sigma(\mathcal{L})$ is marked by thick dots and by the interval $[\lambda_0, \Lambda_0]$ in the sector Σ_{δ,ω_0}. The spectral gap is represented by the strip $\{\lambda \in \mathbb{C} : \mu \leq \operatorname{Re}\lambda \leq M\}$ without elements of $\sigma(\mathcal{L})$.

In [8], we provide a rigorous proof of the nonlinear instability of steady states by using some ideas, so-called *Linearization principle*, from studies of fluid dynamic equations. In that setting, only the existence of a spectral gap of a linearization operator is required to show the instability of steady states. We notice that the operator $\mathcal{L}$ satisfies the "spectral mapping theorem": $\sigma(e^{t\mathcal{L}}) \setminus \{0\} = e^{t\sigma(\mathcal{L})}$. Thus, due to the relation $|e^z| = e^{\operatorname{Re} z}$ for every $z \in \mathbb{C}$, the spectral gap condition holds true if for every $\lambda \in \sigma(\mathcal{L})$, either $\operatorname{Re}\lambda \in (\kappa, \mu)$ or $\operatorname{Re}\lambda \in (M, \Lambda)$.

Sketch of proof of Theorem 2.2.

Part I: Interval $[\lambda_0, \Lambda_0]$. For each $\lambda \in [\lambda_0, \Lambda_0]$, the operator

$$\mathcal{L} - \lambda I : L^2(\Omega) \times W^{2,2}(\Omega) \to L^2(\Omega) \times L^2(\Omega)$$

defined by formula

$$(\mathcal{L} - \lambda I)(\varphi, \psi) = \big((f_u - \lambda)\varphi + f_v\psi,\ D\Delta\psi + g_u\varphi + (g_v - \lambda)\psi\big),$$

where $f_u = f_u\big(U(x), V(x)\big)$, *etc.*, cannot have a bounded inverse. Suppose that $(\mathcal{L} - \lambda I)^{-1}$ exists and is bounded. Then, for a constant $K = \|(\mathcal{L} - \lambda I)^{-1}\|$, we have

$$\|\varphi\|_{L^2(\Omega)} + \|\psi\|_{W^{2,2}(\Omega)} \\ \leq K\big(\|(f_u - \lambda)\varphi + f_v\psi\|_{L^2(\Omega)} + \|D\Delta\psi + g_u\varphi + (g_v - \lambda)\psi\|_{L^2(\Omega)}\big)$$

for all $(\varphi, \psi) \in L^2(\Omega) \times W^{2,2}(\Omega)$.

We observe that, for each $\lambda \in [\lambda_0, \Lambda_0]$, there exists $x_0 \in \overline{\Omega}$ such that $f_u\big(U(x_0), V(x_0)\big) - \lambda = 0$. Hence, for every $\varepsilon > 0$ there is a ball $B_\varepsilon \subset \Omega$ such that $\|f_u - \lambda\|_{L^\infty(B_\varepsilon)} \leq \varepsilon$. Then, for arbitrary $\psi \in C_c^\infty(\Omega)$ such that $\operatorname{supp}\psi \subset B_\varepsilon$, we can choose $\varphi \in L^2(\Omega)$ such that $\operatorname{supp}\varphi \subset B_\varepsilon$ and in such a way that $\Delta\psi + g_u\varphi + (g_v - \lambda)\psi = \zeta$, where the function

$\zeta \in L^2(\Omega)$ satisfies $\|\zeta\|_{L^2(\Omega)} \le \varepsilon \|\varphi\|_{L^2(\Omega)}$. Using these functions φ, ψ, and ζ, we obtain the estimate

$$\|\varphi\|_{L^2(\Omega)} + \|\psi\|_{W^{2,2}(\Omega)} \le K\big(2\varepsilon\|\varphi\|_{L^2(\Omega)} + \|f_v\|_{L^\infty(\Omega)}\|\psi\|_{L^2(\Omega)}\big). \tag{2.18}$$

Hence, choosing $\varepsilon > 0$ sufficiently small, we obtain the estimate $\|\psi\|_{W^{2,2}(\Omega)} \le K\|f_v\|_{L^\infty(\Omega)}\|\psi\|_{L^2(\Omega)}$, which, obviously, cannot be true for all $\psi \in C_c^\infty(\Omega)$ such that $\operatorname{supp}\psi \subset B_\varepsilon$.

