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Abstract
Coupling a reaction-diffusion equation with ordinary differential equations (ODE) may lead to diffusion-driven instability (DDI) which, in contrast to the classical reaction-diffusion models, causes destabilization of both, constant solutions and Turing patterns. Using a shadow-type limit of a reaction-diffusion-ODE model, we show that in such cases the instability driven by nonlocal terms (a counterpart of DDI) may lead to formation of unbounded spike patterns.

Keywords: shadow system, reaction-diffusion-ODE equations, diffusion-driven instability, unbounded spike patterns
Mathematics Subject Classification numbers: 35M33, 34E13, 35B25, 35K57

(Some figures may appear in colour only in the online journal)
1. Introduction

1.1. Reaction-diffusion-ODE systems

Classical models of pattern formation are based on diffusion-driven instability (DDI) (Turing instability) of constant stationary solutions of reaction-diffusion equations, which leads to emergence of stable Turing patterns formed around that equilibrium. The emerging patterns can be spatially monotone or spatially periodic. Their shape depends on the ratio of diffusion coefficients as well as on a scaling coefficient which reflects the relationship between the diffusion coefficients and the domain size [31].

Interestingly, a variety of possible patterns increases when setting the smaller diffusion coefficient to zero, i.e. considering a single reaction-diffusion equation coupled to an ordinary differential equation (ODE)

\[ u_t = f(u, v), \quad v_t = D\Delta v + g(u, v), \]  

supplemented with the Neumann boundary condition for \( v = v(x, t) \).

Such models arise from coupling of the diffusive processes with processes which are localized in space, such as, for example, growth processes [2, 4, 24–26, 36] or intracellular signaling [11, 14, 18, 44]. 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 a cell-to-cell communication through a diffusion in a cell assembly [19, 28].

The dynamics of such models appears to be very different from that of classical reaction-diffusion models. Systems coupling a single reaction-diffusion equation with ODEs may exhibit DDI as first shown in [18] and discussed more recently on several examples from mathematical biology in [14]. However, in this case all Turing patterns are unstable, i.e. the same mechanism which destabilizes constant solutions, destabilizes also all continuous spatially heterogeneous stationary solutions [16, 20–22]. The question then arises as to which patterns, if any, can be exhibited in such models. Two scenarios have been observed numerically: Either a convergence to stable stationary patterns with jump-discontinuity [10, 11] or an emergence of multimodal dynamical spike structures [9, 36].

In the first case, solutions of the model are uniformly bounded and they converge to a far-from-equilibrium patterns with jump discontinuity which results from the existence of multiple quasi-stationary solutions in the ODE subsystems. The hysteresis in the location of stable branches of those solutions allows the authors of [10] to construct a continuum of stationary solutions with jump discontinuity, which may be either monotone or periodic or irregular. In [10], conditions for linear stability of such patterns in a topology excluding the discontinuity points have been provided. Then, the emergence and stability of the patterns with jump discontinuity has been proved for a receptor-ligand model with DDI and hysteresis.

1.2. Problem formulation

The goal of this paper is to understand the ‘spiky’ unbounded patterns emerging in the second class of models [9, 25, 26, 36]. We consider this problem in a particular case of a model coupling cell growth with receptor-ligand dynamics, which was proposed in [25, 26] as a three-equation model and reduced to a reaction-diffusion-ODE system of the form (1.1) in [9, 21].

So far, analysis of the model showed instability of all stationary solutions, including the solutions with jump-discontinuity [21, 22], while model simulations indicated emergence of dynamical spike patterns [9]. To understand the underlying dynamics, we propose to further reduce the model and focus on its shadow-limit. It results in the following nonlocal system
with two unknown nonnegative functions $u = u(x,t)$ and $\xi = \xi(t)$, describing an evolution of a density of growing cells and a uniformly distributed growth factor, respectively,

$$u_t = \left( \frac{au\xi}{1 + u\xi} - d \right) u \quad \text{for} \quad x \in \Omega, \ t > 0, \quad (1.2)$$

$$\xi_t = -\xi - \xi \int_{\Omega} u^2 \, dx + \kappa_0 \quad \text{for} \quad t > 0. \quad (1.3)$$

Here, $a, d, \kappa_0$ are positive constants, $\Omega \subset \mathbb{R}^n$ is an arbitrary bounded measurable set of a finite nonzero measure and we assume that $|\Omega| = 1$, without loss of generality. Moreover, we supplement equations (1.2) and (1.3) with nonnegative initial conditions

$$u(0,x) = u_0(x), \quad \xi(0) = \xi_0. \quad (1.4)$$

The reduction of a reaction-diffusion model to a nonlocal problem can be obtained after passing with the diffusion coefficient $D$ in second equation to the limit $D \to \infty$, see theorem A.2 in appendix A for a rigorous proof of this claim. The shadow-limit has attracted a considerable interest in the literature in the case where the first equation is a quasilinear parabolic equation, starting from the papers of Keener [13], Nishiura [34], and Hale and Sakamoto [8]; see also the review article by Nishiura [35] for other references. It has been introduced and used to consider the stationary problem: If a steady state solution of the shadow system is found, then one can find a steady-state solution of the original system with large diffusion coefficient of the fast diffusing component, provided that the linearized operator around the steady-state solution of the shadow system is invertible. The approach was applied to study spike-layer solutions in different versions of the activator-inhibitor models [45] and also interior transition layers [34]. Monotonicity of stable patterns for such nonlocal system has been shown by Ni et al [32].

In this paper, we apply the shadow limit to reduce a reaction-diffusion-ODE model (1.1) to a system of integro-differential equations (1.2)–(1.4) (see appendix A for details). The finite-time limit has been recently studied by Marciniak-Czochra and Mikelić in [27]. An approach using semigroup convergence has been undertaken by Bobrowski [3]. Asymptotic shadow-limit remains an open problem. In general, nonstationary solutions of the original reaction-diffusion system and of the shadow system may behave differently, as was found by Li and Ni [17] showing that the shadow limit in a model with unbounded growth may cause a finite-time blow-up not appearing in the original reaction-diffusion system. Applicability of the shadow-limit to the model considered in this paper has been also tested numerically. Comparing emerging patterns in the system with a large diffusion coefficient to those in the shadow limit motivated our study on the analysis of the reduced model, see simulations in [9] and in section 1.3.

1.3. Content of the paper

In this work we focus on the asymptotic behavior of the solutions of problem (1.2)–(1.4).

In the first steps, we show the following results on the nonlocal initial value problem (1.2)–(1.4) where, to streamline the analysis, we assume that $u_0 \in C(\overline{\Omega})$ as well as $u_0(x) \geq 0$ for all $x \in \Omega$ and $\xi_0 \geq 0$.

- Problem (1.2)–(1.4) has a unique global-in-time nonnegative solution for every nonnegative initial condition (1.4), see proposition 2.1, below.
The ‘total mass’ \( \int_{\Omega} u(x,t) \, dx \) of every nonnegative solution to problem (1.2)-(1.4) is bounded on \([0, \infty)\) (proposition 2.1).

- Each \( x \)-independent solution of problem (1.2)-(1.4) is bounded on the half-line \([0, \infty)\), see proposition 2.3.

- All stationary solutions of problem (1.2)-(1.4) are unstable (section 2.2).

However, our main result (theorem 3.1) shows that the nonlocal coupling may lead to a loss of boundedness of solutions. More specifically, we prove that although space homogeneous solutions of the model are uniformly bounded in time, there exist space heterogeneous solutions with an unbounded growth as \( t \to \infty \), as depicted in figure 1.

**Remark 1.1 (Numerical simulations of the model).** Our mathematical results on a growth of unbounded patterns are motivated by numerical simulations of solutions to the nonlocal system (1.2)-(1.4) which we present in figure 1. Each graph of figure 1 shows the function \( u = u(x,t) \) on the interval \( \Omega = [0, 1] \) which is a solution (together with a suitable function \( \xi = \xi(t) \)) to system (1.2) and (1.3) with the parameters \( a = 2, d = 1, \kappa_0 = 65/8 \). Note that, in this case, the constant vector \( (\bar{u}, \bar{\xi}) = (8, 1/8) \) is an asymptotically stable solution of the corresponding ODE system (2.4) (see [22, theorem B.2] and remark 2.4). Thus, each figure shows a destabilization of the spatially homogeneous steady state \( (\bar{u}, \bar{\xi}) = (8, 1/8) \) of the nonlocal system (1.2)-(1.4) due to the Turing instability. In particular, in figure 1 we can observe the following unbounded patterns:

- **Single spike pattern.** For the initial data \( u_0(x) = 8 - 0.05(\cos(2\pi x) + 0.25(1 - x)) \) (with one global maximum) and \( \xi_0 = 1/8 \), we observe a formation of an unbounded single spike at the point of the global maximum of the initial function \( u_0(x) \).

- **Spike competition.** For the initial data \( u_0(x) = 8 + 0.05 \sin(3\pi x)(1 + 0.1x) \) (with two local maxima of different values) and \( \xi_0 = 1/8 \), we observe that initially, after the destabilization of the spatially homogeneous steady state \( (\bar{u}, \bar{\xi}) = (8, 1/8) \), a pattern with two
peaks develops. The spikes are located at two points of the local maxima of the initial function $u_0$. However, when time is elapsing, the spike corresponding to a larger initial value persists and grows to $+\infty$, while the other one decays.

