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On a new mechanism of the emergence of spatial distributions in biological models

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ABSTRACT

Non-uniform distributions of various biological factors can be essential for tissue growth control, morphogenesis or tumor growth. The first model describing the emergence of such distributions was suggested by A. Turing for the explanation of cell differentiation in a growing embryo. In this model, diffusion-driven instability of the homogeneous in space solution appears due to the interaction of two or more morphogens described by a reaction–diffusion system of equations. In this work we suggest another mechanism of the emergence of spatial distributions in biological tissues based on local cell communication and global inhibition, and described by a nonlocal reaction–diffusion equation. Instability of the homogeneous in space solution leads to the emergence of stationary pulses and not of periodic solutions as in the case of Turing instability.

1. Introduction

Formulating the question about cell differentiation in a growing embryo, A. Turing proposed a mechanism of pattern formation in a model of two (or more) reaction–diffusion equations for the concentration of morphogens [1]. The main idea of this mechanism is that a stable stationary point of the corresponding ODE system can lose its stability due to diffusion. This instability emerges if the size of the domain is sufficiently large leading to the biological interpretation that all cells in the embryo are similar to each other if the embryo is small enough, and they begin to differentiate if its size exceeds some critical value because the distribution of the morphogens becomes non-homogeneous. Analysis of Turing (or dissipative) structures became one of the most popular topics in mathematical biology. Let us mention beautiful modeling results by H. Meinhardt on sea shell patterns [2] and animal skin models [3] among other modeling results.

In spite of the huge amount of modeling works on the subject, the biological justification of this approach, applied in particular to cell differentiation, is often problematic. Not only it is difficult to identify the corresponding morphogens but also their diffusivities should be essentially different, and they should act in a specific way which can be formulated as short range activation long range inhibition. It is likely that other mechanisms are involved in cell differentiation and pattern formation in morphogenesis.

Consenting on the beauty of this approach and its importance in mathematical biology, we will discuss in this work another mechanism of the emergence of non-homogeneous distributions in biological models in the context of tissue growth regulation. For

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simplicity of presentation we will consider a single nonlocal reaction–diffusion equation

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial x^2} + F(u, J(u)) \tag{1.1}$$

either on the whole real axis or in a bounded interval with homogeneous Neumann boundary conditions. Here

$$J(u) = \int_{-\infty}^{\infty} u(x,t)dx$$

(in case of the whole axis), and a typical example of the function F is as follows:

$$F(u, J(u)) = (a + bu)u(1 - u) - kJ(u)u.$$

More general functions will be considered in other studies. We will interpret here $u(x,t)$ as a normalized cell concentration. The diffusion term characterizes random cell motion, and the function F describes cell proliferation and death. The first term in this function (proliferation rate) is proportional to the cell density u and to the expression $(1 - u)$ signifying density-dependent proliferation. This means that increasing cell density down-regulates their division. Expression $(a + bu)$ describes the increase of proliferation rate with the increasing cell density due to cell–cell interaction (autocrine, paracrine or juxtacrine signaling [4]).

The second term in the function F describes cell death by apoptosis or other mechanisms. The death rate includes a constant factor k and the total cell density $J(u)$. This term is particularly important in the analysis below, so let us discuss it in more detail. Tissue growth is often controlled by a negative feedback by some factors (hormones, growth factors, immune system). Denote by C the level of this controlling factor in the organism (tissue), and consider the following equation:

$$\frac{dC}{dt} = k_1 J(u) - k_2 C. \tag{1.2}$$

We assume here that its production rate is proportional to the total cell density. In the case of tumor growth, for example, C corresponds to the anti-tumor immune response determined by the tumor antigens with the concentration proportional to the total tumor volume. The second term in the right-hand side of this equation describes depletion or degradation of this factor.

