

Self-similar dynamics of morphogen gradients

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Morphogen gradients are concentration fields of molecules acting as spatial regulators of cell differentiation in developing tissues and play a fundamental role in various aspects of embryonic development. We discovered a family of self-similar solutions in a canonical class of nonlinear reaction-diffusion models describing the formation of morphogen gradients. These solutions are realized in the limit of infinitely high production rate at the tissue boundary and are given by the product of the steady state concentration profile and a function of the diffusion similarity variable. We solved the boundary value problem for the similarity profile numerically and analyzed the implications of the discovered self-similarity on the dynamics of morphogenetic patterning.

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I. INTRODUCTION

Reaction-diffusion processes are involved in multiple aspects of embryogenesis. In particular, a combination of extracellular diffusion and degradation of locally produced proteins can establish concentration fields of chemical signals that control spatial and temporal gene expression patterns in developing tissues [1]. Such concentration fields are known as *morphogen gradients* and have been identified in contexts as diverse as neural development in vertebrates and wing morphogenesis in insects [2,3].

Starting with the classical works of Turing and Wolpert [4,5] (see also [6]), the formation of morphogen gradients has been the subject of many theoretical studies (for recent reviews, see, e.g., [7–10]). A canonical model of morphogen gradient formation is given by the following initial boundary value problem [8–12]:

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial x^2} - k(C)C, \quad C(x, t = 0) = 0, \quad (1)$$

$$-D \left. \frac{\partial C}{\partial x} \right|_{x=0} = Q, \quad C(x = \infty, t) = 0. \quad (2)$$

Here $C = C(x, t)$ is the concentration of a morphogen as a function of distance $x \geq 0$ to the tissue boundary and time $t \geq 0$. The morphogen is produced with a constant rate Q at the tissue boundary ($x = 0$), diffuses with diffusivity D in the tissue ($x > 0$), and is degraded in the tissue following some rate law characterized by the pseudo-first-order rate constant $k(C) > 0$. This model provides a minimal description of complex biochemical and cellular processes in real tissues and has been recently used to quantitatively describe morphogen gradients in a number of experimental systems [11,13–15].

Let us emphasize that morphogens function as regulators of gene expression. Some of the genes controlled by morphogens are directly involved in cell differentiation. Other genes contribute indirectly by regulating processes of gradient formation. For example, a morphogen can induce the expression of molecules involved in morphogen binding and degradation. This phenomenon is indeed very common in experimental systems [2,16,17]. The dependence of gene expression on local morphogen concentration can be highly nonlinear, reflecting

the presence of cooperative and threshold effects in networks responsible for intracellular interpretation of morphogens [3].

Based on the ability of morphogens to increase the rate of their own degradation and the nonlinearity of morphogen-dependent gene expression, Eldar *et al.* proposed a model in which the morphogen degradation rate is given by a power law [11]:

$$k(C) = k_n C^{n-1}, \quad n > 1, \quad (3)$$

and demonstrated that power law degradation kinetics may generate gradients that are robust with respect to large variations in the source strength. They based their conclusions on the analysis of the steady version of Eq. (1). Specifically, they demonstrated that, unlike the solutions of the corresponding linear problem, i.e., Eqs. (1) and (2) with $k(C) \equiv \text{const}$ (in which the solution depends on Q multiplicatively), the stationary solution $C_s(x)$ of Eqs. (1)–(3) approaches an asymptotic limit when $Q \rightarrow \infty$. As a consequence, the steady state of a system operating in the regime of large Q 's will be insensitive to variations in the strength of the source. This has important implications for robustness of steady morphogen gradients established by localized production, diffusion, and self-induced degradation.

We found that robustness of the steady state solutions of Eqs. (1)–(3) discussed above carries over to the solutions of the full time-dependent problem. Remarkably, we found that for large values of Q the solution of the initial boundary value problem given by Eqs. (1)–(3) approaches a *self-similar* form:

$$C(x, t) = C_s(x) \phi(x/\sqrt{Dt}), \quad (4)$$

where $\phi(\xi)$ is a universal function of $\xi = x/\sqrt{Dt}$ which depends only on n and decreases monotonically from $\phi = 1$ at $\xi = 0$ to $\phi = 0$ at $\xi = \infty$. The self-similar profile function $\phi(\xi)$ is obtained by considering the singular version of the initial boundary value problem with $Q = \infty$.