- **Double spike pattern.** For the the initial data $u_0(x) = 8 + 0.05 \sin(3\pi x)$ (with two local maxima of the same value) and $\xi_0 = 1/8$, we observe Turing instability of the spatially homogeneous steady state $(\bar{u}, \bar{\xi}) = (8, 1/8)$ leading to formation of two spikes at two points of the local maxima of the initial function $u_0$.

- **Plateau pattern.** For the initial data $u_0(x) = 8 - 0.05 \sin(2\pi x + 0.5\pi)$ for $x \notin (0.25, 0.75)$ (a maximal value achieved at an interval) and $\xi_0 = 1/8$, we observe that the Turing instability of the spatially homogeneous steady state $(\bar{u}, \bar{\xi}) = (8, 1/8)$ leads to destabilization of this constant equilibrium and the solution converges to a bounded, discontinuous pattern, see remark 2.9 below for more explanation.

Mathematical results reported in this paper combined with numerical investigations of model (1.2)–(1.4) led us to a conjecture that the model solutions tend asymptotically to unbounded patterns supported on sets of measure zero (which resemble a sum of weighted Dirac measures). This is a new pattern formation phenomenon in the systems of reaction-diffusion-type which has not been studied analytically so far.

Additionally, we extend some results to nonlocal equations with general nonlinearities:

\begin{align*}
  u_t &= f(u, \xi), \quad \text{for } x \in \Omega, \ t > 0, \\
  \xi_t &= \int_{\Omega} g(u(x, t), \xi(t)) \, dx \quad \text{for } t > 0,
\end{align*}

with arbitrary $C^1$-functions $f = f(u, \xi)$ and $g = g(u, \xi)$ and supplemented with suitable initial conditions. Since the obtained results are only a slight modification of those shown recently for reaction-diffusion-ODE models, we place them in Appendix.

In appendix B, we show that, although model (1.5) and (1.6) is not a reaction-diffusion system, it may exhibit a pattern formation phenomenon based on the same principle as the classical Turing mechanism, i.e. there exists a spatially constant steady state, which is stable to spatially homogeneous perturbations, but unstable to spatially heterogeneous perturbations. However, we prove much more than it us usually shown in the case of studies of DDI phenomena in reaction-diffusion equations. First, we characterize stationary solutions of problem (1.5) and (1.6). Then, we show that they are unstable (more precisely, nonlinearly unstable in the Lyapunov sense) under so called autocatalysis assumption, i.e. when $f_u > 0$, which is a condition typical for models exhibiting Turing instability (see theorem B.1 below for more details). This indicates that, in the considered class of models, the Turing-type mechanism destabilizes not only constant steady states but also non-constant stationary solutions. A similar mechanism, where DDI destabilizes all non-constant stationary solutions of reaction-diffusion-ODE of the form (1.1), has been recently studied in our papers [21, 22].

Moreover, in appendix C we provide another particular example of system (1.5) and (1.6), which shows that the Turing phenomenon may lead not only to formation of unbounded patterns as those shown in figure 1 but also to a blow-up of solutions in a finite time. Analogous results for reaction-diffusion-ODE systems (1.1) with particular nonlinearities were published in [12, 19].

Let us conclude this introduction by a remark explaining how the nonlocal model (1.5) and (1.6) may contribute to the theory of pattern formation described by reaction-diffusion systems. In a classical Turing-type system

\[ 1761 \]
\[ u_t = \varepsilon \Delta u + f(u, v), \quad v_t = D \Delta v + g(u, v) \quad \text{with } \varepsilon > 0 \text{ and } D > 0 \quad (1.7) \]

(with nonlinearities such as e.g. in the Gierer–Meinhardt activator-inhibitor model), the activator diffuses slowly (i.e. \( \varepsilon > 0 \) is small) while the inhibitor diffuses rapidly (\( D > 0 \) is large) to generate patterns. \[6, 15, 30, 31, 33, 41–43\] In the shadow type reduction of this system

\[ u_t = \varepsilon \Delta u + f(u, v), \quad \xi_t = \int_{\Omega} g(u(x, t), \xi(t)) \, dx \quad \text{with } \varepsilon > 0 \]

only monotone steady states can be stable, see \[32\]. On the other hand, in the case of the reaction-diffusion-ODE systems

\[ u_t = f(u, v), \quad v_t = D \Delta v + g(u, v) \quad \text{with } D > 0 \quad (1.8) \]

a constant steady state, which is stable for \( D = 0 \), looses its stability as soon as \( D \) becomes positive due to the Turing mechanism, see \[21, 22\]. Moreover, as \( D \) increases, this constant steady state becomes more unstable and finally, for \( D \) sufficiently large, it is unstable against all disturbances of arbitrary wave numbers. This Turing-type mechanism destabilizes not only constant steady states but also non-constant stationary solutions \[21, 22\]. Therefore, the shadow type limit (1.5) and (1.6) of the reaction-diffusion-ODE system (1.8) seems to be the most unstable limit case of the classical reaction-diffusion systems (1.7).

On the other hand, as mentioned above, reaction-diffusion-ODE systems may exhibit a broad range of pattern formation phenomena, some of them having similar properties to the classical Turing patterns. Hence, they may provide an alternative to explain symmetry breaking and pattern formation in biological systems in which molecular components satisfying the classical Turing mechanism have not been identified so far. Different models may produce similar patterns. Therefore, identifiability, i.e. the ability to distinguish among different models and the corresponding mechanisms, is of a primary importance. The latter requires better understanding of the underlying mechanisms and hence motivates analysis of the models exhibiting different pattern formation phenomena. The study presented in this paper is a step towards understanding of the complexity of the dynamics of reaction-diffusion-ODE models.

2. Model of early carcinogenesis

2.1. Preliminary properties of solutions

For completeness of the paper, we provide basic properties of the nonlocal model (1.2)–(1.4).

**Proposition 2.1.** Assume that \( u_0 \in C(\bar{\Omega}) \) is nonnegative and \( \xi_0 > 0 \). Then the initial value problem (1.2)–(1.4) has a unique, global-in-time, nonnegative solution \( u \in C([0, \infty)), C(\bar{\Omega}) \), \( \xi \in C^1([0, \infty)) \). This solution satisfies equation (1.2) in a classical sense, because \( u(x, \cdot) \in C^1([0, \infty)) \) for every \( x \in \Omega \). The following pointwise estimates hold true:

\[ 0 \leq u(x, t) \leq e^{(a-d)t} u_0(x) \quad \text{and} \quad 0 < \xi(t) \leq \max \{ \xi_0, \kappa_0 \} \quad (2.1) \]

for all \( x \in \Omega \) and \( t \geq 0 \). Moreover, the 'total mass' of \( u(x, t) \) is bounded:

\[ \sup_{t > 0} \int_{\Omega} u(x, t) \, dx < \infty. \quad (2.2) \]
**Proof.** A construction of a unique local-in-time continuous solution to problem (1.2)–(1.4) on the set \( \Omega \times [0, T] \) with certain \( T > 0 \) is more-or-less standard and we recall it in the beginning of appendix B.

This solution is nonnegative in case of nonnegative initial conditions, which can be proved in the following way. Let \( T > 0 \) be arbitrary. First, we notice that since \( \sup_{x \in \Omega, t \in [0, T]} |u(x, t)| < \infty \), we have got \( \sup_{0 \leq t \leq T} \int_{\Omega} u^2(x, t) \, dx < \infty \). Suppose that there exists \( T_1 \in (0, T] \) such that \( \xi(T_1) = \kappa_0 > 0 \) which implies immediately that \( \xi(t) \) cannot decrease in a neighborhood of \( T_1 \). Hence, we obtain that \( \xi(t) > 0 \) for all \( t \in [0, T] \). On the other hand, given an arbitrary \( \xi(t) \), equation (1.2) is an ordinary differential equation for \( u(x, \cdot) \) for each \( x \in \Omega \). This equation has a trivial solution \( u \equiv 0 \) for each \( \xi(t) \). Hence, by a standard argument for ordinary differential equations involving the uniqueness of solution, we obtain that if for some \( x \in \Omega \) we have \( u(x, 0) = 0 \), then \( u(x, t) = 0 \) for all \( t \in [0, T] \) and the inequality \( u(x, 0) > 0 \) implies \( u(x, t) > 0 \) for all \( t \in [0, T] \).

Nonnegative local-in-time solutions can be continued global-in-time by a standard continuation argument provided we prove estimates (2.1) which may be obtained in the following way. Applying to equation (1.2) the inequality \( u\xi/(1 + u\xi) \leq 1 \) (valid for a nonnegative solution \( (u, \xi) \)) we obtain the differential inequality \( u_t \leq (a - d)u \) which implies first estimate in (2.1). The second one in (2.1) is a direct consequence of the inequality \( \xi_t \leq -\xi + \kappa_0 \) resulting from equation (1.3) for nonnegative \( \xi \).

