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Physical interpretation of mean local accumulation time of morphogen gradient formation

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The paper deals with a reaction-diffusion problem that arises in developmental biology when describing the formation of the concentration profiles of signaling molecules, called morphogens, which control gene expression and, hence, cell differentiation. The mean local accumulation time, which is the mean time required to reach the steady state at a fixed point of a patterned tissue, is an important characteristic of the formation process. We show that this time is a sum of two times, the conditional mean first-passage time from the source to the observation point and the mean local accumulation time in the situation when the source is localized at the observation point. © *2011 American Institute of Physics*. [doi:10.1063/1.3654159]

I. INTRODUCTION

Gene expression and, hence, cell differentiation in a developing embryo are controlled by time-dependent concentration fields of signaling molecules called morphogens.[1–5] These concentration fields may be formed by reaction-diffusion mechanisms that involve local production of the morphogen, its diffusion through the tissue, and degradation.[6–13] In the course of time the morphogen concentration monotonically increases from zero to its steady-state (ss) value at long times. One of the most important characteristics of the morphogen concentration profile is the mean time required to reach the steady state at a given point of the patterned tissue, called the mean local accumulation time.[14–16]

This paper focuses on this time, more specifically, on its physical interpretation. In a recent paper,[17] Kolomeisky insightfully indicated that there is a deep relation between the mean local accumulation time and the conditional mean first-passage (FP) time required for diffusing morphogen molecules to reach the observation point before being degraded. Here we derive a general relation between these two times, which is given at the end of Sec. II, after we introduce the model, Eq. (2.5). The derivation is given in Sec. III. In Sec. IV we show how the earlier obtained results[14–16] can be recovered from Eq. (2.5). Some concluding remarks are made in the final Sec. V.

II. MODEL

Consider a one-dimensional model of a patterned tissue, in which point particles (morphogen molecules) diffuse with diffusivity D and are degraded with the rate constant k on an interval of length L, $0 < x < L$, terminated by reflecting boundaries. The particles are injected into the interval with the position-dependent injection rate $q(x_0)$, which is independent of time. Injection starts at $t = 0$ when the interval is free from particles. The source of the particles is characterized by the total injection rate, $Q = \int_0^L q(x_0)dx_0$, and the injection density, $p_q(x_0) = q(x_0)/Q$, normalized to unity.

The particle concentration $c(x, t)$ monotonically increases with time from zero at $t = 0$ to its steady-state value $c_{ss}(x)$ as $t \to \infty$. Using the local relaxation function, denoted by $R(t|x)$, one can always write $c(x, t)$ as

$$c(x,t) = c_{ss}(x) + [c(x,0) - c_{ss}(x)]R(t|x). \tag{2.1}$$

The notation $R(t|x)$ is used to stress the point that our analysis focuses on time course of the concentration at a fixed point x. In the case under consideration $c(x, 0) = 0$ and Eq. (2.1) takes the form

$$c(x,t) = c_{ss}(x)[1 - R(t|x)]. \tag{2.2}$$

This leads to

$$R(t|x) = 1 - \frac{c(x,t)}{c_{ss}(x)}. \tag{2.3}$$

Since the concentration monotonically increases with time from zero to $c_{ss}(x)$, the relaxation function monotonically decreases from unity at $t = 0$ to zero as $t \to \infty$.

The mean local accumulation time, $\tau(x)$, is defined in terms of the relaxation function by[14–16]

$$\tau(x) = \int_0^\infty R(t|x)dt = \hat{R}(s = 0|x), \tag{2.4}$$

where $\hat{R}(s|x)$ is the Laplace transform of the local relaxation function. (The Laplace transform of a function $f(t)$ is denoted by $\hat{f}(s)$: $\hat{f}(s) = \int_0^\infty e^{-st} f(t)dt$.) In this paper, we show that the mean local accumulation time is a sum of two times. The first of the two is the conditional (c) mean first-passage time to the observation point, $\langle \tau_{FP}^{(c)}(x_0 \to x)\rangle$, where the angular brackets, $\langle \ldots \rangle$, indicate that the uncertainty in the particle injection point x_0 has been taken into account (see the formal

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definition of $\langle \tau_{FP}^{(c)}(x_0 \to x)\rangle$ in Eq. (3.12)). The second is the mean local accumulation time $\tau(x|x)$ that characterizes formation of the steady-state concentration at point x on condition that the particle source is localized at the same point, $p_q(x_0) = \delta(x - x_0)$ (see the formal definition of $\tau(x|x)$ in Eq. (3.13)). Thus,

$$\tau(x) = \langle \tau_{FP}^{(c)}(x_0 \to x)\rangle + \tau(x|x). \tag{2.5}$$

This is one of our main results. We derive Eq. (2.5) in Sec. III and use it to recover known results for $\tau(x)$ (Refs. 14–16) in Sec. IV. A physical interpretation of the mean local accumulation time, Eq. (5), is discussed in Sec. V.