Assuming that these processes are fast in the time scale of cell proliferation, we use the quasi-stationary approximation for Eq. (1.2) and express $C = k_1 J(u)/k_2$. Thus, the death rate, which is proportional to Cu, can be written as $kJ(u)u$, where $k = k_1/k_2$. We do not delve here into a more detailed biological justification of the model since it should take into account specific conditions of the considered processes (e.g., tumor growth), and will use this model problem to illustrate the mechanism of pattern formation.

In the next section we will study a possible instability of the homogeneous in space solution in a bounded interval. This instability leads to the emergence of spatially distributed solutions corresponding to a pulse solution further from the stability boundary. Section 3 is devoted to the analysis of the existence and stability of pulses on the whole axis. We conclude this paper by the discussion of this mechanism of the emergence of spatially non-uniform solutions and comparison with the Turing instability.

2. Bifurcations from a homogeneous solution

We will consider in this section the stationary version of Eq. (1.1) in a bounded interval $0 < x < L$ with the boundary conditions $u'(0,t) = u'(L,t) = 0$. In order to clarify the ideas, we will begin with two particular cases. In the first one, $a = 0, b > 0$, in the second one, $a > 0, b = 0$.

First case, $a = 0$. Consider the problem

$$Dw'' + bw^2(1 - w) - kJ(w)w = 0, \quad w'(0) = w'(L) = 0, \tag{2.1}$$

where $J(w) = \int_0^L w(x)dx$. Its homogeneous in space solution w_0 is determined by the formula $w_0 = 1 - kL/b$. Linearizing the equation about this solution, we obtain the eigenvalue problem:

$$Dv'' + (2b - 3bw_0 - kL)w_0 v - kw_0 J(v) = \lambda v, \quad v'(0) = v'(L) = 0. \tag{2.2}$$

We look for the eigenfunctions in the form:

$$v_n(x) = \cos\left(\frac{\pi n x}{L}\right), \quad n = 0, 1, 2, \ldots,$$

and determine the corresponding eigenvalues:

$$\lambda_0 = -(kL - b)^2/b, \quad \lambda_n = (2kL - b)(1 - kL/b) - D\left(\frac{\pi n}{L}\right)^2, \quad n = 1, 2, 3... \tag{2.3}$$

The integral $J(v_n)$ is positive for $n = 0$ and vanishes for all other eigenfunctions. Therefore, $\lambda_0 < 0$ but $\lambda_1 > 0$ if

$$kL < b < 2kL \tag{2.4}$$

and D is sufficiently small,

$$D < \frac{L^2(2kL - b)(b - kL)}{b\pi^2}. \tag{2.5}$$

Proposition 2.1. *If conditions (2.4), (2.5) are satisfied, then the eigenvalues of problem (2.2) are such that* $\lambda_0 < 0$ *and* $\lambda_1 > 0$.

In order to better clarify the emergence of this instability, let us consider the problem

$$Dw'' + bw^2(1-w) - kLw^2 = 0, \quad w'(0) = w'(L) = 0, \tag{2.6}$$

where we replace $J(w)$ by its value Lw for the homogeneous in space solution. It has the same homogeneous in space solution $w_0 = 1 - kL/b$. The corresponding eigenvalue problem becomes as follows:

$$Dv'' + (2b - 3bw_0 - 2kL)w_0 v = \lambda v, \quad v'(0) = v'(L) = 0, \tag{2.7}$$

and the eigenvalues

$$\lambda_n^\dagger = -(kL-b)^2/b - D\left(\frac{\pi n}{L}\right)^2, \quad n = 0, 1, 2, 3... \tag{2.8}$$

These eigenvalues are decreasing with n, and

$$\lambda_0^\dagger = \lambda_0, \quad \lambda_n^\dagger < \lambda_n, \quad n = 1, 2, 3, \ldots$$

Therefore, the presence of the integral in the model changes the order of eigenvalues such that it is possible to have $\lambda_1 > 0$, while $\lambda_0 < 0$. Thus, the instability can emerge due to the nonlocal term in the equation.