To show property (2.2), we use a differential inequality \( u_t \leq au^2 \xi - du \) obtained from equation (1.2) with \( u\xi \geq 0 \). Integrating this inequality over \( \Omega \) and using the equation for \( \xi \) in (1.3), we have got the estimate

\[
\frac{d}{dt} \left( \int_{\Omega} u \, dx + a\xi \right) \leq -d \int_{\Omega} u \, dx - a\xi + a\kappa_0
\]

\[
\leq -\min\{1, d\} \left( \int_{\Omega} u \, dx + a\xi \right) + a\kappa_0,
\]

which implies that the quantity \( \int_{\Omega} u(t) \, dx + a\xi(t) \) is bounded for \( t \in (0, \infty) \), because the constants \( a \) and \( d \) are positive. Since \( \xi(t) > 0 \), we immediately obtain (2.2).

Details of an analogous proof in the case of a reaction-diffusion-ODE system corresponding to (1.2) and (1.3) can be found in [21, section 3].

**Remark 2.2.** Under the assumptions of proposition 2.1, if \( u_0(x_1) \leq u_0(x_2) \) for some \( x_1, x_2 \in \partial \Omega \), then \( u(x_1, t) \leq u(x_2, t) \) for all \( t \geq 0 \). This is a consequence of the uniqueness of solutions to the ordinary differential equation (1.2) with fixed \( \xi \in C^1([0, \infty)) \) (see the proof of lemma 3.4, below). In particular, if for some \( x_* \in \partial \Omega \), we have got the relation \( u_0(x_*) = \max_{x \in \partial \Omega} u_0(x) \), then \( u(x_*, t) = \max_{x \in \partial \Omega} u(x, t) \) for all \( t \in [0, \infty) \).

Next, we discuss space homogeneous solutions of problem (1.2)–(1.4).

**Proposition 2.3.** If \( u_0(x) \equiv u_0 \) is independent of \( x \), then the corresponding solution of (1.2)–(1.4) 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

\[
\frac{d}{dt} u = \left( \frac{a u \xi}{1 + u \xi} - d \right) u, \quad \frac{d}{dt} \xi = -\xi - \xi u^2 + \kappa_0,
\]
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.** A solution of problem (1.2)–(1.4) with constant $u_0(x) = \bar{u}_0$ does not depend on $x$ which is an immediate consequence of the uniqueness of solutions established in proposition 2.1. From now, the study of the system of ordinary differential equation (2.4) is completely standard. In particular, we have the differential inequality $\frac{du}{dt} \leq au^2 - d\bar{u}$ for nonnegative solutions which together with the second equation in (2.4) yields the estimate

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

Thus, the sum $u + a\xi$ (and so each of its term) is bounded on $[0, \infty)$. □

**Remark 2.4 (Constant stationary solutions).** System of ODEs (2.4) has a trivial steady state $(u,\xi) = (0,\kappa_0)$ which is its asymptotically stable solution (see also remark 2.8, below). Detailed analysis of positive steady states of system (2.4) can be found in our recent work [22, appendix B]. It is shown that for $a > d$ and $\kappa_0^2 > 4(d/(a-d))^2$, there exist two positive steady states of system (2.4). One of these solutions is always unstable. Conditions on the coefficients in equation (2.4) under which the second constant solution is an asymptotically stable solution of the system of ordinary differential equation (2.4) can be found in [22, appendix B].

**Remark 2.5 (Turing instability of constant solutions).** By theorem 2.6 below, both constant steady states discussed in remark 2.4 are unstable solutions to the nonlocal problem (1.2)–(1.4). In particular, we obtain that this problem describes the Turing instability of that constant steady state which is stable as a solution to the kinetic ODE system (2.4).

### 2.2. Instability of spatially heterogeneous nonnegative stationary solutions

Now, we study non-constant nonnegative stationary solutions of system (1.2) and (1.3), namely, we look for a function $U \in L^\infty(\Omega)$ and a constant $\xi \in \mathbb{R}$ satisfying

$$\left(\frac{aU\xi}{1 + U\xi} - d\right)U = 0 \quad \text{for } x \in \Omega, \quad (2.5)$$

$$-\xi - \xi \int_\Omega U^2 \, dx + \kappa_0 = 0. \quad (2.6)$$

For this purpose, we decompose the set $\Omega$ into an arbitrary disjoint sum of two measurable sets $\Omega = \Omega_1 \cup \Omega_2$, where $\Omega_1 \cap \Omega_2 = \emptyset$ and $|\Omega_1| > 0$, and solving equation (2.5) with respect to $U$ we define

$$U(x) = \begin{cases} 
\frac{d}{(a-d)\xi} & \text{if } x \in \Omega_1, \\
0 & \text{if } x \in \Omega_2.
\end{cases} \quad (2.7)$$

Then, for $a > d$, one calculates $\xi$ from equation (2.6) which for $U$ defined by formula (2.7) reduces to the quadratic equation
\[ \xi^2 - \kappa_0 \xi + \frac{d^2}{(a - d)^2} |\Omega_1| = 0 \]  \hspace{1cm} (2.8)

with two positive roots, provided \( \kappa_0^2 > 4 (d/(a - d))^2 |\Omega_1| \).

Now, we prove that all such stationary solutions are unstable.

**Theorem 2.6 (Instability of all stationary solutions).** Nonnegative stationary solution \((U, \xi)\) of system (1.2) and (1.3) exist under the assumptions \( a > d \) and \( \kappa_0^2 > 4 (d/(a - d))^2 |\Omega_1| \).

They are given by formula (2.7) with \( |\Omega_1| > 0 \) and \( \xi \) satisfying equation (2.8). The couple \((U, \xi)\) is an unstable solution of the initial value problem for the nonlocal system (1.2) and (1.3).

**Proof.** The construction of nonnegative stationary solutions is given above. To show their instability, we apply theorem B.1 from appendix B. Here, the autocatalysis assumption (B.8) holds true because for \( U(x) = d/(a - d) \) with \( x \in \Omega_1 \) we have

\[ f_a(U(x), \xi) = \frac{aU(x)\xi}{1 + U(x)\xi} - d + \frac{aU(x)\xi}{(1 + U(x)\xi)^2} = \frac{d(a - d)}{a} > 0 \quad \text{for all} \quad x \in \Omega_1. \]

\[ \square \]

**Remark 2.7.** Theorem 2.6 states that the Turing-type mechanism destabilizes not only constant steady states of system (1.2) and (1.3) but also all non-constant stationary solutions.

Further discussion of stationary solutions of nonlocal systems with general nonlinearities is contained in appendix B. This instability property motivated us to study non-stationary growing structures which we report in the next section.

**Remark 2.8.** On the other hand, one can prove that the ‘trivial’ stationary solution \((U(x), \xi) = (0, \kappa_0)\) is a nonnegative solution of system (1.2) and (1.3). Indeed, it follows from equation (1.2) that the nonnegative function \( u \leq au^2 K - du \), where the constant \( K = \sup_{x \geq 0} \xi(t) \) is finite by second inequality in (2.1).

Hence, if \( u_0 \in L^\infty(\Omega) \) is nonnegative and sufficiently small then \( u(x,t) \to 0 \) as \( t \to \infty \) uniformly in \( x \in \Omega \). This decay of \( u \) implies \( \int_\Omega u^2(x,t) \, dx \to 0 \) as \( t \to \infty \). Hence, using equation (1.3) we can easily show that \( \xi(t) \to \kappa_0 \) as \( t \to \infty \). See e.g. [21, theorem 2.2] for an analogous reasoning in the case of the corresponding reaction-diffusion-ODE system.

**Remark 2.9.** Notice that if for some \( x_1 \neq x_2 \) we have \( u_0(x_1) = u_0(x_2) \), then \( u(x_1,t) = u(x_2,t) \) for all \( t \geq 0 \), because both quantities \( u(x_1,t) \) and \( u(x_2,t) \) satisfy equation (1.2) with the same function \( \xi = \xi(t) \) and the same initial conditions, see remark 2.2. Consequently, if the measure of \( \Omega_+ \equiv \{ x \in \Omega : u_0(x) = \max_{x \in \Omega} u_0(x) \} \) is positive, the function \( u(x,t) \) cannot escape to \( +\infty \) for any \( x \in \Omega \) due to the boundedness of the mass (2.2). In such a case, one can show (by using lemma 3.4 below) that

\[ u(x,t) \to U(x) = \begin{cases} \hat{u} & \text{if} \quad x \in \Omega_+, \\ 0 & \text{if} \quad x \in \Omega \setminus \Omega_+ \end{cases} \quad \text{and} \quad \xi(t) \to \bar{\xi} \]

as \( t \to \infty \), where \((U(x), \bar{\xi})\) is a discussed-above stationary solution of system (1.2) and (1.3). Thus, there are bounded (and also continuous) initial conditions such that the corresponding
solutions converge pointwise for every $x \in \Omega$ towards discontinuous stationary solutions. Obviously, such convergence result does not contradict the instability of a steady state $(U, \xi)$ proved in theorem 2.6. We refer the reader to figure 1 (the graph in the second row and the second column) for a numerical illustration of such a phenomena.

3. Formation of unbounded spikes

Now, we are in a position to prove our main result on unbounded growth of solutions to system (1.2) and (1.3).