III. DERIVATION

As shown in Ref. 16, $\tau(x)$ is the first moment of the probability density of the local accumulation time, $\varphi(t|x)$, given by

$$\varphi(t|x) = \frac{\langle G(x,t|x_0)\rangle_q}{\langle \hat{G}(x,0|x_0)\rangle_q}. \tag{3.1}$$

Here $G(x, t|x_0)$ is the propagator (the Green's function) of the particle that starts from x_0 at $t = 0$, $\hat{G}(x,0|x_0) = \hat{G}(x,s|x_0)|_{s=0}$ is the Laplace transform of this propagator at $s = 0$, and the angular brackets, $\langle \ldots \rangle_q$, denote averaging over x_0 using the normalized injection rate, $p_q(x_0)$, as a weight factor, $\langle f(x_0)\rangle_q = \int_0^L f(x_0)p_q(x_0)dx_0$. The propagator satisfies the reaction-diffusion equation

$$\frac{\partial G(x,t|x_0)}{\partial t} = D\frac{\partial^2 G(x,t|x_0)}{\partial x^2} - kG(x,t|x_0),\ \ 0 < x, x_0 < L, \tag{3.2}$$

with initial and boundary conditions of the form $G(x, 0|x_0) = \delta(x - x_0)$ and $\partial G(x,t|x_0)/\partial x|_{x=0,L} = 0$.

The propagator $G(x, t|x_0)$ can be written as a convolution of the propagator $G(x, t|x)$ and the flux $f(t|x_0 \to x)$, formed by trajectories that started from x_0 at $t = 0$ and reach point x for the first time at time t. To find the flux one has to consider an auxiliary problem in which the observation point is an ideal trap for diffusing particles. By solving the problem, one can find the flux entering the trap at time t, which is just the flux $f(t|x_0 \to x)$. We use this flux to write the propagator as

$$G(x,t|x_0) = \int_0^t G(x,t-t'|x)f(t'|x_0 \to x)dt'. \tag{3.3}$$

From this it follows that the denominator in Eq. (3.1) is

$$\begin{aligned}\langle \hat{G}(x,0|x_0)\rangle_q &= \left\langle \int_0^\infty G(x,t|x_0)dt\right\rangle_q \\ &= \hat{G}(x,0|x)\left\langle \int_0^\infty f(t|x_0 \to x)dt\right\rangle_q.\end{aligned} \tag{3.4}$$

The time integral of the flux is the probability to reach point x before being degraded, for a particle that starts from point x_0, $P(x_0 \to x)$,

$$P(x_0 \to x) = \int_0^\infty f(t|x_0 \to x)dt = \hat{f}(0|x_0 \to x), \tag{3.5}$$

where $\hat{f}(0|x_0 \to x)$ is the Laplace transform of the flux $f(t|x_0 \to x)$ at $s = 0$. Thus the denominator in Eq. (3.1) is given by

$$\langle \hat{G}(x,0|x_0)\rangle_q = \langle P(x_0 \to x)k\rangle_q \hat{G}(x,0|x). \tag{3.6}$$

Using Eqs. (3.3) and (3.6) we can write the probability density of the local accumulation time, Eq. (3.1), as

$$\varphi(t|x) = \int_0^t \frac{G(x,t-t'|x)}{\hat{G}(x,0|x)}\frac{\langle f(t'|x_0 \to x)\rangle_q}{\langle P(x_0 \to x)\rangle_q}dt'. \tag{3.7}$$

The ratio of the averaged flux, $\langle f(t|x_0 \to x)\rangle_q$, to the averaged transition probability, $\langle P(x_0 \to x)\rangle_q$, is the conditional probability density for the first-passage time to point x assuming that the starting points are distributed according to $p_q(x_0)$, $\langle \varphi_{FP}^{(c)}(t|x_0 \to x)\rangle$,

$$\left\langle \varphi_{FP}^{(c)}(t|x_0 \to x)\right\rangle = \frac{\langle f(t|x_0 \to x)\rangle_q}{\langle P(x_0 \to x)\rangle_q} = \frac{\langle f(t|x_0 \to x)\rangle_q}{\langle \hat{f}(0|x_0 \to x)\rangle_q}. \tag{3.8}$$

Note that the averaging denoted by the angular brackets, $\langle \ldots \rangle$, differs from the averaging denoted by $\langle \ldots \rangle_q$. The latter is the averaging of a function of x_0 over x_0 using the normalized injection density $p_q(x_0)$ as a weight factor. The probability density in Eq. (3.8) is conditional, since it is determined only by those realizations of the particle trajectory, which reach the observation point x before being degraded.