II. SCALING ARGUMENTS

We begin by introducing the dimensionless variables

$$x' = x/L, \quad t' = t/T, \quad u = C/C_0, \quad (5)$$

where

$$L = \sqrt{D/(k_n C_0^{n-1})}, \quad T = k_n^{-1} C_0^{1-n}, \quad (6)$$

and C_0 is some reference morphogen concentration, corresponding, e.g., to the threshold of expression of a downstream regulated gene. In these new variables, the initial boundary value problem in Eqs. (1)–(3) takes the form

$$\begin{aligned} u_t &= u_{xx} - u^n, & (x,t) &\in [0,\infty) \times (0,\infty), \\ u_x(0,t) &= -\alpha, & t &\in (0,\infty), \\ u(x,0) &= 0, & x &\in [0,\infty), \end{aligned} \quad (7)$$

where

$$\alpha = Q/\sqrt{Dk_n C_0^{n+1}} \quad (8)$$

is the dimensionless source strength. From now on we drop the primes from the independent variables.

Let us now discuss the approach of the solutions of Eq. (7) to the unique steady state, which for this problem is given explicitly by the following expression [18]:

$$v_\alpha(x) = \left\{ \frac{2(n+1)}{[2^n(n+1)\alpha^{1-n}]^{1/(n+1)} + (n-1)x^2} \right\}^{1/(n-1)}. \quad (9)$$

It is not difficult to see that $u(x,t)$ approaches $v_\alpha(x)$ from below as $t \rightarrow \infty$, implying that the fraction of the steady concentration $u(x,t)/v_\alpha(x)$ reached at a given point $x \geq 0$ at time $t > 0$ will approach unity for $t \gg 1$ [18]. In view of the diffusive nature of the processes involved in establishing the steady concentration profile, one may expect that the approach to the steady state occurs on the scale associated with diffusion. Therefore, to better understand the dynamics, we plot this fraction versus x/\sqrt{t} for the solution of Eq. (7) with $n = 2$ and $\alpha = 1$ obtained numerically for several values of t . The result is presented in Fig. 1. One can see from Fig. 1 that the solution of Eq. (7) at different values of t collapses onto a single master curve for $t \gg 1$. Furthermore, increasing the value of α makes this collapse sooner. We also checked that the same phenomenon occurs for different values of n . This strongly suggests [19] the existence of a hidden self-similarity in the underlying dynamical behavior of the solutions of Eq. (7).

Note that the solutions of Eq. (7) are invariant with respect to the following scaling transformation:

$$\begin{aligned} \alpha' &= \lambda\alpha, & t' &= \lambda^{2(1-n)/(1+n)}t, & x' &= \lambda^{(1-n)/(n+1)}x, \\ u' &= \lambda^{2/(n+1)}u. \end{aligned} \quad (10)$$

In other words, increasing the source strength α by a factor of λ decreases the time scale of approach to the steady state by a factor of $\lambda^{2(n-1)/(n+1)}$ at fixed value of x/\sqrt{t} . Therefore, the approach to the universal curve in Fig. 1 must occur on the time scale $\tau_n \sim \alpha^{2(1-n)/(n+1)}$. This scale was recently identified by us in the analysis of the local accumulation time in the particular case of Eq. (7) [18]. Observe that $\tau_n \rightarrow 0$ as $\alpha \rightarrow \infty$ for all $n > 1$. Thus, our numerical results suggest that in the limit $\alpha \rightarrow \infty$ the ratio $u(x,t)/v_\alpha(x)$ depends only on x/\sqrt{t} for all $t > 0$, exhibiting self-similar behavior.

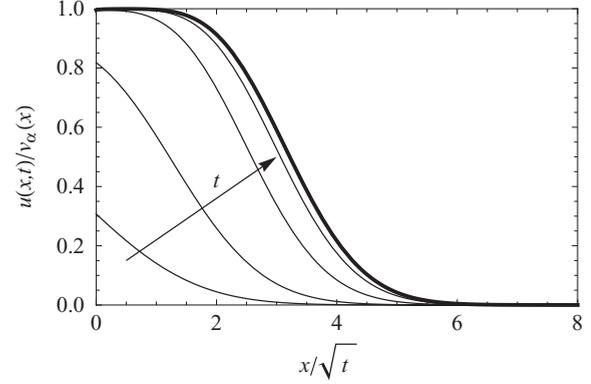


FIG. 1. Example of the collapse of the solutions of Eq. (7) onto a universal master curve at large times. Results of the numerical solution of Eq. (7) with $n = 2$ and $\alpha = 1$. Thin lines show snapshots of the solutions corresponding to $t = 0.1, 1, 10, 100$ (the direction of time increase is indicated by the arrow). The bold line shows the asymptotic master curve.