Second case, $b = 0$. Consider now the problem

$$Dw'' + aw(1-w) - kJ(w)w = 0, \quad w'(0) = w'(L) = 0 \tag{2.9}$$

which differs from the previous one by the power of w in the proliferation term. The homogeneous in space solution is $w_0 = a/(a+kL)$. Proceeding as before, we consider the eigenvalue problem

$$Dv'' + (a - 2aw_0 - kLw_0)v - kw_0 J(v) = \lambda v, \quad v'(0) = v'(L) = 0, \tag{2.10}$$

and determine the eigenvalues

$$\lambda_0 = -a, \quad \lambda_n = -\frac{a^2}{a+kL} - D\left(\frac{\pi n}{L}\right)^2, \quad n = 1, 2, 3... \tag{2.11}$$

Therefore, all eigenvalues are negative. Though λ_1 can be larger than λ_0, this does not change stability of solution. Comparing the two cases, we arrive to the following conclusion.

- Instability of the homogeneous in space solution of Eq. (2.1) with respect to spatial perturbations can occur only in the presence of self-acceleration bu in the proliferation rate.

General case. If $a > 0, b > 0$, then a similar analysis gives the stationary solution of Eq. (1.1)

$$w_0 = \left(b - a - kL + \sqrt{(b-a-kL)^2 + 4ab}\right)/(2b),$$

and the eigenvalues

$$\lambda_0 = -a - bw_0^2, \quad \lambda_n = -a - bw_0^2 + kLw_0 - D\left(\frac{\pi n}{L}\right)^2, \quad n = 1, 2, 3... \tag{2.12}$$

As before, $\lambda_0 < 0$, $\lambda_1 > \lambda_0$ for D sufficiently small. It is also possible that $\lambda_1 > 0$, as it is the case for $a = 0$, but the explicit conditions on parameters become cumbersome. Numerical calculations show that λ_1 can be positive if a is smaller than some critical value.

3. Existence and stability of pulses

Bifurcation of spatially-dependent solutions from homogeneous solutions can be studied in a bounded interval but not on the whole axis. Indeed, for a positive constant solution, the integral on the whole axis is not defined. For zero constant solution, the bifurcation does not occur. In this section we will discuss the existence of spatially-dependent solutions (pulses) for $x \in \mathbb{R}$. After that we will present numerical simulations of the time-dependent problem in order to study convergence of solutions to the pulses.

3.1. Existence of pulses

We look for positive solutions of the problem

$$Dw'' + (a + bw)w(1-w) - kJ(w)w = 0, \quad w(\pm\infty) = 0 \tag{3.1}$$

on the real axis. Along with this equation, consider also the auxiliary equation

$$Dw'' + (a + bw)w(1-w) - hw = 0, \quad w(\pm\infty) = 0, \tag{3.2}$$

where we replace the unknown integral $J(w)$ by a given constant h/k. The function $F_h(w) = (a+bw)w(1-w) - hw$ can have from one to three non-negative zeros. Suppose that there are three of them, that is,

$$b > a, \quad a < h < \frac{(a+b)^2}{4b}.$$

Denote by $w_0(h)$ the maximal solution of the equation $F_h(w) = 0$. It is known that problem (3.2) has a positive solution $w_h(x)$ if and only if $\int_0^{w_0(h)} F_h(w)dw > 0$ (Appendix B). This inequality holds for $0 < h < h_*$, where $h_* = (2(a+b)^2 + ab)/(9b)$.

Equality

$$kJ(w_h) = h \tag{3.3}$$

provides a solution of problem (3.1). We will prove the existence of solution of this equation with respect to h.

Denote $w_m(h) = \max_{x\in\mathbb{R}} w_h(x)$. Then $w_m(h) < w_0(h)$. If $h \nearrow h_*$, then $w_m(h) \nearrow w_0(h)$, $w_h(x) \to w_0(h)$ uniformly in x on every bounded interval, and, consequently, $J(w_h) \to \infty$ (Appendix B).