Part II: Eigenvalues. In the next step, we show that the remainder of the spectrum of $(\mathcal{L}, D(\mathcal{L}))$ consists of a discrete set of eigenvalues $\{\lambda_n\}_{n=1}^\infty \subset \mathbb{C} \setminus [\lambda_0, \Lambda_0]$, analyzing the corresponding resolvent equations

$$(f_u - \lambda)\varphi + f_v\psi = F \quad \text{in } \overline{\Omega} \tag{2.19}$$
$$\Delta\psi + g_u\varphi + (g_v - \lambda)\psi = G \quad \text{in } \Omega \tag{2.20}$$
$$\partial_\nu\psi = 0 \quad \text{on } \partial\Omega, \tag{2.21}$$

with arbitrary $F, G \in L^2(\Omega)$. Here, one should notice that for every $\lambda \in \mathbb{C} \setminus [\lambda_0, \Lambda_0]$, one can solve equation (2.19) with respect to φ. Thus, after substituting the resulting expression $\varphi = (F - f_v\psi)/(f_u - \lambda) \in L^2(\Omega)$ into (2.20), we obtain the boundary value problem

$$\Delta\psi + q(\lambda)\psi = p(\lambda) \quad \text{for } x \in \Omega, \tag{2.22}$$
$$\partial_\nu\psi = 0 \quad \text{for } x \in \partial\Omega, \tag{2.23}$$

where

$$q(\lambda) = q(x,\lambda) = -\frac{g_u f_v}{f_u - \lambda} + g_v - \lambda \quad \text{and} \quad p(\lambda) = p(x,\lambda) = G - \frac{g_u F}{f_u - \lambda}. \tag{2.24}$$

For a fixed $\lambda \in \mathbb{C} \setminus [\lambda_0, \Lambda_0]$, by the Fredholm alternative, either the inhomogeneous problem (2.22)-(2.23) has a unique solution (so, λ is not an element of $\sigma(\mathcal{L})$) or else the homogeneous boundary value problem

$$\Delta\psi + q(\lambda)\psi = 0 \quad \text{for } x \in \Omega, \tag{2.25}$$
$$\partial_\nu\psi = 0 \quad \text{for } x \in \partial\Omega, \tag{2.26}$$

has a nontrivial solution ψ. Hence, it suffices to consider those $\lambda \in \mathbb{C} \setminus [\lambda_0, \Lambda_0]$, for which problem (2.25)-(2.26) has nontrivial solution.

Part III: Nonlinear instability. Now, letting $\Phi = {}^t(\widetilde{u}, \widetilde{v})$, we write the equation (2.16) as the following:

$$\Phi_t = \mathcal{L}\Phi + \mathcal{N}(\Phi), \qquad \mathcal{N}(0) = 0.$$

Then, the operator $\mathcal{L}$ with the domain $D(\mathcal{L}) = L^2(\Omega) \times W^{2,2}(\Omega)$ generates an analytic semigroup $\{e^{t\mathcal{L}}\}_{t\ge 0}$ of linear operators on $L^2(\Omega) \times L^2(\Omega)$, which satisfies the spectral mapping theorem. Therefore, if the linear operator $\mathcal{L}$ has a spectral gap: for every $\lambda \in \sigma(\mathcal{L})$,

$$\operatorname{Re}\lambda \in (\kappa, \mu) \quad \text{or} \quad \operatorname{Re}\lambda \in (M, \Lambda), \tag{2.27}$$

where $-\infty \leq \kappa < \mu < M < \Lambda < \infty$ for some $M > 0$, and if the nonlinear term $\mathcal{N}$ satisfies the inequality

$$\|\mathcal{N}(\Phi)\|_{L^2\times L^2} \leq C_0\|\Phi\|_{L^\infty\times L^\infty}\|\Phi\|_{L^2\times L^2} \tag{2.28}$$

for all $\Phi \in L^\infty(\Omega) \times L^\infty(\Omega)$ satisfying $\|\Phi\|_{L^\infty\times L^\infty} < \rho$ for some constants $C_0 > 0$ and $\rho > 0$, then the trivial solution $\Phi_0 \equiv 0$ is nonlinearly unstable in $L^2(\Omega) \times L^2(\Omega)$.