III. SINGULAR SOLUTIONS

The numerical observations discussed above suggest the need to consider the following singular initial boundary value problem:

$$\begin{aligned} u_t &= u_{xx} - u^n, & (x,t) &\in (0,\infty) \times (0,\infty), \\ u(0,t) &= \infty, & t &\in (0,\infty), \\ u(x,0) &= 0, & x &\in (0,\infty). \end{aligned} \quad (11)$$

Note that for each $n > 1$ this problem possesses a *singular* stationary solution

$$v_\infty(x) = \left(\frac{2(n+1)}{(n-1)^2} \right)^{1/(n-1)} \left(\frac{1}{x} \right)^{2/(n-1)}, \quad (12)$$

which is the limit of $v_\alpha(x)$ as $\alpha \rightarrow \infty$ for each $x > 0$. Therefore, in view of the discussion above, the solution of Eq. (11) is expected to take the form

$$u(x,t) = v_\infty(x)\phi(x/\sqrt{t}), \quad (13)$$

for some universal function $\phi(\xi)$ with values between zero and 1, which depends only on n .

A. Similarity ansatz

Let us substitute the similarity ansatz from Eq. (13) into Eq. (11). After some algebra, this leads to the following equation for the self-similar profile ϕ :

$$\xi^2 \frac{d^2\phi}{d\xi^2} + \left(\frac{\xi^3}{2} - \frac{4\xi}{n-1} \right) \frac{d\phi}{d\xi} + \frac{2(n+1)}{(n-1)^2} \phi(1 - \phi^{n-1}) = 0, \quad (14)$$

which must hold for all $\xi \in (0,\infty)$. Consistent with the interpretation of Eq. (11), this equation needs to be supplemented with the boundarylike conditions

$$\lim_{\xi \rightarrow 0} \phi(\xi) = 1, \quad \lim_{\xi \rightarrow \infty} \phi(\xi) = 0. \quad (15)$$

We note that it is possible to prove that Eqs. (14) and (15) have a unique solution for each $n > 1$ in a natural mathematical setting [20].

B. Numerics

We next construct the self-similar profiles for several values of $n > 1$ numerically. We used the shooting method to construct the solutions of Eq. (14), which requires knowledge of the asymptotic behavior of $\phi(\xi)$ near $\xi = 0$ and $\xi = \infty$. To obtain this behavior, we linearize Eq. (14) around the equilibria $\phi = 0$ and $\phi = 1$. Denote the corresponding solutions of the linearized equations as ϕ_0 and ϕ_1 , respectively. By a direct computation

$$\begin{aligned} \phi_0(\xi) = & C_1 \xi^{2/(n-1)} M\left(\frac{1}{n-1}, \frac{1}{2}, -\frac{\xi^2}{4}\right) \\ & + C_2 e^{-\xi^2/4} \xi^{2/(n-1)} U\left(\frac{1}{2} + \frac{1}{1-n}, \frac{1}{2}, \frac{\xi^2}{4}\right), \end{aligned} \quad (16)$$

where $M(a, b, z)$ and $U(a, b, z)$ are the confluent hypergeometric functions of the first and second kind, respectively [21]. Using the asymptotic expansions of these functions for large z [21], one can see that $\phi_0(\xi) \rightarrow 0$ as $\xi \rightarrow \infty$, if and only if the constant $C_1 = 0$. Therefore, from the asymptotic expansion of U we have

$$\phi(\xi) \sim e^{-\xi^2/4} \xi^{(5-n)/(n-1)}, \quad \xi \rightarrow \infty. \quad (17)$$

Similarly

$$\begin{aligned} \phi_1(\xi) = & \xi^{2(n+1)/(n-1)} \left\{ C_1 M\left(\frac{n+1}{n-1}, \frac{5n-1}{2n-2}, -\frac{\xi^2}{4}\right) \right. \\ & \left. + C_2 U\left(\frac{n+1}{n-1}, \frac{5n-1}{2n-2}, -\frac{\xi^2}{4}\right) \right\}. \end{aligned} \quad (18)$$