Next, suppose that $h \searrow a$ and set $h = a + \epsilon$. Then Eq. (3.2) can be written as follows:

$$Dw'' + (b-a)w^2 - bw^3 - \epsilon w = 0. \tag{3.4}$$

Let us introduce a new function $v(y)$ by the equality $w(x) = \epsilon v(\sqrt{\epsilon}x)$. Then it satisfies the equation

$$Dv'' + (b-a)v^2 - v - b\epsilon v^3 = 0, \tag{3.5}$$

where prime denotes the derivative with respect to y. If $b > a$ and ϵ is sufficiently small, then the conditions for the pulse existence are satisfied (Appendix B), and this equation has a positive solution $v_\epsilon(y)$ vanishing at infinity. Then

$$J(w_h) = \int_{-\infty}^{\infty} w_h(x)dx = \epsilon \int_{-\infty}^{\infty} v_\epsilon(\sqrt{\epsilon}x)dx = \sqrt{\epsilon}\int_{-\infty}^{\infty} v_\epsilon(y)dy \sim \sqrt{\epsilon}\int_{-\infty}^{\infty} v_0(y)dy \to 0$$

as $\epsilon \to 0$. Here we use the fact that the integral of solution is a continuous function of ϵ (Appendix B).

Thus, $J(w_h) = 0$ for $h = a > 0$ and $J(w_h) \to \infty$ as $h \to h_*$. Since it is a continuous function, then Eq. (3.3) has a solution for some $h \in (a, h_*)$. We proved the following theorem.

Theorem 3.1. *If $b > a > 0$, then problem (3.1) has a positive solution.*

This result does not allow us to determine the number of solutions. If we consider non-degenerate solutions of Eq. (3.3), that is, $dJ(w_h)/dh \neq 1$ at the intersection points, then the number of solutions is odd. It is interesting to note that in another nonlocal equation considered in [5], the number of solutions is even (zero or two). Another remark concerns the condition $b > a$. If it is not satisfied, then the function F_h has at most two non-negative zeros, and the pulse does not exist. Finally, if $a = 0$, then $J(w_h) = 0$ for $h = 0$, and existence of solution of Eq. (3.3) does not follow from the intermediate value theorem. Since $J(w_h) \sim \sqrt{h}$, we can expect that it has a solution for k small enough.

3.2. Stability of pulses

If spatially homogeneous solution in a bounded interval loses its stability, then a non-homogeneous solution bifurcates from it. Stability of the bifurcating solutions follows from the topological degree theory (see, e.g., [5], Vol. 1, p. 522). Stability of this solution far from the bifurcation point and stability of pulses on the whole axis are not proved. Let us recall that pulses are unstable for the conventional local bistable equation. We make a conjecture that pulses described by Eq. (1.1) are stable (or some of them in the case of non-uniqueness) due to the presence of the integral $J(u)$ in the equation. We will verify this conjecture in numerical simulations.

We consider Eq. (1.1) in a bounded and sufficiently large interval with the Neumann boundary conditions. The results of numerical simulations can be summarized as follows.

- If $b > a > 0$, then solution $u(x,t)$ of this problem converges to the pulse solution for any non-negative initial condition $u_0(x) \not\equiv 0$. It is interesting to note that even small initial conditions provide convergence of solution to the pulse solution (Fig. 1, left), though this is not usually the case for the bistable equation for which the solution with a small initial condition converges to zero. If $J(u_0)$ is small enough, then the nonlinearity is monostable providing growth of solution and, respectively, of the integral $J(u)$. When this integral becomes sufficiently large, then the nonlinearity becomes bistable. Thus, equation changes its type in time due to the presence of the integral.

- If $a > b \geq 0$, then solution $u(x,t)$ of this problem uniformly converges to 0, while $J(u)$ converges to some positive constant (Fig. 1, right). In order to explain this behavior (this is not a rigorous proof), consider the case $b = 0$. Integrating the equation on the whole interval and neglecting the quadratic term (for small u), we obtain that $J(u) \to a/k$ as $t \to \infty$. However, if we replace $J(u)$ by a/k in the equation, the nonlinearity becomes negative and the solution converges to 0.
- If $a = 0, b > 0$, then behavior of solution depends on the constant k and the choice of initial condition. It can either converge to zero or to the pulse. More detailed results will be presented elsewhere.