**Theorem 3.1.** Let $\Omega \subset \mathbb{R}^n$ be a bounded and closed set with non-empty interior and satisfying $|\Omega| = 1$. Let $(u, \xi)$ be a nonnegative solution of problem (1.2)–(1.4), where positive constants in those equations satisfy the following inequalities

- the parameter $a$ is large:
  \[ 2(a - d) \geq 1, \]  
  \[ (3.1) \]
- the constant $\kappa_0$ is large:
  \[ \kappa_0 \geq 4a. \]  
  \[ (3.2) \]

Let $\lambda$ satisfy

\[ \frac{1}{2} \leq \lambda \leq 1 - \frac{2a}{\kappa_0}. \]  
\[ (3.3) \]

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

\[ \xi_0 \int_\Omega u_0^2(x) \, dx > \lambda \kappa_0 \quad \text{and} \quad 0 < \xi_0 \leq (1 - \lambda) \kappa_0. \]  
\[ (3.4) \]

Suppose that the set

\[ \Omega_* = \{ x_* \in \overline{\Omega} : u_0(x_*) = \max_{x \in \overline{\Omega}} u_0(x) \} \]

has measure zero. Then

\[ \sup_{t > 0} u(x_*, t) = +\infty \quad \text{for each } x_* \in \Omega_*, \]  
\[ (3.5) \]
\[ \sup_{t > 0} u(x, t) < \infty \quad \text{for each } x \in \Omega \setminus \Omega_*, \]  
\[ (3.6) \]
\[ \inf_{t > 0} \xi(t) = 0. \]  
\[ (3.7) \]

We show on figure 1 numerical simulations of solutions to the nonlocal system (1.2) and (1.3), illustrating in this way the analytical results presented in theorem 3.1.

We proceed the proof of theorem 3.1 by auxiliary results.

**Lemma 3.2.** Under the assumptions of theorem 3.1, the solution $(u(x, t), \xi(t))$ of problem (1.2)–(1.4) satisfies
\[
\xi(t) \int_{\Omega} u^2(x, t) \, dx \geq \lambda \kappa_0 \quad \text{and} \quad 0 < \xi(t) \leq (1 - \lambda) \kappa_0
\]  
for all \( t \geq 0 \).

**Proof.** By the first inequality in (3.4) and by the continuity of the solution \((u, \xi)\) (see proposition 2.1), there exists \( T_1 > 0 \) such that
\[
\int_{\Omega} u^2(x, t) \, dx - \frac{\lambda \kappa_0}{\xi(t)} > 0 \quad \text{for} \quad 0 \leq t < T_1.
\]  
(3.9)

Suppose that
\[
\int_{\Omega} u^2(x, T_1) \, dx - \frac{\lambda \kappa_0}{\xi(T_1)} = 0.
\]  
(3.10)

First, notice that using (3.9) in equation (1.3) we obtain the differential inequality \( \xi \leq -\xi + (1 - \lambda) \kappa_0 \). This implies \( \xi(t) \leq (1 - \lambda) \kappa_0 \) for \( 0 \leq t \leq T_1 \) due to the assumption (3.4). Thus, we obtain from (3.9) and (3.3) the following estimate
\[
\int_{\Omega} u^2(x, t) \, dx \geq \frac{\lambda \kappa_0}{\xi(t)} \geq \frac{\lambda}{1 - \lambda} \geq 1 \quad \text{for} \quad 0 \leq t \leq T_1.
\]  
(3.11)

Next, multiplying equation (1.2) by \( u \) and integrating it over \( \Omega \) results in the equation
\[
\frac{1}{2} \frac{d}{dt} \int_{\Omega} u^2(x, t) \, dx = \int_{\Omega} \left( \frac{au(x, t) \xi(t)}{1 + u(x, t) \xi(t)} - d \right) u^2(x, t) \, dx.
\]  
(3.12)

Hence, by a direct calculation involving equations (3.12) and (1.3), we obtain the identity
\[
\frac{d}{dt} \left[ \int_{\Omega} u^2(x, t) \, dx - \frac{\lambda \kappa_0}{\xi(t)} \right] = 2(a - d) \int_{\Omega} u^2(x, t) \, dx - 2a \int_{\Omega} \frac{u^2(x, t)}{1 + u(x, t) \xi(t)} \, dx
\]
\[
- \lambda \frac{\kappa_0}{\xi(t)} - \lambda \frac{\kappa_0}{\xi(t)} \int_{\Omega} u^2(x, t) \, dx + \lambda \left( \frac{\kappa_0}{\xi(t)} \right)^2.
\]  
(3.13)

Here, using a minor rearrangement of terms on the right-hand side and the following simple inequalities (which are valid because the solution is nonnegative and because \(|\Omega| = 1\))
\[
\int_{\Omega} \frac{u^2(x, t)}{1 + u(x, t) \xi(t)} \, dx \leq \frac{1}{\xi(t)} \int_{\Omega} u(x, t) \, dx \leq \frac{1}{\xi(t)} \left( \int_{\Omega} u^2(x, t) \, dx \right)^{1/2},
\]
we obtain the lower bound
\[
\frac{d}{dt} \left[ \int_{\Omega} u^2(x, t) \, dx - \frac{\lambda \kappa_0}{\xi(t)} \right] \geq - \left( \frac{\kappa_0}{\xi(t)} - 1 \right) \left[ \int_{\Omega} u^2(x, t) \, dx - \frac{\lambda \kappa_0}{\xi(t)} \right]
\]
\[
+ (2(a - d) - 1) \int_{\Omega} u^2(x, t) \, dx
\]
\[
+ (1 - \lambda) \frac{\kappa_0}{\xi(t)} \int_{\Omega} u^2(x, t) \, dx - \frac{2a}{\xi(t)} \left( \int_{\Omega} u^2(x, t) \, dx \right)^{1/2}.
\]

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In this inequality, the second term on the right-hand side is nonnegative by the assumption (3.1). So is the difference of last two terms on the right-hand side, because $\int_{\Omega} u^2(x, t) \, dx \geq 1$ (see (3.11)) and because $(1 - \lambda)\kappa_0 z - 2u^{1/2}_\lambda \geq 0$ for all $z \geq 1$ if $\lambda \leq 1 - 2\kappa_0/\kappa_0$.

Therefore, for $0 \leq t \leq T_1$, we have the differential inequality

$$\frac{d}{dt} \left[ \int_{\Omega} u^2(x, t) \, dx - \lambda \frac{\kappa_0}{\xi(t)} \right] \geq - \left( \frac{\kappa_0}{\xi(t)} - 1 \right) \left[ \int_{\Omega} u^2(x, t) \, dx - \lambda \frac{\kappa_0}{\xi(t)} \right],$$

which for $\xi(t) > 0$ leads to the estimate

$$\int_{\Omega} u^2(x, t) \, dx - \lambda \frac{\kappa_0}{\xi(t)} \geq e^{-\left( \max_{t \in [t_0, t]} \xi(t) - 1 \right) t} \left[ \int_{\Omega} u_0^2(x) \, dx - \lambda \frac{\kappa_0}{\xi_0} \right] > 0.$$

This inequality for $t = T_1$ contradicts identity (3.10). Hence, we have completed the proof of inequalities (3.8) for all $t \geq 0$.

Now, let us emphasize the following immediate consequence of lemma 3.2.

**Corollary 3.3.** Let the assumptions of lemma 3.2 hold true. Denote by $x_* \in \Omega$ a point of the maximum of $u_0$, namely, $u_0(x_*) = \max_{x \in \Omega} u_0(x)$. Then

$$u^2(x_*, t) \geq \int_{\Omega} u^2(x, t) \, dx \geq 1 \quad \text{for all } t > 0. \quad (3.14)$$

**Proof.** First inequality in (3.14) holds true because $|\Omega| = 1$. The second one results immediately from inequalities (3.8) in the same way as in the proof of (3.11).

**Lemma 3.4.** Let the assumptions of theorem 3.1 hold true. Choose $x_* \in \Omega_*$ (hence $u_0(x_*) = \max_{x \in \Omega} u_0(x)$) and suppose that $u_* (t) \equiv u(x_*, t) = \max_{x \in \Omega} u(x, t)$ is a bounded function of $t \in [0, \infty)$. Then, for each $x \in \Omega$ such that $u_0(x) < u_0(x_*)$ it holds $u(x, t) \to 0$ exponentially as $t \to \infty$.