Once again, for a bounded solution at $\xi = 0$ we must set $C_2 = 0$, which leads to

$$1 - \phi(\xi) \sim \xi^{2(n+1)/(n-1)}, \quad \xi \rightarrow 0. \quad (19)$$

The results of the numerical solution of Eq. (14) whose asymptotic behavior is governed by Eqs. (16) and (18) are presented in Fig. 2. One can see that the self-similar profiles form a monotonically decreasing family of functions parametrized by n . The solutions $\phi(\xi)$ approach $\bar{\phi}(\xi) = 1$ on finite intervals as $n \rightarrow 1$ and $\bar{\phi}(\xi) = 1 - \text{erf}(\xi/2)$ as $n \rightarrow \infty$ [the latter solves Eq. (14) corresponding to $n = \infty$]. We also found that for the biophysically important case $n = 2$, in which the morphogen-induced positive feedback for degradation is mediated by the simplest bimolecular interaction, the self-similar profile can be approximated within $\sim 1\%$ accuracy by the following simple expression:

$$\phi(\xi) \approx \frac{4000 + \xi^9}{4000 + 5\xi^6 e^{\xi^2/4}}, \quad n = 2. \quad (20)$$

The graph of this function, which essentially coincides with that of the numerical solution of Eq. (14), is shown in Fig. 2 with a thick line. Note that this profile also coincides with the limiting profile in Fig. 1 for $t = \infty$.

C. Dynamics

Let us now discuss the dynamical behavior of the obtained self-similar solutions of Eq. (11). The picture remains qualitatively the same for all $n > 1$, so in the following we restrict our attention to the biophysically important case of $n = 2$.

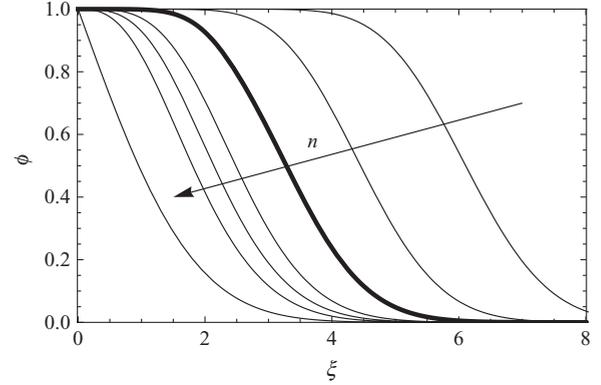


FIG. 2. Self-similar profiles $\phi(\xi)$ for different values of n . Results of the numerical solution of Eqs. (14) and (15) for $n = 1.25, 1.5, 2, 3, 4, 6, \infty$. The thick line is the graph of the function given by Eq. (20) overlaying the profile for $n = 2$.

First consider the time course of the solution $u(x, t)$ given by Eq. (13) at a fixed location, i.e., at a fixed value of $x > 0$. From the self-similarity ansatz in Eq. (13) it is clear that the time scale of these dynamics is governed by diffusion, i.e., $t \sim x^2$. A convenient characterization of local dynamical time scale can be made in terms of the local accumulation time $\tau^\infty(x) = \int_0^\infty t p(x, t) dt$, where the probability-density-like quantity $p(x, t) = \frac{1}{v_\infty(x)} \frac{\partial u(x, t)}{\partial t}$ [18,22]. Upon substitution of Eq. (13) into this formula and an integration by parts, one obtains

$$\tau^\infty(x) = ax^2, \quad a = 2 \int_0^\infty \xi^{-3} [1 - \phi(\xi)] d\xi, \quad (21)$$

where numerically $a \simeq 0.122$. We note that by Eq. (19) the integral in Eq. (21) converges for all $n > 1$. The solution for several values of x is shown in Fig. 3. Furthermore, as follows from Eqs. (17) and (19), when $t \ll \tau^\infty(x)$, we have $u(x, t) \sim (x/t^{3/2})e^{-x^2/(4t)}$, which is exponentially small. At the same time, for $t \gg \tau^\infty(x)$ we have $[v_\infty(x) - u(x, t)]/v_\infty(x) \sim [\tau^\infty(x)/t]^3$, i.e., u approaches the stationary solution, with the distance to the stationary solution decaying as $O(t^{-3})$.