Comparison with Eq. (3.1) shows that the ratio $G(x,t|x)/\hat{G}(x,0|x)$ is the probability density of the local accumulation time at point x on condition that the particle source is localized at the same point, $p_q(x_0) = \delta(x - x_0)$. Denoting this probability density by $\varphi(t|x|x)$,

$$\varphi(t|x|x) = \frac{G(x,t|x)}{\hat{G}(x,0|x)}, \tag{3.9}$$

we can write Eq. (3.7) as

$$\varphi(t|x) = \int_0^t \varphi(t-t'|x|x)\left\langle \varphi_{FP}^{(c)}(t'|x_0 \to x)\right\rangle dt'. \tag{3.10}$$

This leads to

$$\tau(x) = \int_0^\infty t\varphi(t|x)dt = \left\langle \tau_{FP}^{(c)}(x_0 \to x)\right\rangle + \tau(x|x), \tag{3.11}$$

where $\langle \tau_{FP}^{(c)}(x_0 \to x)\rangle$ is the conditional mean first-passage time,

$$\begin{aligned}\left\langle \tau_{FP}^{(c)}(x_0 \to x)\right\rangle &= \int_0^\infty t\left\langle \varphi_{FP}^{(c)}(t|x_0 \to x)\right\rangle dt \\ &= \frac{\int_0^\infty t\langle f(t|x_0 \to x)\rangle_q dt}{\langle \hat{f}(0|x_0 \to x)\rangle_q},\end{aligned} \tag{3.12}$$

and $\tau(x|x)$ is the mean local accumulation time at point x on condition that the particle source is localized at the same point, $p_q(x_0) = \delta(x - x_0)$,

$$\tau(x|x) = \frac{\int_0^\infty tG(x,t|x)dt}{\hat{G}(x,0|x)}. \tag{3.13}$$

The expression for the local accumulation time given in Eqs. (2.5) and (3.11), as well as the convolution formula for the probability density of the local accumulation time, Eq. (3.10), are the main results of this paper.

IV. KNOWN RESULTS FROM THE NEW FORMULA

In this section, we show how known results for $\tau(x)$ (Refs. 14–16) can be obtained from the formula in Eq. (2.5).

A. Localized source, semi-infinite interval

First, we consider the case of semi-infinite interval, $L \to \infty$, with the particle source localized at the origin, $p_q(x_0) = \delta(x_0)$. In such a case, the general expression for $\tau(x)$ in Eq. (2.5) simplifies and takes the form

$$\tau(x) = \tau_{FP}^{(c)}(0 \to x) + \tau(x|x), \tag{4.1}$$

where $\tau_{FP}^{(c)}(0 \to x)$ is the conditional mean first-passage time from the origin to point x.

The propagator $G(x, t|x)$ of a particle that diffuses and is degraded on the semi-infinite interval, $x > 0$, is given by

$$G(x,t|x) = \frac{1}{2\sqrt{\pi D t}} e^{-kt}\left(1 + e^{-x^2/(Dt)}\right). \tag{4.2}$$

Using this, one can find $\tau(x|x)$ by Eq. (3.13). The result is

$$\tau(x|x) = \frac{1}{2k}\left(1 + \frac{x e^{-x/\lambda}}{\lambda \cosh(x/\lambda)}\right), \tag{4.3}$$

where $\lambda = \sqrt{D/k}$ is the characteristic length that determines the x-dependence of the steady-state concentration profile in this case, $c_{ss}(x) = c_{ss}(0)e^{-x/\lambda}$. One can see that time $\tau(x|x)$, Eq. (4.3), is a non-monotonic function of x: as $x \to \infty$, it approaches its value at $x = 0$, $\tau(0|0) = 1/(2k)$, having a maximum in-between. The identity $\tau(x|x)|_{x\to\infty} = \tau(0|0)$ follows from the identity of the propagators, $G(x, t|x)|_{x\to\infty} = G(0, t|0)$. The latter is a consequence of the fact that the propagator $G(x, t|x)$ is formed by those realizations of the particle trajectory that return to the starting point in time t after the particle was injected. The point is that these returns near the reflecting boundary at the origin and at infinity are identical.