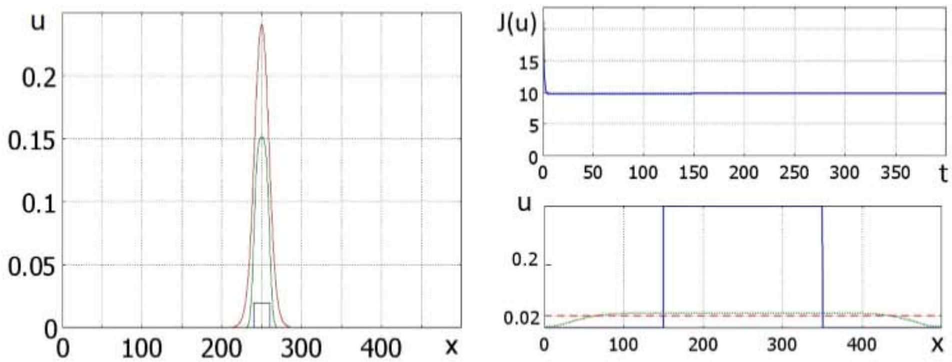

Fig. 1. Left: solution of Eq. (1.1) converges to the stationary pulse solution. Initial condition is a small function with support at the center of the interval. The values of parameters: $a = 0.5, b = 1, k = 0.1, D = 1$, the times: 0, 5, 1200. Right: convergence of solution of Eq. (1.1) to a constant solution (dashed line, bottom). Its value decreases and tends to 0 with the increase of interval length L. Initial condition is a step-wise constant function (blue). The integral of solution converges to a positive constant (top). The values of parameters: $a = 1, b = 0.5, k = 0.1, D = 1$, the times: 0 (blue line), 400 (green line), 1200 (red line).

4. Discussion

In spite of the simplicity of the stability analysis in Section 2, the result is nontrivial because it provides the loss of stability of the homogeneous in space solution with a space-dependent eigenfunction and bifurcation of spatial structures. Let us compare this result with the Turing instability (also derived in a simple analysis).

- For a fixed value of b and other parameters, condition (2.4) is satisfied if L exceed the critical value $L_* = b/(2k)$. However, the interval length should be less than the second critical value $L^* = b/k$. Hence, similar to Turing structures, the length of the interval should be sufficiently large, but the difference is that it is limited from above.
- For a fixed value of L and other parameters, condition (2.4) is satisfied if b is sufficiently large. Let us recall that parameter b describes the dependence of cell proliferation on cell–cell communication, which can be considered as self-activation. Hence, similar to the Turing instability formulated in terms of activator and inhibitor, self-activation should be sufficiently large, but, as before, limited from above.
- Self-activation due to paracrine ou juxtacrine signaling occurs locally and can be considered as short-range activation. On the other hand, the inhibition rate proportional to $J(u)$ is space-independent, and it can be considered as long-range inhibition. Formulated in this way, these properties are similar to the Turing instability, but their realization in the model is different.
- The diffusion coefficient of inhibitor in the Turing instability should be larger than the diffusion coefficient of activator. Admitting some liberty of formulation, we can interpret the model considered here as zero diffusion for activator and infinite diffusion for inhibitor. Turing instability is diffusion-driven instability, it does not occur if the diffusion coefficients are sufficiently small. At the same time, condition (2.5) implies that the diffusion coefficient for cells should be sufficiently small.
- The eigenfunction providing the Turing instability can have any frequency determined by the length of the interval. As a consequence, Turing structures can have many spatial periods in a given interval. This is different for Eq. (2.1). The maximal positive eigenvalue necessarily corresponds to $n = 1$, and the corresponding eigenfunction has a single maximum. In terms of bifurcating patterns, this case corresponds to the emergence of a single pulse and not of a periodic structure.
- Finally, Turing instability can occur for two (or more) reaction–diffusion equations, it cannot take place for a single equation. The instability studied here occurs already for the single equation. However, the second equation is implicitly taken into account by the integral term.