**Proof.** The equality $u(x_*, t) = \max_{x \in \Omega} u(x, t)$ for all $t \geq 0$ has been already justified in remark 2.2. If $u_*(t)$ is a bounded function, there exists a constant $R_1 > 0$ such that $u_*(t) \leq R_1$ for all $t > 0$. Thus, we have $\int_{\Omega} u^2(x, t) \, dx \leq R_1^2$ for all $t > 0$ (because $|\Omega| = 1$). Hence, using equation (1.3) we obtain the differential inequality $\xi \geq -(1 + R_1^2)\xi + \kappa_0$, which implies the lower bound

$$\xi(t) \geq \min \left\{ \xi_0, \frac{\kappa_0}{1 + R_1^2} \right\} \equiv R_2 \quad \text{for all } t \geq 0. \quad (3.15)$$

Now, for simplicity of notation, we denote $u = u(x, t)$ and $u_* = u(x_*, t)$. Hence, by a direct calculation involving equation (1.2), we obtain

$$\frac{\partial}{\partial t} \left( \frac{u}{u_*} \right) = -\frac{u}{u_*} \left( \frac{u_* \xi(1 - u/u_*)}{(1 + u\xi)(1 + u_* \xi)} \right). \quad (3.16)$$

This differential equation for the function $w = u/u_*$ implies the inequalities

$$w(t) = \frac{u(x, t)}{u(x_*, t)} \leq w(0) = \frac{u(x_*, 0)}{u(x_*, 0)} < 1 \quad \text{for all } t \geq 0. \quad (3.17)$$
Moreover, using the estimate $u_\ast(t) \geq 1$ for all $t \geq 0$ (see corollary 3.3), inequality (3.15), the bound $\xi(t) \leq \kappa_0$ (see (3.8)), and the estimate

$$(1 + u_\ast \xi)(1 + u_\ast \xi) \leq (1 + R_1 \kappa_0)^2$$

we obtain the differential inequality

$$\frac{\partial}{\partial t} \left( \frac{u}{u_\ast} \right) \leq -\frac{d u}{u_\ast} \left( \frac{R_2 (1 - u_0(x)/u_0(x_\ast))}{(1 + R_1 \kappa_0)^2} \right)$$

(3.18)

which implies the exponential decay in $t$ of $u/u_\ast$, because $u_0(x)/u_0(x_\ast) < 1$. However, since we assume that $u_\ast$ is bounded, we obtain immediately the exponential decay of $u = u(x,t)$. \hfill \Box

We are in a position to complete the proof of our first theorem.

Proof of theorem 3.1. Suppose that $u = u(x,t)$ is bounded on $\Omega \times [0, \infty)$. Thus, by lemma 3.4, we have got $u(x,t) \to 0$ as $t \to \infty$ for every $x \in \Omega \setminus \Omega_*$. In particular, applying the Lebesgue dominated convergence theorem we have $\int_{\Omega} u^2(x,t) \, dx \to 0$ as $t \to \infty$, because $|\Omega_*| = 0$. This is, however, in contradiction with the inequality in corollary 3.3. Hence, we conclude that $u_\ast(t) = \max_{x \in \Omega} u(x,t)$ is unbounded for $t \in [0, \infty)$.

Assume a contrario that $\sup_{t>0} u(x_1,t) = +\infty$ for some $x_1 \notin \Omega_*$. By the continuity of the initial datum $u_0$, the set $\Omega_1 \equiv \{ x \in \Omega : u_0(x_1) < u_0(x) < u_0(x_\ast) \}$ has a positive Lebesgue measure. Moreover, using differential equations for $w_1(x,t) = u(x_1,t)/u(x,t)$ and for $w_2(x,t) = u(x,t)/u(x_\ast,t)$, analogous to that one in (3.16), we obtain (in the same way as in the proof of inequalities (3.17)) that

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

These inequalities lead to a contradiction with the boundedness of the mass (2.2), because

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

Thus, we have proved that

$$\sup_{t>0} u(x,t) < \infty \quad \text{for each } \ x \in \Omega \setminus \Omega_*.$$ 

(3.19)

Next, suppose that there is a constant $\xi_1 > 0$ such that $\xi(t) \geq \xi_1$ for all $t > 0$. Since we assume $a > d$ and since we have proved already that $\sup_{t>0} u(x,t) = \infty$, we may find $t_1 > 0$ and $\delta > 0$ such that

$$\frac{a u(x_\ast,t_1) \xi_1}{1 + u(x_\ast,t_1) \xi_1} - d > \delta.$$ 

(3.20)

By the continuity of $u(x,t)$, inequality (3.20) holds true at $t_1$ and in a neighborhood $\mathcal{U} \subset \Omega$ of $x_\ast$, such that $|\mathcal{U}| > 0$. Moreover, using equation (1.2) we immediately obtain the differential inequality

$$u_t(x,t) \geq \left( \frac{a u(x,t) \xi_1}{1 + u(x,t) \xi_1} - d \right) u(x,t) \quad \text{for all } x \in \mathcal{U} \text{ and } t > 0,$$

which together with inequality (3.20) imply
\[ u_t(x, t) \geq \delta u(x, t) \quad \text{for all } x \in \mathcal{U} \text{ and } t \geq t_1. \]

Hence, we have got the estimate \( u(x, t) \geq e^{\delta t} u(x, t_1) \) for all \( x \in \mathcal{U} \) and \( t \geq t_1 \), which contradicts the boundedness of the mass (2.2), because the Lebesgue measure of \( \mathcal{U} \) is greater than zero. This contradiction means that necessarily \( \inf_{t \geq 0} \xi(t) = 0 \). \( \square \)

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Appendix A. Derivation of the nonlocal system

In this part of this paper, we show that solutions of the system

\[ u_t = f(u, \xi), \quad \xi_t = \int_{\Omega} g(u(x, t), \xi(t)) \, dx \quad \text{for } x \in \Omega, \quad t > 0, \]

with arbitrary \( C^1 \)-functions \( f = f(u, \xi) \) and \( g = g(u, \xi) \) and supplemented with the initial conditions

\[ u(\cdot, 0) = u_0 \in L^\infty(\Omega), \quad \xi(0) = \xi_0 \in \mathbb{R}, \]

are limits of solutions to reaction-diffusion-ODE systems (1.1) when \( D \to \infty \).

First, however, we recall certain properties of the heat semigroup.

Lemma A.1. Let \( \{e^{tD\Delta}\}_{t \geq 0} \) be the heat semigroup with the Neumann boundary condition in a bounded domain \( \Omega \subset \mathbb{R}^n \) with a smooth boundary and such that \(|\Omega| = 1\).

i. For every constant \( C \in \mathbb{R} \), we have \( e^{tD\Delta}C = C \) for all \( t \geq 0 \).

ii. For every \( w_0 \in L^1(\Omega) \) there exists a number \( C(\|w_0\|_1) > 0 \) independent of \( D > 0 \) such that we have

\[ \sup_{r \geq 0} \left( r^{n/2} \left\| e^{tD\Delta} \left( w_0 - \int_{\Omega} w_0 \, dx \right) \right\|_\infty \right) \leq C(\|w_0\|_1)D^{-n/2} \]

for all \( D > 0 \).

iii. Let \( q > n/2 \) and \( T > 0 \). There exists a number \( C = C(q, T) > 0 \) such that for every \( R \in L^\infty([0, T], L^q(\Omega)) \) satisfying \( \int_{\Omega} R(x, t) \, dx = 0 \) for each \( t \in [0, T] \) we have

\[ \sup_{0 \leq t \leq T} \left( r^{q/2} \int_0^t \left\| e^{(t-s)D\Delta} R(s) \right\|_\infty \, ds \right) \leq CD^{-1} \sup_{r \in [0, T]} \|R(\cdot, t)\|_q. \]

Proof. The first part of this lemma is well-known because every constant \( C \in \mathbb{R} \) is a solution of the heat equation in a bounded domain with the Neumann boundary conditions.
To show the second part, we recall the following estimate (see e.g. [39, p 25] and [1, proposition 12.5]) of the heat semigroup with the Neumann boundary conditions: each 
\[ 1 \leq q \leq p \leq \infty \] and every \( z_0 \in L^q(\Omega) \) such that \( \int_\Omega z_0 \, dx = 0 \), we have
\[
\| e^{t\Delta} z_0 \|_p \leq C \left( 1 + (tD)^{-\left(\frac{n}{2}\right)\left(\frac{1}{q-1/p}\right)} \right) e^{-\lambda_1 t} \| z_0 \|_q
\] \quad (A.6)
for all \( t > 0 \), where \( \lambda_1 > 0 \) denotes the first nonzero eigenvalue of \(-\Delta\) in \( \Omega \) under the Neumann boundary conditions and the number \( C > 0 \) is independent of \( t, D \), and \( z_0 \). We use inequality (A.6) with \( z_0 = w_0 - \int_\Omega w_0 \, dx \) in the following way:
\[
\left\| e^{t\Delta} \left( w_0 - \int_\Omega w_0 \, dx \right) \right\|_\infty \leq C \left( 1 + (tD)^{-\frac{n}{2}} \right) e^{-\lambda_1 t} \left\| w_0 - \int_\Omega w_0 \, dx \right\|_1
\] \quad (A.7)
for all \( t > 0 \) and a constant \( C > 0 \) independent of \( t, D \), and \( w_0 \). Since
\[
\sup_{\tau > 0} \left( \tau^{\frac{p}{2}} \left( 1 + (tD)^{-\frac{n}{2}} \right) e^{-\lambda_1 \tau} \right) = D^{-\frac{n}{2}} \sup_{s > 0} \left( s^{\frac{p}{2}} \left( 1 + s^{-\frac{n}{2}} \right) e^{-\lambda_1 s} \right) < \infty,
\]
we obtain immediately estimate (A.4).