It is easy to see that (2.28) is satisfied. Concerning the spectral gap, we notice that there exists $\delta \in (0, \pi/2]$ such that $\sigma(\mathcal{L}) \subset \Sigma_{\delta,\omega_0} \equiv \{\lambda \in \mathbb{C} \, : \, |\arg(\lambda - \omega_0)| \geq \pi/2 + \delta\}$. The part of the spectrum $\sigma(\mathcal{L})$ in the triangle $\Sigma_{\delta,\omega_0} \cap \{\lambda \in \mathbb{C} \, : \, \mathrm{Re}\, \lambda > 0\}$ consists of all numbers from the interval $[\lambda_0, \Lambda_0]$ with $\lambda_0 > 0$ and of a discrete sequence of eigenvalues with accumulation points from the interval $[\lambda_0, \Lambda_0]$, only. Thus, we can easily find infinitely many $0 \leq \mu < M \leq \lambda_0$, for which the spectrum $\sigma(\mathcal{L})$ can be decomposed as (2.27). □

3 Blowup of solutions in finite or infinite time

In order to understand the large time behavior of solutions of (2.1)-(2.4), as a first step, we consider the following nonlocal problem related to a reaction-diffusion-ODE model:

$$u_t = f(u, \xi), \qquad \text{for} \quad x \in \overline{\Omega},\ t > 0 \tag{3.1}$$

$$\xi_t = \int_\Omega g\big(u(x,t), \xi(t)\big)\, dx \qquad \text{for} \quad t > 0 \tag{3.2}$$

supplemented with the initial conditions

$$u(\cdot, 0) = u_0 \in L^\infty(\Omega), \qquad \xi(0) = \xi_0 \in \mathbb{R}. \tag{3.3}$$

Here, $u = u(x,t)$ and $\xi = \xi(t)$ are unknown functions and $\Omega \subset \mathbb{R}^n$ is a bounded measurable set. In the following, the symbol $|\Omega|$ denotes the Lebesgue measure of Ω and, without loss of generality, we assume that $|\Omega| = 1$. This problem (3.1)-(3.3) is obtained from the initial-boundary value problem (2.1)-(2.4) after passing with the diffusion coefficient D in second equation to the limit $D \to \infty$.

Remark 3.1. It is well-known that for a system of two reaction-diffusion equations

$$u_t = \varepsilon\Delta u + f(u, v), \qquad v_t = D\Delta v + g(u, v), \tag{3.4}$$

with $\varepsilon > 0$ and $D > 0$, a regular perturbation problem is obtained, under some conditions, by passing to the limit $D \to \infty$. The obtained system of a reaction-diffusion equation coupled to an ordinary differential equation with a nonlocal term (as the one in (3.2)) is exhibiting dynamics qualitatively similar to that of the original reaction-diffusion system with the diffusion coefficient D being large. It is called a *shadow system.* Let us emphasize that, in this work, we consider the shadow approximation of system (3.4) with $\varepsilon = 0$. Such systems give a singular limit of reaction-diffusion models with small $\varepsilon > 0$. Moreover, since they arise in modeling of processes with non-diffusing components, as described above, it is important to understand how their dynamics differ from dynamics of non-degenerated systems.

We begin with studying stability properties of stationary solutions of the nonlocal system (3.1)-(3.2). Here, a couple $(U,\bar{\xi}) \in L^\infty(\Omega) \times \mathbb{R}$ is called a stationary solution if

$$f\big(U(x),\bar{\xi}\big) = 0 \qquad \text{almost everywhere in } \Omega, \tag{3.5}$$

$$\int_\Omega g\big(U(x),\bar{\xi}\big)\,dx = 0. \tag{3.6}$$

Now, if equation (3.5) can be solved (locally and not necessarily uniquely) with respect to $U(x)$, we obtain that U has to be constant on a subset of Ω.

Theorem 3.2 (Instability of stationary solutions). *Assume that there exists $\Omega_1 \subset \Omega$ with $|\Omega_1| > 0$, a constant $\bar{u} \in \mathbb{R}$, and a stationary solution $(U,\bar{\xi})$ of system* (3.1)-(3.2) *such that $U(x) = \bar{u}$ for all $x \in \Omega_1$. If the autocatalysis condition holds, i.e. if*

$$f_u(\bar{u},\bar{\xi}) > 0, \tag{3.7}$$

then $(U,\bar{\xi})$ is unstable solution of the nonlocal problem (3.1)-(3.3).