The modern theory of morphogenesis is essentially based on the presence of morphogenetic gradients [6]. We propose here a plausible mechanism of the emergence of such gradients under the assumptions that local cell–cell communication accelerates cell division while global feedback promotes cell death. These assumptions are biologically justified for various examples including tumor growth.

Conventional (local) bistable reaction–diffusion equation can have stationary pulse solutions but they are always unstable [7] which essentially limits their applications, contrary to the reaction–diffusion waves which are stable and largely used in numerous applications [5]. Introduction of the nonlocal term in the equation can make the pulse stable, as discussed above. This opens various applications of such models in morphogenesis and cancer modeling (tumor growth).

Nonlocal reaction–diffusion equations are used in various biological applications (see [8] and the references therein). Nonlocal terms in these models can lead to the instability of a homogeneous in space stationary solution and to bifurcations of spatial structures. However, the models there are different and the instability occurs due some particular properties of the kernel of the integral defining the nonlocal terms. In the present work we considered a new equation and illustrated the emergence of spatially distributed solutions due to another mechanism. Other equations will be studied in the subsequent works in the context of various applications.

Acknowledgments

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Appendix A. Numerical implementation

Solutions to Eq. (1.1) have been obtained by using Comsol 3.5a software in the Comsol Multiphysics 1D PDE-coefficient mode. The calculations were performed on the finite interval $(0, 500)$ and repeated on the interval $(0, 1000)$, when necessary. The spatial mesh consisted of 1920 subintervals of equal length. The integral $J(u)$ was calculated by choosing in the Subdomain Integration Variables command "Name" J with "Expression" equal to u. Eq. (1.1) was solved either with no-flux boundary conditions or with zero Dirichlet boundary conditions. In the left panel of Fig. 1 we show an example of the pulse solution obtained as the time asymptotics of the solution generated by the initial data $u_{01}(x) = 0.02 \cdot H(x-240)H(260-x)$ for $b = 1$, $a = 0.5$, $k = 0.1$. The final shape of the pulse is achieved practically for $t = 250$, however we wait until $t = 1200$ to infer that the solution is stationary. The same pulse can be obtained from the initial data $u_{02}(x) = 1 \cdot H(x-100)H(400-x)$ and, in fact, by all single jump initial conditions $u_0(x)$ satisfying the inequality $u_{01}(x) \le u_0(x) \le u_{02}(x)$. Similar attractive pulses have been obtained for other values of parameters satisfying the conditions $b > a > 0$, $k > 0$, in particular for $b = 1$, $a = 0.5$, $k = 0.02$. In the right panel of Fig. 1, the calculations were performed for the interval $(0, 500)$ as well as for the interval $(0, 1000)$. In this way we could state that given the same initial data the asymptotic constant solution to Eq. (1.1) is twice smaller for the interval $(0, 1000)$ than for the interval $(0, 500)$, whereas the asymptotic value of the integral J stays the same for both of the intervals.

Numerical accuracy was verified by decreasing the time and space steps, by the comparison with the analytical results on stability conditions, and by the convergence of the integral of solution to a constant as time increases.

Appendix B. Existence and properties of pulses

We prove here the existence of a positive solution of the problem

$$w'' + f_\tau(w) = 0, \quad w(\pm\infty) = 0 \tag{B.1}$$

considered on the whole axis and establish some properties of such solutions used in the paper. We assume that $f_\tau(0) = 0$, $f_\tau(w_1(\tau)) = f_\tau(w_2(\tau)) = 0$ for $0 < w_1(\tau) < w_2(\tau)$. Moreover, we suppose that $f_\tau(w) < 0$ for $0 < w < w_1(\tau)$, $f_\tau(w) > 0$ for $w_1(\tau) < w < w_2(\tau)$, and

$$I(\tau) \equiv \int_0^{w_2(\tau)} f_\tau(w)dw > 0 \tag{B.2}$$

in some interval of τ. The function $f_\tau(w)$ is supposed to be continuous with respect to w and τ.