The conditional mean first-passage time $\tau_{FP}^{(c)}(0 \to x)$ is derived in Appendix A where we show that

$$\tau_{FP}^{(c)}(0 \to x) = \frac{x}{2k\lambda}\tanh\left(\frac{x}{\lambda}\right). \tag{4.4}$$

Substituting the expression in Eqs. (4.3) and (4.4) into Eq. (4.1), we recover the result for $\tau(x)$,

$$\tau(x) = \frac{1}{2k}\left(1 + \frac{x}{\lambda}\right), \tag{4.5}$$

reported in Refs. 14–16. The x-dependences of times $\tau(x|x)$, $\tau_{FP}^{(c)}(0 \to x)$, and $\tau(x)$ are shown in Fig. 1. As $x \to \infty$, $\tau(x|x)$, Eq. (4.3), and $\tau_{FP}^{(c)}(0 \to x)$, Eq. (4.4), approach their large x asymptotic behavior, $\tau(x|x)|_{x\to\infty} = 1/(2k)$ and $\tau_{FP}^{(c)}(0 \to x)|_{x\to\infty} = x/(2k\lambda)$. Summing $\tau_{FP}^{(c)}(0 \to x)|_{x\to\infty}$ and $\tau(x|x)|_{x\to\infty} = 1/(2k)$, one recovers the result for the mean local accumulation time in Eq. (4.3), which is exact for arbitrary values of x.

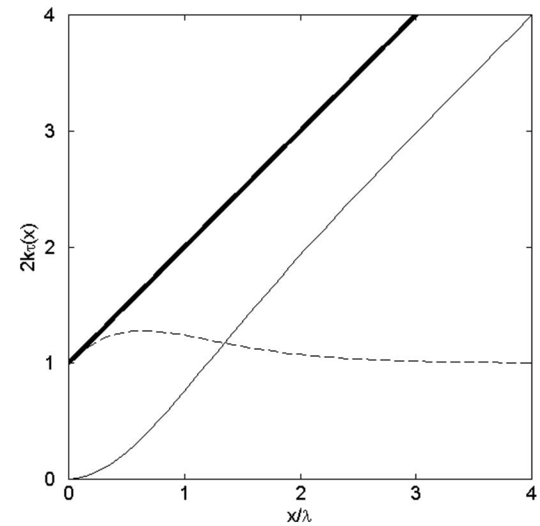

FIG. 1. Times $\tau(x|x)$ (dashed line), $\tau_{FP}^{(c)}(0 \to x)$ (thin line), and $\tau(x)$ (bold line) given in Eqs. (4.3)–(4.5), respectively, as functions of the observation point x.

B. Localized source, finite interval

The formula for the mean local accumulation time in Eq. (4.1) is also applicable when the interval is finite. As before, the conditional mean first-passage time is given by Eq. (4.4) since the particle starting from the origin and trapped at point x is unaware about the reflection boundary at $x = L$. The expression for $\tau(x|x)$ in Eq. (4.3) should now be replaced by

$$\tau(x|x) = \frac{1}{2k}\left[1 + \frac{L}{\lambda}\coth\left(\frac{L}{\lambda}\right) - \frac{x}{\lambda}\tanh\left(\frac{x}{\lambda}\right) - \frac{L-x}{\lambda}\tanh\left(\frac{L-x}{\lambda}\right)\right], \tag{4.6}$$

which is derived in Appendix B. Substituting this $\tau(x|x)$ and $\tau_{FP}^{(c)}(0 \to x)$ in Eq. (4.4) into Eq. (4.1), we obtain

$$\tau(x) = \frac{1}{2k}\left[1 + \frac{L}{\lambda}\coth\left(\frac{L}{\lambda}\right) - \frac{L-x}{\lambda}\tanh\left(\frac{L-x}{\lambda}\right)\right]. \tag{4.7}$$

This result has been reported in Refs. 14–16. As $L \to \infty$, $\tau(x|x)$ in Eq. (4.6) and $\tau(x)$ in Eq. (4.7) reduce to the corresponding expressions derived for the semi-infinite interval, Eqs. (4.3) and (4.5), respectively.

