Kinetics of receptor occupancy during morphogen gradient formation

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(Received 6 February 2013; accepted 5 June 2013; published online 26 June 2013)

During embryogenesis, sheets of cells are patterned by concentration profiles of morphogens, molecules that act as dose-dependent regulators of gene expression and cell differentiation. Concentration profiles of morphogens can be formed by a source-sink mechanism, whereby an extracellular protein is secreted from a localized source, diffuses through the tissue and binds to cell surface receptors. A morphogen molecule bound to its receptor can either dissociate or be internalized by the cell. The effects of morphogens on cells depend on the occupancy of surface receptors, which in turn depends on morphogen concentration. In the simplest case, the local concentrations of the morphogen and morphogen-receptor complexes monotonically increase with time from zero to their steady-state values. Here, we derive analytical expressions for the time scales which characterize the formation of the steady-state concentrations of both the diffusible morphogen molecules and morphogen-receptor complexes at a given point in the patterned tissue. © *2013 AIP Publishing LLC*. [http://dx.doi.org/10.1063/1.4811654]

I. INTRODUCTION

Many complex tissues, including highly folded parts of mammalian brain, develop from epithelia, two-dimensional sheets of cells tightly adhering to each other.[1] The three-dimensional form of adult structures results from coordinated divisions, shape changes, and movements of cells within the sheets.[2] An important part of necessary coordination is provided by morphogens - form-generating molecules that act as regulators of intracellular processes.[3] Morphogens are typically extracellular proteins that are secreted from localized positions within the epithelium and control cell behaviors through binding and activation of cell surface receptors.[4,5] While the mechanisms by which morphogens control cell dynamics are far from being completely understood, for the purposes of this paper it suffices to say that cells exposed to different concentrations of a morphogen have different numbers of occupied cell surface receptors and behave differently. Understanding of the effects of morphogens requires analysis of the dynamics of ligand-receptor complexes.[6–8]

Several studies suggest that morphogens move through tissues in a manner consistent with Fickian diffusion, with effective diffusivity D.[3,9–13] Their binding to surface receptors is reversible and is commonly modeled by two first order reactions with the rate constants k_{on} and k_{off}. A morphogen molecule bound to a receptor can either dissociate, and continue its diffusion through the tissue, or be internalized into the cell through a process called endocytosis, which effectively terminates the spread of the morphogen from the source of its production. The rate constant of endocytosis is denoted by k_e. All these processes are schematically shown in Fig. 1. In addition, diffusing morphogen molecules can be degraded. The simplest model of morphogen gradient formation in this biophysical setting takes the form of two coupled differential equations for the concentrations of diffusible and receptor bound molecules.

The one-dimensional character of the model is motivated by the fact that morphogen production can be localized in stripe-like domains within the tissue. An example of such a one-dimensional pattern in a developing sheet is shown in Fig. 1, which provides an image of a stripe-like domain of ligand production (red) in the early *Drosophila* embryo.[14–17] The ligand is the epidermal growth factor (EGF) that binds to a uniformly distributed receptor (EGFR). Bound receptor activates the intracellular signaling pathway (green) that in turn controls gene expression. Studies of this system suggest that EGFR is present in excess, which means that one can model ligand-receptor dynamics without considering changes in the number of free receptors.

Models such as the one described above can be solved using a number of analytical or numerical techniques, yielding time-dependent concentration profiles of the two components. In a number of applications, one is interested in characteristic time scales of concentration dynamics at a given location.[18–26] Here, we provide analytical expressions for such time scales, with the emphasis on receptor-bound component of the model. This reflects the fact that morphogens control cellular processes through cell surface receptors. Specifically, we introduce two local times $\tau_m(x)$ and $\tau_b(x)$, which provide local time scales that characterize the formation of the steady-state concentration profiles of diffusing morphogen molecules and morphogen-receptor complexes, respectively.