In our examples discussed in the following, autocatalysis condition is satisfied in the case of all "nontrivial" stationary solutions, which can be checked in a simple way. Thus, all such steady states are unstable and this instability arises due to nonlocal effects in shadow problem (3.1)–(3.3), because constant stationary solutions are stable under spatially homogeneous perturbations. A nonlocal effect caused by the integral over Ω in system (3.1)-(3.2) may lead not only to the instability of steady states, but also to a blowup of space-heterogeneous solutions, even in the case when space homogeneous solutions are global-in-time and uniformly bounded on the time half-line $[0,\infty)$. We describe this blowup phenomenon in the case of two problems with nonlinearities which are well-known in mathematical biology. For proofs of theorems below and more details, please refer to [6].

3.1 Resource-consumer type nonlinearity

We consider the following system with resource-consumer type nonlinearity:

$$u_t = -u + u^2\xi, \qquad \text{for } x \in \overline{\Omega},\ t > 0 \tag{3.8}$$

$$\xi_t = -\xi - k\xi \int_\Omega u^2(x,t)\,dx + B \qquad \text{for } t > 0 \tag{3.9}$$

$$u(x,0) = u_0(x), \qquad \xi(0) = \xi_0, \tag{3.10}$$

where $k, B \in \mathbb{R}$ are fixed positive parameters.

Our instability Theorem 3.2 implies that all nontrivial stationary solutions are unstable, a question arises as to what is the long-time behavior of solutions to the initial value problem for system (3.8)-(3.10). First, we emphasize in the following proposition that space homogeneous nonnegative solutions ($i.e$ when u does not depend on x) are global-in-time and bounded.

Proposition 3.3. *All solutions* $(u,\xi) = \big(u(t),\xi(t)\big)$ *of the following initial value problem for ordinary differential equations*

$$\frac{d}{dt}u = -u + u^2\xi, \qquad \frac{d}{dt}\xi = -\xi - ku^2\xi + B \tag{3.11}$$

$$u(0) = u_0 \geq 0, \qquad \xi(0) = \xi_0 \geq 0 \tag{3.12}$$

are nonnegative, global-in-time, and uniformly bounded for $t > 0$.

Proof. We observe that

$$\frac{d}{dt}\big(ku(t) + \xi(t)\big) = -\big(ku(t) + \xi(t)\big) + B.$$

Hence, as long as $u(t)$ and $\xi(t)$ are nonnegative, they have to be uniformly bounded for $t > 0$. □

Our main result on system (3.8)-(3.10) is to show that a space inhomogeneity of initial data may leads not only to instability but also to a blowup in finite time of the corresponding solution.

Theorem 3.4. *For fixed* $x_0 \in \overline{\Omega}$ *and assume that* $u_0 \in C(\Omega)$ *satisfies*

$$u_0(x_0) = 1 \qquad \text{and} \qquad 0 \leq u_0(x) < 1 \quad \text{for} \quad x \neq x_0$$

and

$$A_0 \equiv \int_\Omega \left(\frac{u_0(x)}{1 - u_0(x)}\right)^2 dx < \infty. \tag{3.13}$$

Assume also that

$$\min\left\{\xi_0, \frac{B}{1 + kA_0}\right\} > 1.$$

Then, the corresponding solution of the system

$$u_t = -u + u^2\xi, \qquad \xi_t = -\xi - k\xi \int_\Omega u^2(x,t)\,dx + B$$

blows up in a finite time at x_0.

Remark 3.5. The number A_0 defined in (3.13) is finite if, for example, there exist constants $C > 0$ and $\ell \in (0, n/2)$ such that $u_0(x) \leq u_0(x_0) - C|x_0 - x|^\ell$ for all $x \in \Omega$.

Proof of Theorem 3.4. For fixed $\xi(t)$ and for each $x \in \overline{\Omega}$, we solve the equation $u_t = -u + u^2\xi$:

$$u(x,t) = \frac{e^{-t}}{\dfrac{1}{u_0(x)} - \int_0^t \xi(s)e^{-s}\,ds}.$$

Note that

$$T_{max} = \sup\left\{t > 0 \;:\; \int_0^t \xi(s)e^{-s}\,ds < 1\right\}$$

because $u_0(x_0) = 1$ and $0 \le u_0(x) < 1$ for $x \ne x_0$. Hence, we have an estimate up to the blowup point:

$$u(x,t) \le \frac{e^{-t}}{\frac{1}{u_0(x)} - 1} = \frac{u_0(x)e^{-t}}{1 - u_0(x)} \qquad \text{for all} \quad (x,t) \in \Omega \times [0, T_{max}).$$