C. Distributed source, semi-infinite interval

Finally, we consider the case when the source, injecting the particles into a semi-infinite interval, is distributed, assuming that the normalized injection density is

$$p_q(x_0) = \frac{1}{l_q} e^{-x_0/l_q}, \quad x_0 > 0, \tag{4.8}$$

where $l_q = \int_0^\infty x_0 p_q(x_0)\, dx_0$ is the mean injection length, as $l_q \to 0$, $p_q(x_0) \to \delta(x_0)$. Time $\tau(x|x)$ here is the same as that in the case of the localized source, Eq. (4.3). To find the conditional mean first-passage time we use the relation between this time and the Laplace transform of the averaged flux $\langle f(t|x_0 \to x)\rangle_q$. This relation follows from Eq. (3.12) and has the form

$$\left\langle \tau_{FP}^{(c)}(x_0 \to x)\right\rangle = -\frac{1}{\langle \hat{f}(0|x_0 \to x)\rangle_q} \left.\frac{\partial \langle \hat{f}(s|x_0 \to x)\rangle_q}{\partial s}\right|_{s=0}. \tag{4.9}$$

The Laplace transform of the flux $f(t|x_0 \to x)$ (derived in Appendix C) is given by

$$\hat{f}(s|x_0 \to x) = \begin{cases} \frac{\cosh(x_0\sqrt{1+s/k}/\lambda)}{\cosh(x\sqrt{1+s/k}/\lambda)}, & 0 < x_0 < x, \\ e^{-\sqrt{1+s/k}(x_0-x)/\lambda}, & x < x_0. \end{cases} \tag{4.10}$$

We use this to find $\langle \hat{f}(0|x_0 \to x)\rangle_q$ and $\partial\langle \hat{f}(s|x_0 \to x)\rangle_q/\partial s|_{s=0}$ entering into Eq. (4.9). The results are

$$\langle \hat{f}(0|x_0 \to x)\rangle_q = \frac{\lambda(\lambda - l_q e^{-(\lambda-l_q)x/(\lambda l_q)})}{\left(\lambda^2 - l_q^2\right)\cosh(x/\lambda)}, \tag{4.11}$$

and

$$\begin{aligned} &\frac{\partial}{\partial s}\langle \hat{f}(s|x_0 \to x)\rangle_q\Big|_{s=0} \\ &= \frac{1}{2k\left(\lambda^2 - l_q^2\right)\cosh(x/\lambda)} \\ &\quad \times \left\{ x\left(\lambda \tanh\left(\frac{x}{\lambda}\right) + \frac{l_q e^{-x/l_q}}{\cosh(x/\lambda)}\right) \right. \\ &\quad \left. - \frac{\lambda l_q}{\lambda^2 - l_q^2}\left[2\lambda l_q - \left(\lambda^2 + l_q^2\right)e^{-(\lambda-l_q)x/(\lambda l_q)}\right]\right\} \end{aligned} \tag{4.12}$$

Substituting the expressions given in Eqs. (4.11) and (4.12) into Eq. (4.9), we find the conditional mean first-passage time $\langle \tau_{FP}^{(c)}(t|x_0 \to x)\rangle$. Eventually we obtain the mean local accumulation time, Eq. (2.5), by summing $\langle \tau_{FP}^{(c)}(t|x_0 \to x)\rangle$ and $\tau(x|x)$ given in Eq. (4.3). This leads to the following result

$$\tau(x) = \frac{1}{2k}\left[\left(1 + \frac{x}{\lambda}\right)\frac{\lambda e^{-x/\lambda}}{\lambda e^{-x/\lambda} - l_q e^{-x/l_q}} + \frac{2l_q^2}{l_q^2 - \lambda^2}\right], \tag{4.13}$$

which has been reported in Refs. 14–16. As $l_q \to 0$, $\tau(x)$ in Eq. (4.13) reduces to that in Eq. (4.5) derived under the assumption that the particle source is localized at the origin.

V. CONCLUDING REMARKS

This paper is devoted to the formation of the steady-state concentration profile, $c_{ss}(x)$, on an interval that is initially free from particles. Its major focus is on the mean local accumulation time, $\tau(x)$, that describes the formation of the steady state at a fixed point x. This time is an important characteristic of the formation process. It allows one to obtain an approximate solution for the time-dependent concentration profile, $c(x, t)$, over the entire range of time. This can be done by means of a single-exponential approximation for the local relaxation function,

$$R(t|x) \approx R_{\exp}(t|x) = e^{-t/\tau(x)}. \tag{5.1}$$

(One can see that $R_{\exp}(t|x)$ (i) monotonically decreases from unity to zero as time goes from zero to infinity and (ii) correctly predicts the mean local accumulation time, Eq. (2.4).) By substituting $R_{\exp}(t|x)$ into Eq. (2.2) one obtains

$$c(x, t) \approx c_{ss}(x)[1 - e^{-t/\tau(x)}]. \tag{5.2}$$

This describes variation of $c(x, t)$ from zero to $c_{ss}(x)$ as time goes from zero to infinity.