For the third part, we apply the heat semigroup estimate (A.6) with \( p = \infty \) and with fixed \( q > n/2 \) to obtain the inequality
\[
\int_0^t \left\| e^{(t-s)\Delta} R(s) \right\|_\infty \, ds \leq C \left( \sup_{t \in [0,T]} \| R(t) \|_q \right) \int_0^t \left( 1 + (t-s)D \right)^{-\frac{n}{2}} e^{-\lambda_1 (t-s)} \, ds.
\]
Since \( n/(2q) < 1 \), by a change of variables, we can easily find a finite number \( C = C(T, q) > 0 \) such that
\[
\sup_{0 \leq t \leq T} \left( \int_0^t \left( 1 + (t-s)D \right)^{-\frac{n}{2}} e^{-\lambda_1 (t-s)} \, ds \right) \leq CD^{-1}.
\]
\[ \blacksquare \]

**Theorem A.2.** Let \( f \) and \( g \) be arbitrary \( C^1 \)-nonlinearities and let \( \Omega \subset \mathbb{R}^n \) be a bounded domain with a smooth boundary and such that \( |\Omega| = 1 \). Fix arbitrary \( u_0, v_0 \in L^\infty(\Omega) \) and \( T > 0 \). Assume that, for each \( D > 0 \), the couples \((u^D, v^D)\) are solutions of the initial-boundary value problem
\[
\begin{align*}
  u_t^D &= f(u^D, v^D), & v_t^D &= D\Delta v^D + g(u^D, v^D) & \quad & \text{in } \Omega \quad (A.8) \\
  u^D(x, 0) &= u_0(x), & v^D(x, 0) &= v_0(x) & \quad & \text{in } \Omega \quad (A.9) \\
  \partial_n v^D &= 0 & \quad & \text{on } \partial \Omega \quad (A.10)
\end{align*}
\]
on the common time interval \( [0,T] \). Suppose that
\[
\sup_{D > 0} \left( \sup_{0 \leq t \leq T} \| u^D(t) \|_\infty + \sup_{0 \leq t \leq T} \| v^D(t) \|_\infty \right) < \infty. \quad (A.11)
\]

Then, for each \( t_0 \in (0, T) \),
\[
\lim_{D \to \infty} \sup_{0 \leq t \leq T} \left( \|u^D(t) - u(t)\|_\infty + \|v^D(t) - \xi(t)\|_\infty \right) = 0,
\]

where \((u, \xi)\) is a solution of the nonlocal system (A.1) and (A.2) with \(\xi_0 = \int_\Omega v_0(x) \, dx\).

**Proof.** A solution of the initial-boundary value problem (A.8)–(A.10) satisfies the system of the integral equations

\[
\begin{align*}
  u^D(t) &= u_0 + \int_0^t f(u^D(s), v^D(s)) \, ds, \\
  v^D(t) &= e^{tD\Delta} v_0 + \int_0^t e^{(t-s)D\Delta} g(u^D(s), v^D(s)) \, ds.
\end{align*}
\]

Subtracting from these equations an analogous integral representation of \((u, \xi)\) (see equations (B.4) and (B.5) below) and calculating the \(L^\infty\)-norm we obtain the inequalities

\[
\begin{align*}
  &\|u^D(t) - u(t)\|_\infty \leq \int_0^t \|f(u^D(s), v^D(s)) - f(u(s), \xi(s))\|_\infty \, ds, \\
  &\|v^D(t) - \xi(t)\|_\infty \leq \left\| e^{tD\Delta} \left( v_0 - \int_\Omega v_0(x) \, dx \right) \right\|_\infty \\
  &\quad + \int_0^t \left\| e^{(t-s)D\Delta} \left( g(u^D(s), v^D(s)) - \int_\Omega g(u^D(s), v^D(s)) \, dx \right) \right\|_\infty \, ds \\
  &\quad + \int_0^t \int_\Omega |g(u^D(s), v^D(s)) - g(u(s), \xi(s))| \, dx \, ds.
\end{align*}
\]

Here, we have applied part i of lemma A.1 with \(C = \int_\Omega g(u^D(s), v^D(s)) \, dx\).

Using the Taylor expansion and assumption (A.11), we find a constant \(C\) independent of \(D\) and of \(s\) such that

\[
\|f(u^D(s), v^D(s)) - f(u(s), \xi(s))\|_\infty \leq C \left( \|u^D(s) - u(s)\|_\infty + \|v^D(s) - \xi(s)\|_\infty \right)
\]

and

\[
\|g(u^D(s), v^D(s)) - g(u(s), \xi(s))\|_\infty \leq C \left( \|u^D(s) - u(s)\|_\infty + \|v^D(s) - \xi(s)\|_\infty \right).
\]

Consequently, we obtain the estimate

\[
Y(t) \leq A(t) + C \int_0^t Y(s) \, ds \quad \text{for all} \quad t \in [0, T] \tag{A.12}
\]

where

\[
Y(t) = \left( \|u^D(t) - u(t)\|_\infty + \|v^D(t) - \xi(t)\|_\infty \right)
\]

and

\[
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\]
Now, given $t_0 \in (0, T)$ we choose arbitrary $\varepsilon \in (0, t_0)$ and we obtain the following estimate from (A.12)

$$Y(t) \leq A_{D, \varepsilon, T} + C \varepsilon \sup_{s \in [0, \varepsilon]} Y(s) + C \int_{\varepsilon}^{t} Y(s) \, ds \quad \text{for all} \quad t \in [\varepsilon, T].$$

with $A_{D, \varepsilon, T} = \sup_{t \in [\varepsilon, T]} A(t)$. Thus, the Gronwall lemma implies

$$Y(t) \leq \left( A_{D, \varepsilon, T} + C \varepsilon \sup_{s \in [0, \varepsilon]} Y(s) \right) e^{C(T - \varepsilon)} \quad \text{for all} \quad t \in [\varepsilon, T]. \quad (A.13)$$

By lemma A.1, items ii and iii, we have got $\lim_{D \to \infty} A_{D, \varepsilon, T} = 0$. It follows from assumption (A.11) that the quantity $\sup_{s \in [0, \varepsilon]} Y(s)$ is bounded uniformly in $D > 0$ and in $\varepsilon > 0$. Hence, by inequality (A.13), we may conclude that $\lim_{D \to \infty} \sup_{t \in [\varepsilon, T]} Y(t) = 0$, because $\varepsilon \in (0, t_0)$ can be arbitrary small. \hfill \Box

**Remark A.3 (Shadow-type limit for the model of early carcinogenesis).** It is rather standard to show that the following initial-Neumann boundary value problem for the reaction-diffusion-ODE system

$$
\begin{align*}
    u_t &= \left( \frac{a u v}{1 + uv} - d \right) u \\ 
    \nu_t &= D \Delta \nu - v - u \nu^2 + \kappa_0 \\ 
    \partial_n \nu(x, t) &= 0 \\ 
    u(x, 0) &= u_0(x) \geq 0 \\ 
    \nu(x, 0) &= \nu_0(x) \geq 0
\end{align*}
$$

(A.14)

has a unique global-in-time solution for each $D > 0$ and every initial condition $u_0, \nu_0 \in L^\infty(\Omega)$. For the proof of this claim, it suffices to follow the reasoning from papers [21, section 3] and [22], where such models have been discussed in detail. Now, for a fixed initial datum $u_0, \nu_0 \in L^\infty(\Omega)$, we are going to show that the family of solutions $(u, \nu) = (u^D, \nu^D)$ of problem (A.14) is uniformly bounded with respect to $D > 0$ on each finite time interval $[0, T]$, as required in condition (A.11). Indeed, applying to first equation in (A.14) the inequality $uv/(1 + uv) \leq 1$ (valid for every nonnegative solution $(u, \nu)$) we obtain the differential inequality $u_t \leq (a - d)u$ which implies the estimate

$$0 \leq u(x, t) \leq u_0(x) e^{(a - d) t} \quad \text{for all} \quad x \in \Omega, \quad t > 0. \quad (A.15)$$

Next, by a comparison principle for parabolic equations, we obtain that $\nu(x, t)$ can be estimated from above by a solution $\bar{\nu} = \bar{\nu}(t)$ of the Cauchy problem

$$
\frac{d}{dt} \bar{\nu} = -\bar{\nu} + \kappa_0, \quad \bar{\nu}(0) = \|\nu_0\|_\infty.
$$
Hence,

\[
0 \leq v(x, t) \leq \bar{v}(t) \leq \max\{\kappa_0, \|v_0\|_{\infty}\} \quad \text{for all } x \in \Omega, \ t > 0.
\]  

(A.16)

Both estimates (A.15) and (A.16) imply that the assumption (A.11) hold true. Hence, by theorem A.2, solutions of the initial boundary value problem (A.14) converge as \(D \to \infty\) toward the solution of problem (1.2)–(1.4) with \(\xi_0 = \int_{\Omega} v_0(x) \, dx\).

**Remark A.4.** It is well-known that for a system of two reaction-diffusion equations

\[
\begin{align*}
    u_t &= \varepsilon \Delta u + f(u, v), \\
    v_t &= D \Delta v + g(u, v),
\end{align*}
\]

(A.17)

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 (1.6)) 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* and it is an example of a model with nonlocal kinetics. Shadow systems have been introduced by Keener [13] and their properties have been established e.g. in [8, 13, 32, 34]. Analysis of shadow systems has provided insights into dynamics of the activator-inhibitor model and of other reaction-diffusion models under certain conditions [8]. The necessity of the conditions given in [8] is highlighted by showing discrepancies between the dynamics of a shadow system and the corresponding reaction-diffusion system in [17], i.e. blow-up in finite time versus global existence. Let us emphasize that, in this work, we consider the shadow approximation of system (A.17) 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.