Next, using the estimate of $u(x,t)$ we deduce from the equation for ξ the following differential inequality

$$\xi_t \ge -(1 + kA_0)\xi + B \qquad \text{for all} \quad t \in [0, T_{max}),$$

which implies the lower bound

$$\xi(t) \ge \min\left\{\xi_0, \frac{B}{1 + kA_0}\right\} \qquad \text{for all} \quad t \in [0, T_{max}).$$

Thus, we obtain the lower bound

$$\int_0^t \xi(s)e^{-s}\, ds \ge (1 - e^{-t}) \min\left\{\xi_0, \frac{B}{1 + kA_0}\right\},$$

where the right-hand side is equal to 1 for some $t_0 > 0$. □

3.2 Model of early carcinogenesis

Next, we describe an unbounded behavior of solutions $u = u(x,t)$ and $\xi = \xi(t)$ to the following nonlocal problem

$$u_t = \left(\frac{au\xi}{1 + u\xi} - d\right)u \qquad \text{for } x \in \overline{\Omega},\ t > 0, \tag{3.14}$$

$$\xi_t = -\xi - \xi \int_\Omega u^2\, dx + \kappa_0 \qquad \text{for } t > 0. \tag{3.15}$$

where a, d, κ_0 are positive constants, and we assume $a > d$. Moreover, we supplement this system with nonnegative initial conditions

$$u(0,x) = u_0(x), \qquad \xi(0) = \xi_0. \tag{3.16}$$

Model (3.14)-(3.15) is a shadow-type reduction of (2.14)–(2.15). Contrary to the previous example, nonnegative solutions to the initial value problem (3.14)-(3.16) are always global-in-time.

Proposition 3.6. *Assume that $u_0 \in L^\infty(\Omega)$ is nonnegative and $\xi_0 > 0$. Then the initial value problem (3.14)-(3.16) has a unique, global-in-time, nonnegative solution $u \in C([0,\infty)), L^\infty(\Omega))$, $\xi \in C^1([0,\infty))$. If $u_0 \in C(\Omega)$ then $u \in C(\Omega \times [0,\infty))$. This solution satisfies equation (3.14) in a classical sense because $u(x,\cdot) \in C^1([0,\infty))$ for every $x \in \Omega$. Moreover, it satisfies the following pointwise estimates*

$$0 \le u(x,t) \le e^{(a-d)t}u_0(x) \qquad \textit{and} \qquad 0 < \xi(t) \le \max\{\xi_0, \kappa_0\} \tag{3.17}$$

for all $x \in \Omega$ and $t \ge 0$. Moreover, the "total mass" of $u(x,t)$ is bounded:

$$\sup_{t>0} \int_\Omega u(x,t)\, dx < \infty. \tag{3.18}$$

Sketch of the proof of Proposition 3.6. It is sufficient to prove the estimate (3.17) to obtain nonnegative and unique local-in-time solutions to problem (3.14)-(3.16).

Using in equation (3.14) the inequality $u\xi/(1+u\xi) \leq 1$, valid for a nonnegative solution (u,ξ), we obtain the differential inequality $u_t \leq (a-d)u$ which implies first estimate in (3.17). The second one in (3.17) is a direct consequence of the inequality $\xi_t \leq -\xi + \kappa_0$ resulting form (3.15) for nonnegative ξ.

To show property (3.18), we use a differential inequality $u_t \leq au^2\xi - du$ obtained from equation (3.14) with $u\xi \geq 0$. Integrating this inequality over Ω and using the equation for ξ in (3.15), we have got the estimate

$$\begin{aligned}\frac{d}{dt}\left(\int_\Omega u\,dx + a\xi\right) &\leq -d\int_\Omega u\,dx - a\xi + a\kappa_0 \\ &\leq -\min\{1,d\}\left(\int_\Omega u\,dx + a\xi\right) + a\kappa_0,\end{aligned} \tag{3.19}$$

which implies that $\int_\Omega u(t)\,dx + a\xi(t)$ is bounded for $t > 0$, because the constants a and d are positive.