Having in hand the dependence $\tau(x)$, one can compare this time with the characteristic time of the cell differentiation at point x of the patterned tissue. If the former is much smaller than the latter, then the cell differentiation is controlled by the local concentration of the morphogen $c_{ss}(x)$, which does not change in time. The situation is quite different when the time scale separation does not exist. In this case, the cell differentiation occurs under the action of the morphogen concentration profile varying in time. Crick addressed the question of the time scale separation in the cell differentiation for the first time in his classical paper[2] more than 40 years ago.

One of our main results is the expression for $\tau(x)$ given in Eq. (2.5), which is derived in Sec. III. This expression shows that $\tau(x)$ is a sum of two times, the conditional mean first passage time to the observation point x from the source of the particles, and an additional time, required for the formation of the steady state at the observation point after the particles reach this point. The latter is given by the formula in Eq. (3.13), according to which the additional time is the mean local accumulation time on condition that the particle source is localized at the observation point, $p_q(x_0) = \delta(x - x_0)$. This formula is a consequence of the fact that the probability density of the additional time, entering into Eq. (3.10), is given by $\varphi(t|x|x)$, Eq. (3.9), which is the probability density of the local accumulation time at point x in the situation when the particle source is localized at the same point.

The formula for the probability density of the local accumulation time is another main result of our analysis. This formula shows that the probability density of the local accumulation time is a convolution of the probability density of the local accumulation time when the particle source is localized at the observation point and the probability density of the conditional first-passage time from the particle source to this point.

To make our results more intuitively appealing, consider the flux of the particles entering an observation point x for the first time at time t, which we denote by $\langle F(t|x|x_0)\rangle_q$. As $t \to \infty$, the flux approaches its steady-state value, $\langle F_{ss}(x|x_0)\rangle_q$, given by the product of the total injection rate, Q, and the particle transition probability from the source to the observation point, $\langle P(x_0 \to x)\rangle_q$,

$$\langle F_{ss}(x|x_0)\rangle_q = \langle P(x_0 \to x)\rangle_q Q. \tag{5.3}$$

The exact expression for $\tau(x)$, Eq. (2.5), can be instantly obtained if we accept the step function approximation for the time dependence of the entering flux:

$$\langle F(t|x|x_0)\rangle_q \approx H\left(t - \left\langle\tau_{FP}^{(c)}(x_0 \to x)\right\rangle\right)\langle F_{ss}(x|x_0)\rangle_q, \tag{5.4}$$

where $H(t)$ is the Heaviside step function. In fact, this approximation is quite reasonable since (as shown in Appendix D) the conditional mean first-passage time, $\langle\tau_{FP}^{(c)}(x_0 \to x)\rangle$, is identical to the mean relaxation time that describes transition of the flux $\langle F(t|x|x_0)\rangle_q$ to its steady-state value. Thus, one can consider the formation of the steady-state concentration as a result of the delayed injection at the observation point, Eq. (5.4), with the delay time given by $\langle\tau_{FP}^{(c)}(x_0 \to x)\rangle$.

The above consideration focuses on the linear reaction-diffusion model which is widely discussed in the literature.[6–13] In this model, the degradation rate is assumed to be linear in the morphogen concentration. The question naturally arises of how the results reported in Refs. 14–17 and their interpretation in Ref. 17 and above can be generalized to nonlinear reaction-diffusion models in which the degradation rate is a nonlinear function of the morphogen concentration. There is no need to say that analysis of the local accumulation time in nonlinear models is a much more complex task than that for linear models. A first step in this direction has been made recently in Ref. 18, where the mean local accumulation time was evaluated for a certain class of nonlinear reaction-diffusion models. The question of interpretation of the results of Ref. 18 is currently under consideration.

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APPENDIX A: CONDITIONAL MEAN FIRST-PASSAGE TIME IN EQ. (4.4)

Consider a particle diffusing and being degraded on an interval of length l, $0 < x < l$, terminated by a reflecting boundary at the origin and a perfectly absorbing boundary at $x = l$. The particle starts from the reflecting boundary at $x = 0$. The particle propagator $g(x, t)$ satisfies the reaction-diffusion equation

$$\frac{\partial g(x,t)}{\partial t} = D\frac{\partial^2 g(x,t)}{\partial x^2} - kg(x,t), \quad 0 < x < l, \tag{A1}$$

with initial and boundary conditions given by $g(x, 0) = \delta(x)$ and $\partial g(x, t)/\partial x|_{x=0} = g(l, t) = 0$.