**Appendix B. Instability of stationary solutions**

A study of the general nonlocal initial value problem for the system (1.5) and (1.6), namely,

\[
\begin{align*}
    u_t &= f(u, \xi), \\
    \xi_t &= \int_{\Omega} g(u(x, t), \xi(t)) \, dx \quad \text{for } t > 0,
\end{align*}
\]

(B.1)

\[
\begin{align*}
    u(x, 0) &= u_0(x), \\
    \xi(0) &= \xi_0
\end{align*}
\]

(B.3)

should begin by noticing that it has a unique local-in-time solution for every \(u_0 \in L^\infty(\Omega)\), \(\xi_0 \in \mathbb{R}\), and for arbitrary locally Lipschitz nonlinearities \(f = f(u, \xi)\) and \(g = g(u, \xi)\). For the proof of this claim, it suffices to apply the Banach fixed point theorem to the following integral formulation of problem (B.1)–(B.3)

\[
\begin{align*}
    u(x, t) &= u_0(x) + \int_0^t f(u(x, s), \xi(s)) \, ds, \\
    \xi(t) &= \xi_0 + \int_0^t \int_{\Omega} g(u(x, s), \xi(s)) \, dx \, ds
\end{align*}
\]

(B.4)

(B.5)
in order to obtain a solution \( u \in C([0, T], L^\infty(\Omega)) \) and \( \xi \in C([0, T]) \) for some \( T > 0 \) depending on initial conditions and on nonlinearities. Then, a classical argument applied to system (B.4) and (B.5) allows us to show that, in fact, \( u(x, \cdot), \xi(\cdot) \in C^1([0, T]) \) for every \( x \in \Omega \). Moreover, if \( u_0 \in C(\Omega) \), then \( u \in C([0, T] \times \Omega) \) (see e.g. [46, chapter 3] for results on differential equations in Banach spaces).

Our goal in this part of appendix is to study stability properties of stationary solutions of the general nonlocal system (B.1) and (B.2). Here, a couple \((U, \xi) \in L^\infty(\Omega) \times \mathbb{R}\) is called a stationary solution if

\[
f(U(x), \xi) = 0 \quad \text{almost everywhere in } \Omega, \tag{B.6}
\]

\[
\int_\Omega g(U(x), \xi) \, dx = 0. \tag{B.7}
\]

Now, if equation (B.6) 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 \( \Omega \). This is indeed the case of the particular model of early carcinogenesis discussed by us in section 2.2, where a characterization of all stationary solutions is possible.

Our main result on stationary solutions to the nonlocal system (B.1) and (B.2) provides a simple and natural condition under which a steady state is unstable.

**Theorem B.1 (Instability of stationary solutions).** Let \( f = f(u, \xi) \) and \( g = g(u, \xi) \) be arbitrary \( C^2 \)-functions. Assume that there exists \( \Omega_1 \subset \Omega \) with \(|\Omega_1| > 0\), a constant \( \bar{u} \in \mathbb{R} \), and a solution \((U, \xi)\) of system (B.6) and (B.7) such that \( U(x) = \bar{u} \) for all \( x \in \Omega_1 \). If the autocatalysis condition holds, i.e. if

\[
f_u(\bar{u}, \xi) > 0, \tag{B.8}
\]

then \((U, \xi)\) is an unstable solution (in the Lyapunov sense) of the nonlocal problem (B.1)–(B.3).

**Remark B.2.** The autocatalysis assumption (B.8) is a condition typical for models exhibiting Turing instability. Indeed, we have shown in our recent work [22] that it is satisfied in the case of nonlinearities from well-known models in mathematical biology as well as it has to be satisfied (in some sense) in all models with the Turing instability. Thus, in the considered class of models, the Turing-type mechanism destabilizes not only constant steady states but also non-constant stationary solutions. A similar mechanism, where DDI destabilizes all non-constant stationary solutions of reaction-diffusion-ODE of the form (1.1), has been recently studied in our papers [21, 22].

**Proof of theorem B.1.** In conformity with regular practice, we consider an initial value problem for the perturbation \( w(x, t) = u(x, t) - U(x) \) and \( \eta(t) = \xi(t) - \xi \), where \((u, \xi)\) is a solution of the nonlocal problem (B.1)–(B.3) and \((U, \xi)\) is a stationary solution satisfying the assumptions of theorem B.1. Thus, the couple \( z = (w, \eta)\) is a solution of the initial value problem

\[
z_t = \mathcal{L}z + \mathcal{N}(z), \quad z(0) = z_0 \equiv (u_0 - U, \xi_0 - \xi), \tag{B.9}
\]

where

\[
\mathcal{L}z = \mathcal{L}
\left(
\begin{array}{c}
w(x) \\
\eta
\end{array}
\right)
\equiv
\left(
\begin{array}{c}
f_u(U(x), \xi) w(x) + f_\xi(U(x), \xi) \eta \\
\int_\Omega g_u(U(x), \xi) w(x) \, dx + \int_\Omega g_\xi(U(x), \xi) \eta \, dx
\end{array}
\right) \tag{B.10}
\]
and $\mathcal{N}$ is a nonlinear term obtained in a usual way via the Taylor expansion from the nonlinearities in system (B.1) and (B.2).

The linear operator $\mathcal{L} : L^\infty(\Omega) \times \mathbb{R} \to L^\infty(\Omega) \times \mathbb{R}$ is bounded, hence, it generates a strongly continuous semigroup (in fact, a group) of linear operators on the Banach space $X = L^\infty(\Omega) \times \mathbb{R}$ equipped with the usual norm $\| (w, \eta) \|_X \equiv \| w \|_{L^\infty(\Omega)} + | \eta |$.

Now, we show that the number $\lambda_0 = f_u(u, \xi) > 0$ (cf. assumption (B.8)) is an eigenvalue of $\mathcal{L}$. To do it, it suffices to check that $\tilde{z} = (w_0, 0)$ is the corresponding eigenvector for every non-trivial $w_0 \in L^\infty(\Omega)$ satisfying $\int_{\Omega_1} w_0(x) \, dx = 0$ and $w_0(x) = 0$ for all $x \in \Omega \setminus \Omega_1$. One can always construct such bounded, non-trivial function $w_0$ due to the condition $|\Omega_1| > 0$. Thus, by the assumptions on $U(x)$, we have

$$\int_{\Omega} g_u(U(x), \xi) w(x) \, dx = g_u(\bar{u}, \xi) \int_{\Omega_1} w(x) \, dx = 0$$

and, consequently, we obtain $\mathcal{L}(w_0, 0)^T = \lambda_0(w_0, 0)^T$.

Finally, since $U$ is a bounded function, using the Taylor expansion of the $C^2$-functions $f = f(u, \xi)$ and $g = g(u, \xi)$ we find two constants $R > 0$ and $C > 0$ such that the the nonlinear term $\mathcal{N}$ in (B.9) satisfies $\| \mathcal{N}(z) \|_X \leq C \| z \|_X^2$ for all $\| z \|_X \leq R$.

We have thus checked all assumptions of [40, theorem 1] which assure that the zero solution of the initial value problem (B.9) is nonlinearly unstable in the Laypunov sense.

\section*{Appendix C. Blow-up of solutions in finite time}

A nonlocal effect caused by the integral over $\Omega$ in system (1.5) and (1.6) may lead not only to the instability of steady states, but also to a blow-up of space-heterogeneous solutions, even in the case when space homogeneous solutions are global-in-time and uniformly bounded on the time half-line $[0, \infty)$. In this part of Appendix, we describe this phenomenon in the case of a particular nonlocal problem with a well-known nonlinearity from mathematical biology. More precisely, we consider a nonlocal problem with the nonlinearity as in the celebrated Gray-Scott system describing pattern formation in chemical reactions [7]:

$$u_t = -(B + k)u + u^2 \xi \quad \text{for} \quad x \in \Omega, \ t > 0, \quad (C.1)$$

$$\xi_t = -\xi \int_{\Omega} u^2 \, dx + B(1 - \xi) \quad \text{for} \quad t > 0, \quad (C.2)$$

where $B$ and $k$ are positive constants. As before we assume $|\Omega| = 1$, hence, this is a particular case of system (1.5) and (1.6) with $f(u, \xi) = -(B + k)u + u^2 \xi$ and $g(u, \xi) = -\xi u^2 + B(1 - \xi)$.

Let us first formulate preliminary properties of solutions to the initial value problem for system (C.1) and (C.2).