The paper contains three main results. The first provides a simple relationship between the local times $\tau_b(x)$ and $\tau_m(x)$ given in Eq. (3.14). The second result shows that $\tau_m(x)$ is proportional to a local accumulation time $\tau_{eff}(x)$, Eq. (4.15). The latter time describes the formation of the steady-state morphogen concentration profile assuming irreversible binding of

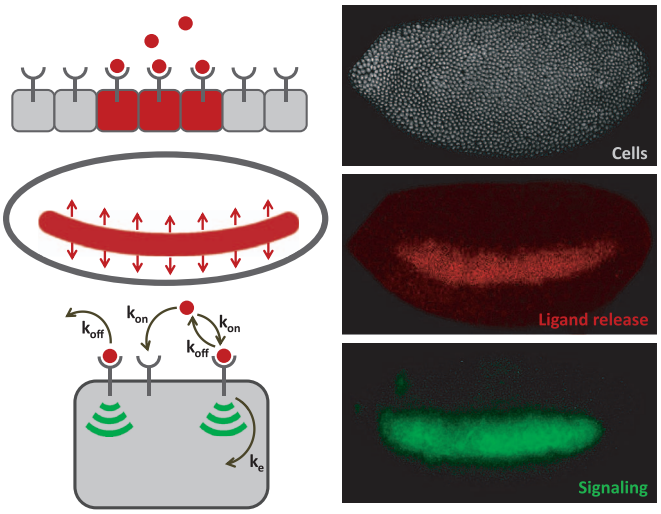

FIG. 1. (Left) Schematic representation a two-dimensional tissue with a quasi one-dimensional distribution of ligand production. Diffusible ligand is produced from the spatially localized source, diffuses through the tissue, binds to cell surface receptors, and can be internalized by cells. (Right) An expertimental example that fits this model. A spatially uniform arrangement of cells in the early *Drosophila* embryo (top panel, gray), spatially restricted source of ligand production (middle panel, red), and the resulting activation of the intracellular signaling pathway (bottom panel, green). The ligand binds to and activates receptors which are uniformly expressed throughout the embryo.

the morphogen to the receptors. The third result of the paper is a general solution for $\tau_{eff}(x)$ given in Eqs. (4.17)–(4.19). The local times $\tau_m(x)$ and $\tau_b(x)$, should not be confused with the local accumulation time $\tau(x)$ studied in Refs. 18, 19, 21, and 22, assuming that morphogen binding to the receptors is irreversible.

The outline of the paper is as follows. In Sec. II we introduce the model and give formal definitions of the local times $\tau_m(x)$ and $\tau_b(x)$. The relationship between these times, mentioned above, is derived in Sec. III. In Sec. IV, we first establish the proportionality of $\tau_m(x)$ and $\tau_{eff}(x)$. Then we derive a general solution for $\tau_{eff}(x)$ and consider an illustrative example. The final Sec. V contains a summary of the results of our analysis and some concluding remarks.

II. MODEL AND DEFINITIONS

Consider a one-dimensional model of a patterned tissue. The model assumes that diffusing morphogen molecules are injected with a position-dependent and time-independent injection rate $q(x)$ into an initially empty interval of length L, $0 < x < L$, terminated by reflecting boundaries. We define the injection rate density $p(x)$ (normalized to unity) as the ratio of $q(x)$ to the total injection rate $Q = \int_0^L q(x)dx$,

$$p(x) = \frac{q(x)}{Q} = \frac{q(x)}{\int_0^L q(x)dx}. \tag{2.1}$$

Diffusing morphogen molecules bind to immobile receptors with the rate constant k_{on} and are degraded with the rate constant $k_{\rm deg}$. Morphogen-receptor complexes either dissociate or are endocytosed with the rate constants k_{off} and k_e, respectively. It is assumed that the receptors are in excess, so that the receptor saturation can be ignored. This model is slightly more general than the model discussed in the Introduction since it assumes that diffusing morphogen molecules can be degraded.

As time goes from zero to infinity, the concentrations of diffusing morphogen molecules, $C_m(x, t)$, and occupied receptors, $C_b(x, t)$, monotonically increase from zero to their steady-state values, $C_m^{ss}(x)$ and $C_b^{ss}(x)$, respectively. Time-dependent concentration profiles $C_m(x, t)$ and $C_b(x, t)$ satisfy

$$\frac{\partial C_m}{\partial t} = D\frac{\partial^2 C_m}{\partial x^2} - (k_{\rm deg} + k_{on})C_m + k_{off}C_b + q(x)H(t), \tag{2.2}$$

$$\frac{\partial C_b}{\partial t} = k_{on}C_m - (k_{off} + k_e)C_b, \tag{2.3}$$

where $H(t)$ is the Heaviside step-function, subject to the initial conditions

$$C_m(x, 0) = C_b(x, 0) = 0. \tag{2.4}$$

In addition, $C_m(x, t)$ satisfies reflecting boundary conditions at the ends of the interval,

$$\left.\frac{\partial C_m(x, t)}{\partial x}\right|_{x=0,\,L} = 0. \tag{2.5}$$

It is convenient to describe the formation of the steady-state concentration profiles using the relaxation functions, $R_\alpha(t|x)$, $\alpha = m, b$, defined as

$$R_\alpha(t|x) = \frac{C_\alpha(x, t) - C_\alpha^{ss}(x)}{C_\alpha(x, 0) - C_\alpha^{ss}(x)} = 1 - \frac{C_\alpha(x, t)}{C_\alpha^{ss}(x)}. \tag{2.6}$$