Eventually, the particle is either degraded or trapped by the absorbing boundary. The probability flux entering the absorbing boundary at time t, $F(t)$, is

$$F(t) = -D\left.\frac{\partial g(x,t)}{\partial x}\right|_{x=l}. \tag{A2}$$

Therefore, the trapping probability, denoted by P, is given by

$$P = \int_0^\infty F(t)dt = \hat{F}(0). \tag{A3}$$

The ratio $F(t)/P$ is the probability density for the particle first passage time to the absorbing boundary, denoted by $\varphi_{FP}^{(c)}(t)$,

$$\varphi_{FP}^{(c)}(t) = \frac{F(t)}{P} = \frac{F(t)}{\hat{F}(0)}. \tag{A4}$$

This probability density is conditional since it is determined only by those realizations of the particle trajectory, which reach the absorbing boundary before being degraded.

The conditional mean first passage time from the origin to the absorbing boundary, denoted by $\tau_{FP}^{(c)}$, is the first moment given by

$$\tau_{FP}^{(c)} = \int_0^\infty t\varphi_{FP}^{(c)}(t)dt = -\frac{1}{\hat{F}(0)}\left.\frac{d\hat{F}(s)}{ds}\right|_{s=0}. \tag{A5}$$

To find $\tau_{FP}^{(c)}$, we first find the Laplace transform of the propagator, $\hat{g}(x, s)$, by solving Eq. (A1) in the Laplace space. The solution is

$$\hat{g}(x,s) = \frac{\sinh[(l-x)\sqrt{1+s/k}/\lambda]}{\sqrt{D(s+k)}\cosh\left(l\sqrt{1+s/k}/\lambda\right)}. \tag{A6}$$

Then we find $\hat{F}(s)$,

$$\hat{F}(s) = -D\left.\frac{\partial\hat{g}(x,s)}{\partial s}\right|_{s=0} = \frac{1}{\cosh(l\sqrt{1+s/k}/\lambda)}. \tag{A7}$$

Finally, we find $\tau_{FP}^{(c)}$ by Eq. (A5),

$$\tau_{FP}^{(c)} = \frac{l}{2k\lambda}\tanh\left(\frac{l}{\lambda}\right). \tag{A8}$$

Replacing here l by x we arrive at the expression for $\tau_{FP}^{(c)}(0 \to x)$ given in Eq. (4.4).

APPENDIX B: MEAN LOCAL ACCUMULATION TIME IN EQ. (4.6)

The mean local accumulation time $\tau(x|x)$, defined in Eq. (3.13), can be written in terms of the Laplace transform of the propagator $G(x, t|x)$ as

$$\tau(x|x) = -\frac{1}{\hat{G}(x,0|x)}\left.\frac{\partial\hat{G}(x,s|x)}{\partial s}\right|_{s=0}. \tag{B1}$$

The propagator $G(x, t|x_0)$ satisfies Eq. (3.2) with initial and boundary conditions given in the text below this equation. Respectively, the Laplace transform of the propagator satisfies

$$D\frac{\partial^2\hat{G}(x,s|x_0)}{\partial x^2} - k\hat{G}(x,s|x_0) = s\hat{G}(x,s|x_0) - \delta(x-x_0), \quad 0 < x, x_0 < L, \tag{B2}$$

with boundary conditions $\partial\hat{G}(x, s|x_0)/\partial x|_{x=0,\,L} = 0$. Solving this equation we find that $\hat{G}(x, s|x)$ is given by

$$\hat{G}(x,s|x) = \frac{\cosh(x\sqrt{1+s/k}/\lambda)\cosh[(L-x)\sqrt{1+s/k}/\lambda]}{\sqrt{D(s+k)}\sinh(L\sqrt{1+s/k}/\lambda)}. \tag{B3}$$

Substituting this into Eq. (B1) we obtain the expression for $\tau(x|x)$ given in Eq. (4.6).