\textbf{Proposition C.1.} System (C.1) and (C.2) supplemented with an initial condition $(u_0, \xi_0) \in L^\infty(\Omega) \times \mathbb{R}$ has a unique solution on an interval $[0, T_{\text{max}})$ with certain maximal $T_{\text{max}} \in [0, \infty]$. If $u_0 \geq 0$ almost everywhere in $\Omega$ and $\xi_0 \geq 0$, then $u(x, t) \geq 0$ almost everywhere in $\Omega$ and $\xi(t) \geq 0$ for all $t \in [0, T_{\text{max}})$. For every nonnegative $\xi_0$ we have the estimate

$$0 \leq \xi(t) \leq \max\{\xi_0, 1\} \quad \text{for all} \quad t \in [0, T_{\text{max}}). \quad (C.3)$$
We skip the proof of this proposition because it is completely analogous to the proof of proposition 2.1. Here, let us only mention that the upper bound (C.3) is an immediate consequence of the differential inequality \( \xi_t \leq B(1 - \xi) \) which is obtained from (C.2) with non-negative \( \xi(t) \).

**Remark C.2.** We skip the discussion of stability properties of stationary solutions the non-local system (C.1) and (C.2), because it is completely analogous to that one in appendix B, in the case of model (1.2) and (1.3). Here, let us only mention that piecewise constant stationary solutions exist and they are all unstable (because an autocatalysis condition is satisfied) except the trivial steady state \((U, \xi) = (0, 1)\).

Since all nontrivial stationary solutions are unstable, a question arises as to what is the long-time behavior of (large) solutions to the initial value problem for system (C.1) and (C.2).

First, we emphasize in the following corollary that space homogeneous nonnegative solutions (i.e. when \( u \) does not depend on \( x \)) are global-in-time and bounded. Here, we recall that such solutions satisfy the corresponding system of ordinary differential equations under our standing assumption \(|\Omega| = 1\).

**Proposition C.3.** All solutions \((u, \xi) = (u(t), \xi(t))\) of the following initial value problem for ordinary differential equations

\[
\frac{d}{dt}u = -(B + k)u + u^2 \xi, \quad \frac{d}{dt}\xi = -\xi u^2 + B(1 - \xi)
\]

\((C.4)\)

\[u(0) = u_0 \geq 0, \quad \xi(0) = \xi_0 \geq 0\]

\((C.5)\)

are nonnegative, global-in-time, and uniformly bounded for \( t > 0 \).

**Proof.** The proof of this proposition is completely standard if we observe that all nonnegative solutions of problem (C.4) and (C.5) satisfy the relation

\[
\frac{d}{dt}(u(t) + \xi(t)) = -(B + k)u(t) - B\xi(t) + B \leq -B(u(t) + \xi(t)) + B.
\]

Hence, as long as \( u \) and \( \xi \) stay nonnegative, the sum \( u(t) + \xi(t) \) has to be bounded on the half line \([0, \infty)\). \( \square \)

Our main result on system (C.1) and (C.2) ascertains that a space inhomogeneity of initial data may lead not only to instability but also to a blow-up in finite time of the corresponding solution.

**Theorem C.4.** Fix \( x_0 \in \Omega \) and assume that \( u_0 \in L^\infty(\Omega) \) satisfies

\[0 \leq u_0(x) < u_0(x_0) \quad \text{for all} \quad x \neq x_0\]

\((C.6)\)

and

\[A_0 \equiv \int_{\Omega} \left( \frac{u_0(x_0)u_0(x)}{u_0(x_0) - u_0(x)} \right)^2 \, dx < \infty.\]

\((C.7)\)

Assume also that

\[
\frac{1}{B + k} \min \left\{ \xi_0, \frac{B}{A_0 + b} \right\} > \frac{1}{u_0(x_0)}.
\]

\((C.8)\)
Then, the corresponding solution of system (C.1) and (C.2) supplemented with the initial conditions $u(x,0) = u_0(x)$ and $\xi(0) = \xi_0$ blows up in a finite time at $x_0$ in the following sense. There exists $T_{\text{max}} \in (0,\infty)$ such that

- the solution $(u(x,t), \xi(t))$ exists on $\Omega \times [0, T_{\text{max}})$ and it is continuous on $[0, T_{\text{max}})$ for every fixed $x \in \Omega$; $u(x_0,t)$ blows up at $T_{\text{max}}$: $u(x_0,t) \to +\infty$ as $t \to T_{\text{max}}$;
- the following estimates hold true for all $(x,t) \in (\Omega \setminus \{x_0\}) \times [0, T_{\text{max}})$:

$$0 \leq u(x,t) \leq \frac{u_0(x_0)u_0(x)e^{-t(B+k)}}{u_0(x_0) - u_0(x)} \quad \text{(C.9)}$$

and

$$\min \left\{ \frac{\xi_0 - B}{A_0 + B}, \xi_0 \right\} \leq \xi(t) \leq \max \{\xi_0, 1\} \quad \text{(C.10)}$$

Notice that, for an initial condition described in theorem C.4, the corresponding $u(x,t)$ escapes to $+\infty$ for $x = x_0$ as $t \to T_{\text{max}}$ and remains bounded for all other $x \in \Omega$. On the other hand, the function $\xi(t)$ is bounded and separated from zero on the interval $[0, T_{\text{max}})$.

**Remark C.5.** The number $A_0$ defined in (C.7) is finite if, for example, there exist constants $C > 0$ and $\ell \in (0, n/2)$ such that $u_0(x_0) - u_0(x) \geq C|x_0 - x|^\ell$ (or equivalently, $u_0(\xi) \leq u_0(x_0) - C|x_0 - \xi|^\ell$) in a neighborhood of $x_0$. If $u_0$ is a $C^2$-function and strictly concave, then we have $u_0(x_0) - u_0(x) \leq C|x_0 - x|^2$ in a neighborhood of $x_0$, because $u_0$ has a global maximum at $x_0$. Thus, the constant $A_0$ in (C.7) is finite in dimension $n \leq 4$ if $u_0$ is more 'sharp' at the maximum point $x_0$ than a $C^2$-function. However, our numerical simulations performed for a model of early carcinogenesis considered in section 2 suggest that such assumptions may not be optimal and an unbounded growth of spikes could be possible for smooth initial conditions, as well.

**Proof of theorem C.4.** By proposition C.1, the solution $(u, \xi)$ of the initial value problem for system (C.1) and (C.2) exists on a maximal time interval $[0, T_{\text{max}})$ and it is nonnegative. Moreover, the function $\xi(t)$ satisfies the upper bound in (C.10) which is an immediate consequence of proposition C.1. For fixed $\xi$ and for each $x \in \Omega$, we solve equation (C.1) proceeding in the usual way: first, one should check that $w(x,t) = u(x,t)e^{(B+k)t}$ satisfies the ordinary differential equation $w_t = u^2\xi e^{-t(B+k)}$ with separate variables. Thus, the function $u$ can be expressed via $\xi$ in the following way

$$u(x,t) = \frac{e^{-t(B+k)}}{u_0(x_0) - \int_0^t \xi(s) e^{-s(B+k)} \, ds}. \quad \text{(C.11)}$$

By assumption (C.6), we have $1/u_0(x) > 1/u_0(x_0)$ for all $x \in \Omega \setminus \{x_0\}$; thus, it follows from formula (C.11) that the solution $(u(x,t), \xi(t))$ of (C.1) and (C.2) exists for all $t \in [0, T_{\text{max}})$, where

$$T_{\text{max}} = \sup \left\{ t > 0 : \int_0^t \xi(s) e^{-s(B+k)} \, ds < \frac{1}{u_0(x_0)} \right\}. \quad \text{(C.12)}$$
Our goal is to show that \( T_{\text{max}} < \infty \).

First, applying the definition of \( T_{\text{max}} \) from (C.12) in formula (C.11) we obtain the following estimate

\[
u(x, t) \leq \frac{e^{-r(B+k)}}{u_0(x_0)} = \frac{u_0(x_0)u_0(x)e^{-r(B+k)}}{u_0(x_0) - u_0(x)} \quad \text{for all} \quad (x, t) \in \Omega \times [0, T_{\text{max}})
\]

which gives inequality (C.9). Next, using this estimate of \( u(x, t) \) together with the inequality

\[e^{-r(B+k)} \leq 1\]

we deduce from equation (C.2) the differential inequality

\[
\xi_t \geq -\xi A_0 + B(1 - \xi) \quad \text{for all} \quad t \in [0, T_{\text{max}}).
\]

where the constant \( A_0 \) is defined in (C.7). This inequality for \( \xi(t) \) implies that

\[
\xi(t) \geq \min \left\{ \xi_0, \frac{B}{A_0 + B} \right\} \quad \text{for all} \quad t \in [0, T_{\text{max}}).
\]

Thus, we obtain the lower bound

\[
\int_0^t \xi(s)e^{-r(B+k)} \, ds \geq \frac{1 - e^{-r(B+k)}}{B + k} \min \left\{ \xi_0, \frac{B}{A_0 + B} \right\},
\]

where the right-hand side is equal to \( 1/u_0(x_0) \) for some \( t_0 > 0 \) under assumption (C.8). In particular, the denominator of the fraction in (C.11) is equal to zero at \( x = x_0 \) and some \( t_1 \leq t_0 \) and this completes the proof that \( T_{\text{max}} < \infty \). \( \square \)

**Remark C.6.** In particular, we provide an example, for which a nonlocal (long-range) ‘diffusion’ leads to a blow-up of space heterogeneous solutions. In this way, we identify a large class of models with the diffusion induced blow-up in the same spirit as e.g. in the works [23, 29, 37]; see also the review article [5] and the chapter [38, chapter 33.2] for other references.

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