Details of an analogous proof in the case of a reaction-diffusion-ODE system corresponding to (3.14)-(3.15) can be found in [7, Sec. 3]. □

Next, we discuss space homogeneous solutions of the shadow problem (3.14)-(3.16).

Proposition 3.7. *If $u_0(x) \equiv \bar{u}_0 \geq 0$ is independent of x, then the corresponding solution of (3.14)-(3.16) is independent of x as well. Thus, for $|\Omega| = 1$, the function $u(x,t) = u(t)$ and $\xi = \xi(t)$ satisfy the following system of ordinary differential equations*

$$\frac{d}{dt}u = \left(\frac{au\xi}{1+u\xi} - d\right)u, \qquad \frac{d}{dt}\xi = -\xi - \xi u^2 + \kappa_0, \tag{3.20}$$

which after supplementing with initial data $\bar{u}_0 > 0$ and $\xi_0 > 0$, has a unique global-in-time positive solution $(\bar{u}(t), \xi(t))$. This solution is bounded for $t > 0$.

Proof. The differential inequality $du/dt \leq au^2\xi - du$ yields the estimate

$$\frac{d}{dt}\big(u(t) + a\xi(t)\big) = -du(t) - a\xi(t) + a\kappa_0 \leq -\min\{1,d\}(u(t) + a\xi(t)) + a\kappa_0.$$

Hence, the sum $u(t) + a\xi(t)$ is bounded on $[0,\infty)$. □

Proposition 3.6 implies that there is no solution blowing up in finite time, and, from Proposition 3.7, nonnegative space homogeneous solutions are bounded. Now, we can prove that an unbounded growth of solutions to the problem (3.14)-(3.16) as $t \to +\infty$.

Theorem 3.8. *Let a and κ_0 be large so that $2(a-d) \geq 1$ and $\kappa_0 \geq 4a$, and let λ satisfy*

$$\frac{1}{2} \leq \lambda \leq 1 - \frac{2a}{\kappa_0}.$$

Assume that nonnegative initial conditions $u_0 \in C(\Omega) \cap L^\infty(\Omega)$ and $\xi_0 \in \mathbb{R}$ satisfy

$$\xi_0 \int_\Omega u_0^2(x)\,dx > \lambda\kappa_0 \quad \textit{and} \quad 0 < \xi_0 \leq (1-\lambda)\kappa_0$$

and suppose that the set

$$\Omega_* \equiv \{x_* \in \Omega \mid u_0(x_*) = \max_{x\in\Omega} u_0(x)\}$$

has measure zero. Then,

$$\sup_{t>0} u(x_*, t) = +\infty \quad \textit{if } x_* \in \Omega_*, \qquad \sup_{t>0} u(x,t) < +\infty \quad \textit{if } x \in \Omega \setminus \Omega_*,$$
$$\inf_{t>0} \xi(t) = 0.$$

The proof of Theorem 3.8 is based on the following two lemmas.

Lemma 3.9. *Under the assumptions of Theorem 3.8, the solution* $(u(x,t), \xi(t))$ *of* (3.14)–(3.16) *satisfies*

$$\xi(t) \int_\Omega u^2(x,t)\, dx > \lambda\kappa_0 \quad \textit{and} \quad 0 < \xi(t) \le (1-\lambda)\kappa_0$$

for all $t \ge 0$.

Lemma 3.10. *Let the assumptions of Theorem 3.8 true. If* $u(x,t)$ *is bounded on* $\Omega \times [0,\infty)$*, then*

$$u(x,t) \to 0 \quad \textit{exponentially as} \quad t \to \infty$$

for every $x \in \Omega \setminus \Omega_*$.

Sketch of proof of Theorem 3.8. First, we show that $u(x_*, t) \to +\infty$ as $t \to +\infty$ for every $x \in \Omega_*$. Suppose that $u = u(x,t)$ is bounded on $\Omega \times [0,\infty)$. Thus, by Lemma 3.10, we see that $u(x,t) \to 0$ as $t \to \infty$ for every $x \in \Omega \setminus \Omega_*$. Applying the Lebesgue dominated convergence theorem we have

$$\int_\Omega u^2(x,t)\, dx \to 0 \quad \text{as} \quad t \to \infty,$$

because $|\Omega_*| = 0$. This is, however, in contradiction with the inequality from Lemma 3.9. Hence, we conclude that $u(x,t)$ is unbounded for $t > 0$.