APPENDIX C: LAPLACE TRANSFORM OF THE FLUX IN EQ. (4.10)

Consider a particle diffusing and being degraded on a semi-infinite interval, $x > 0$, terminated by a reflecting boundary at the origin. The interval contains an ideally absorbing trap located at $x = x_a$. Depending on the particle initial position x_0, the probability flux $F(t|x_0)$ entering the trap at time t is

$$F(t|x_0) = D\left.\frac{\partial G(x,t|x_0)}{\partial x}\right|_{x=x_a}[H(x_0-x_a)-H(x_a-x_0)], \tag{C1}$$

where $H(x)$ is the Heaviside step function, and $G(x, t|x_0)$ is the particle propagator. The propagator satisfies the reaction diffusion equation

$$\frac{\partial G(x,t|x_0)}{\partial t} = D\frac{\partial^2 G(x,t|x_0)}{\partial x^2} - kG(x,t|x_0), \tag{C2}$$

with the initial condition $G(x, 0|x_0) = \delta(x - x_0)$ and boundary conditions $G(x_a, t|x_0) = 0$ and $\partial G(x,t|x_0)/\partial x|_{x=0} = 0$, if $x_0 < x_a$, or $G(x, t|x_0) \to 0$, as $x \to \infty$, if $x_0 > x_a$. After the Laplace transformation, Eqs. (C1) and (C2) take the form

$$\hat{F}(s|x_0) = D\left.\frac{\partial \hat{G}(x,s|x_0)}{\partial x}\right|_{x=x_a}[H(x_0-x_a)-H(x_a-x_0)], \tag{C3}$$

and

$$D\frac{\partial^2 \hat{G}(x,s|x_0)}{\partial x^2} - k\hat{G}(x,s|x_0) = s\hat{G}(x,s|x_0) - \delta(x-x_0). \tag{C4}$$

Respectively, the boundary conditions take the form $\hat{G}(x_a,s|x_0) = 0$ and $\partial\hat{G}(x,s|x_0)/\partial x\big|_{x=0} = 0$, if $x_0 < x_a$ or $\hat{G}(x,s|x_0) \to 0$, as $x \to \infty$, if $x_0 > x_a$. Solving Eq. (C4) with $x_0 < x_a$ and $x_0 > x_a$, and substituting the solutions into Eq. (C.3), we find that

$$\hat{F}(s|x_0) = \begin{cases} \frac{\cosh\left(x_0\sqrt{1+s/k}/\lambda\right)}{\cosh\left(x_a\sqrt{1+s/k}/\lambda\right)}, & 0 < x_0 < x_a, \\ e^{-\sqrt{1+s/k}(x_0-x_a)/\lambda}, & x_a < x_0. \end{cases} \tag{C5}$$

Replacing here x_a by x, we arrive at the formula for the flux given in Eq. (4.10).

APPENDIX D: MEAN FLUX RELAXATION TIME

The flux $\langle F(t|x|x_0)\rangle_q$ of the particles entering an observation point x for the first time at time t is given by

$$\langle F(t|x|x_0)\rangle_q = Q\int_0^t \langle f(t|x_0 \to x)\rangle_q dt'. \tag{D1}$$

The relaxation function of the flux, denoted by $R_F(t|x)$ is defined as

$$R_F(t|x) = \frac{\langle F(t|x|x_0)\rangle_q - \langle F_{ss}(x|x_0)\rangle_q}{\langle F(0|x|x_0)\rangle_q - \langle F_{ss}(x|x_0)\rangle_q}, \tag{D2}$$

where $\langle F_{ss}(x|x_0)\rangle_q$ is the steady-state flux given in Eq. (5.3). The mean flux relaxation time, $\tau_F(x)$, is defined in terms of the flux relaxation function by

$$\tau_F(x) = \int_0^\infty R_F(t|x)dt = \hat{R}_F(0|x). \tag{D3}$$

In our case $\langle F(0|x|x_0)\rangle_q = 0$, and the Laplace transform of $R_F(t|x)$ is

$$\hat{R}_F(s|x) = \frac{1}{s}\left(1 - \left\langle \hat{\varphi}_{FP}^{(c)}(s|x_0 \to x)\right\rangle\right), \tag{D4}$$

where we have used the definition of the conditional probability density of the first-passage time, Eq. (3.8). Using the Taylor expansion of the Laplace transform of the conditional probability density of the first-passage time near $s = 0$,

$$\left\langle \hat{\varphi}_{FP}^{(c)}(s|x_0 \to x)\right\rangle \approx 1 - s\left\langle \tau_{FP}^{(c)}(x_0 \to x)\right\rangle, \tag{D5}$$

we find that the mean flux relaxation time, Eq. (D3), is identical to the conditional mean first-passage time from the source to the observation point,

$$\tau_F(x) = \left\langle \tau_{FP}^{(c)}(x_0 \to x)\right\rangle, \tag{D6}$$

as stated in Sec. V.

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