Let us note that solution of problem (B.1) is invariant with respect to translation in space. Therefore, without loss of generality, we can suppose that it reaches its maximum at $x = 0$, $w_m = w(0)$. Note that w_m can also depend on τ. Instead of the problem on the whole axis, we will consider the same equation on the half-axis $x > 0$ with the boundary condition $w'(0) = 0$. We will look for a decreasing solution with zero limit at infinity.

Eq. (B.1) can be reduced to the system of first-order equations

$$w' = p, \; p' = -f_\tau(w) \tag{B.3}$$

and to the single equation with the corresponding boundary conditions:

$$p\frac{dp}{dw} = -f_\tau(w), \quad p(0) = 0, \quad p(w_m) = 0.$$

Integrating this equation, we obtain

$$p(w) = -\sqrt{-2\int_0^w f_\tau(u)du}.$$

Set $\mathcal{J}(w) = \int_0^w f_\tau(u)du$. Then $\mathcal{J}(w) < 0$ for positive and sufficiently small w. On the other hand, it follows from condition (B.2) that this integral vanish for some w, and it is exactly the value $w_m = w(0)$.

The function $p(w)$ is well defined since $\mathcal{J}(w) < 0$ for $0 < w < w_m$. Furthermore, $p(0) = p(w_m) = 0$. Solution $w_\tau(x)$ of Eq. (B.1) on the half-axis can be found from the equation $w'_\tau(x) = p(w_\tau)$.

Suppose now that $I(\tau) \to 0$ as $\tau \to \tau_0$ for some τ_0, assuming that condition (B.2) is satisfied. Since $\int_0^{w_m(\tau)} f_\tau(w)dw = 0$, then $w_2(\tau) - w_m(\tau) \to 0$ as $\tau \to \tau_0$.

Therefore, we can deduce for the solution $w_\tau(x)$ of system (B.3) that $w_\tau(x) \to w_2(\tau_0)$ as $\tau \to \tau_0$ uniformly in x on every bounded interval. Indeed, $(w_2(\tau_0), 0)$ is a stationary point of system (B.3) for $\tau = \tau_0$. Since the point $(w_m(\tau), 0)$ of the trajectory $(w_\tau(x), w'_\tau(x))$ (corresponding to $x = 0$) approaches this stationary point as $\tau \to \tau_0$, then the interval of x, where the solution remains in a vicinity of this stationary point, increases as $\tau \to \tau_0$.

Hence, we can conclude that $\int_{-\infty}^{\infty} w_\tau(x)dx \to \infty$ as $\tau \to \tau_0$.

Finally, let us note that the integral of solution is a continuous function of τ.

Data availability

No data was used for the research described in the article.

References

[1] A.M. Turing, The chemical basis of morphogenesis, Philos. Trans. R. Soc. London [Biol.] 237 (641) (1952) 37–72.
[2] H. Meinhardt, The Algorithmic Beauty of Sea Shells, fourth ed., Springer, Berlin, 2009.
[3] J.D. Murray, Mathematical Biology II: Spatial Models and Biomedical Applications, third ed., Springer, NewYork, 2003.
[4] M. Enomoto, T. Igaki, Cell–cell interactions that drive tumorigenesis in Drosophila, Fly 16 (1) (2022) 367–381.
[5] V. Volpert, Elliptic Partial Differential Equations. Volumes 1 and 2, Birkhäuser, Basel, 2014.
[6] L. Wolpert, The Development of Pattern and Form in Animals, Carolina Biological, Burlington, 1977.
[7] R.G. Casten, C.J. Holland, Instability results for reaction–diffusion equations with Neumann boundary conditions, J. Differential Equations 27 (1978) 266–273.
[8] M. Banerjee, M. Kuznetsov, O. Udovenko, V. Volpert, Nonlocal reaction–diffusion equations in biomedical applications, Acta Biotheor. 70 (2) (2022) 12.