Next, we show that $\sup_{t>0} u(x,t) < +\infty$ for all $x \in \Omega \setminus \Omega_*$. Suppose $\sup_{t>0} u(x_1, t) = +\infty$ for some $x_1 \notin \Omega_*$. By the continuity of the initial data u_0, the set

$$\Omega_1 \equiv \{x \in \Omega \mid u_0(x_1) < u_0(x) < u_0(x_*)\}$$

has a positive measure. Moreover, we obtain

$$u(x_1, t) < u(x,t) < u(x_*, t) \quad \text{for all } x \in \Omega_1 \text{ and all } t \ge 0.$$

These inequalities lead to a contradiction with the boundedness of mass:

$$\sup_{t>0} \int_\Omega u(x,t)\, dx \ge \sup_{t>0} \int_{\Omega_1} u(x,t)\, dx \ge \sup_{t>0} u(x_1,t)|\Omega_1| = +\infty.$$

□

References

[1] S. Härting and A. Marciniak-Czochra, *Spike patterns in a reaction-diffusion-ode model with Turing instability*, Math. Methods in the Applied Sciences (2013), to appear. preprint, arXiv:1303.5362 [math.AP]

[2] S. Hock, Y. Ng, J. Hasenauer, D. Wittmann, D. Lutter, D. Trumbach, W. Wurst, N. Prakash, and F.J.. Theis *Sharpening of expression domains induced by transcription and microRNA regulation within a spatio-temporal model of mid-hindbrain boundary formation.* BMC Syst Biol 7 (2013) 48.

[3] V. Klika, R.E.. Baker, D. Headon, E.A. Gaffney, *The influence of receptor-mediated interactions on reaction-diffusion mechanisms of cellular self-organization*, Bull. Math. Biol. **74** (2012), 935–957.

[4] A. Marciniak-Czochra, Receptor-based models with diffusion-driven instability for pattern formation in *Hydra*. *J. Biol. Sys.* **11** (2003) 293–324 .

[5] A. Marciniak-Czochra, Strong two-scale convergence and corrector result for the receptor-based model of the intercellular communication. *IMA J. Appl. Math.* (2012) doi:10.1093/imamat/hxs052.

[6] A. Marciniak-Czochra, S. Härting, G. Karch and K. Suzuki, *Dynamical spike solutions in a nonlocal model of pattern formation*, (2013), arXiv:1307.6236 [math.AP].

[7] A. Marciniak-Czochra, G. Karch, & K. Suzuki, *Unstable patterns in reaction-diffusion model of early carcinogenesis*, J. Math. Pures Appl. (9) **99** (2013), 509–543

[8] A. Marciniak-Czochra, G. Karch, and K. Suzuki *Unstable patterns in autocatalytic reaction-diffusion-ODE systems*, (2013), arXiv:1301.2002 [math.AP].

[9] A. Marciniak-Czochra, M. Kimmel, *Dynamics of growth and signaling along linear and surface structures in very early tumors*, Comput. Math. Methods Med. **7** (2006), 189–213.

[10] A. Marciniak-Czochra, M. Kimmel, *Modelling of early lung cancer progression: influence of growth factor production and cooperation between partially transformed cells*, Math. Models Methods Appl. Sci. **17** (2007), suppl., 1693–1719.

[11] A. Marciniak-Czochra, M. Kimmel, *Reaction-diffusion model of early carcinogenesis: the effects of influx of mutated cells*, Math. Model. Nat. Phenom. **3** (2008), 90–114.

[12] A. Marciniak-Czochra, M. Ptashnyk, *Derivation of a macroscopic receptor-based model using homogenisation techniques*, SIAM J. Mat. Anal. **40** (2008), 215–237.

[13] K. Pham, A. Chauviere, H. Hatzikirou, X. Li, H.M.. Byrne, V. Cristini, J. Lowengrub, *Density-dependent quiescence in glioma invasion: instability in a simple reaction-diffusion model for the migration/proliferation dichotomy*, J. Biol. Dyn. **6** (2011) 54–71.

[14] A. M. Turing, *The chemical basis of morphogenesis*, Phil. Trans. Roy. Soc. B **237** (1952), 37–72.

[15] D.M. Umulis, M. Serpe, M.B. O'Connor, and H.G. Othmer, *Robust, bistable patterning of the dorsal surface of the Drosophila embryo,* PNAS **103** (2006), 11613–11618.