We now consider the motion of the level sets of the solutions of Eq. (11). For a given $c > 0$, let us define $x_c(t)$ as the unique value of x , such that $u(x, t) = c$ for each $t > 0$. As follows from Eqs. (13), the function $x_c(t)$ can be determined

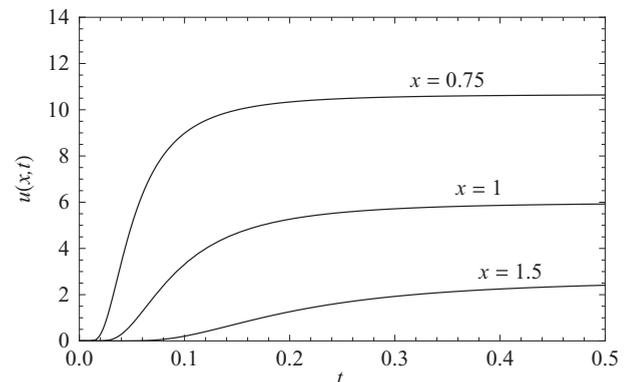


FIG. 3. Self-similar solutions $u(x, t)$ of Eq. (11) at several values of x for $n = 2$.

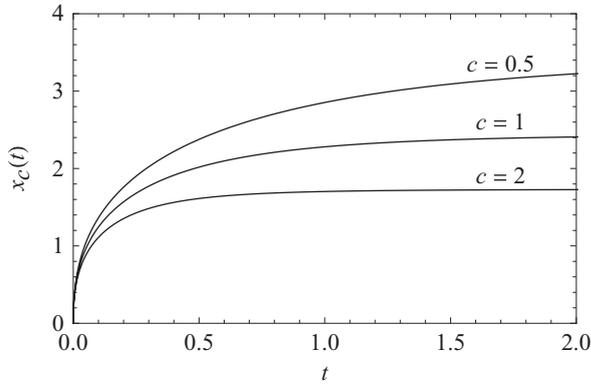


FIG. 4. The positions $x_c(t)$ of level sets $\{u(x, t) = c\}$ of the self-similar solution of Eq. (11) at several values of c for $n = 2$.

parametrically as

$$x_c = [6\phi(\xi)/c]^{1/2}, \quad t = 6\phi(\xi)/(c\xi^2), \quad n = 2. \quad (22)$$

The graphs of $x_c(t)$ for a few values of c are shown in Fig. 4. Once again, the dynamics of x_c can be characterized by the local accumulation time $\tau^\infty(x_c^\infty)$ given by Eq. (21), where $x_c^\infty = (6/c)^{1/2}$ is the asymptotic value of $x_c(t)$ as $t \rightarrow \infty$. One can see from Eqs. (17) and (22) that for $t \ll \tau^\infty(x_c^\infty)$ we have $x_c \simeq 2(t \ln t^{-1})^{1/2}$. Thus, all level sets move together for short times, as can also be seen from Fig. 4. On the other hand, for $t \gg \tau^\infty(x_c^\infty)$ the level set position $x_c(t)$ approaches x_c^∞ as $x_c^\infty - x_c(t) = O(t^{-3})$. Within $\sim 2\%$ accuracy the functions $x_c(t)$ can be approximated by the following simple expression:

$$x_c(t) \approx \left(\frac{4t \ln[3.2 + 6/(ct)]}{1 + 0.76ct} \right)^{1/2}, \quad n = 2. \quad (23)$$

This formula implies that $x_c(t)$ comes within 5% of x_c^∞ at $t \simeq 2\tau^\infty(x_c^\infty)$.

IV. CONCLUSION

In conclusion, we characterized the dynamics of morphogen gradients in models with self-induced morphogen degradation. Our results reveal the presence of self-similarity in the course of the approach of the concentration profiles to their steady states in either the limit of large source strengths or for large distances away from the source. In addition to demonstrating the self-similar nature of the dynamics, we constructed these self-similar solutions numerically for several values of n . The obtained solutions may be readily used to study various characteristics of the local kinetics of morphogen concentration. In particular, Eqs. (22) and (23) obtained from the numerical self-similar solutions provide a characterization of threshold self-similar events, which determine the times at which a morphogen gradient switches the gene expression on or off at a given point.

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