The arguments of the relaxation functions are written so that to stress the point that the focus of our analysis is on the time dependence of the relaxation function at a given point x, so that x is considered as a parameter. The relaxation functions monotonically decrease from unity to zero, as time goes from zero to infinity.

We use the relaxation functions to define the local times $\tau_\alpha(x)$, which provide time scales that characterize the formation of the steady-state concentration profiles at point x,

$$\tau_\alpha(x) = \int_0^\infty R_\alpha(t|x)dt = \hat{R}_\alpha(s|x)\big|_{s=0}. \tag{2.7}$$

Here $\hat{R}_\alpha(s|x)$ is the Laplace transform of $R_\alpha(t|x)$ and s is the Laplace parameter. The Laplace transform of function $f(t)$ denoted by $\hat{f}(s)$ is defined as

$$\hat{f}(s) = \int_0^\infty e^{-st} f(t)dt. \tag{2.8}$$

In what follows we derive a general relationship between the times $\tau_m(x)$ and $\tau_b(x)$, and a general formula which shows that $\tau_m(x)$ is proportional to an effective local accumulation time $\tau_{eff}(x)$ that describes the formation of the steady-state concentration profile in the absence of receptors. In addition, we obtain a solution for the local accumulation time, which gives $\tau_{eff}(x)$ at arbitrary L and $q(x)$.

III. GENERAL RELATIONSHIP BETWEEN THE LOCAL TIMES $\tau_m(x)$ AND $\tau_b(x)$

Since Eqs. (2.2) and (2.3) are linear, the concentration profiles can be written in terms of the two-component propagator (the Green's function) $G_\alpha(x, t|x_0)$,

$$C_\alpha(x,t) = \int_0^t dt' \int_0^L G_\alpha(x, t-t'|x_0) q(x_0) dx_0 = Q \int_0^t \langle G_\alpha(x, t-t'|x_0)\rangle dt', \tag{3.1}$$

where the angular brackets denote the averaging over the injection point,

$$\langle G_\alpha(x,t|x_0)\rangle = \int_0^L G_\alpha(x,t|x_0) p(x_0) dx_0. \tag{3.2}$$

The two components of the propagator satisfy

$$\frac{\partial G_m}{\partial t} = D\frac{\partial^2 G_m}{\partial x^2} - (k_{\rm deg} + k_{on}) G_m + k_{off} G_b, \tag{3.3}$$

$$\frac{\partial G_b}{\partial t} = k_{on} G_m - (k_{off} + k_e) G_b, \tag{3.4}$$

subject to the initial conditions

$$G_m(x, 0|x_0) = \delta(x - x_0),\ G_b(x, 0|x_0) = 0. \tag{3.5}$$

In addition, $G_m(x, t|x_0)$ satisfies reflecting boundary conditions at the ends of the interval,

$$\left.\frac{\partial G_m(x,t|x_0)}{\partial x}\right|_{x=0,\,L} = 0. \tag{3.6}$$

As follows from Eq. (3.1), the steady-state concentration profiles are given by

$$C_\alpha^{ss}(x) = \int_0^\infty dt \int_0^L G_\alpha(x,t|x_0) q(x_0) dx_0 = Q\langle \hat{G}_\alpha(x, 0|x_0)\rangle, \tag{3.7}$$

where $\hat{G}_\alpha(x, s|x_0)$ is the Laplace transform of $G_\alpha(x, t|x_0)$. Using Eqs. (3.1) and (3.7), we can write the relaxation function, Eq. (2.6), in terms of the propagator,

$$R_\alpha(t|x) = 1 - \frac{1}{\langle \hat{G}_\alpha(x, 0|x_0)\rangle} \int_0^t \langle G_\alpha(x, t-t'|x_0)\rangle dt'. \tag{3.8}$$

Substituting this into the definition of the local time, Eq. (2.7), we arrive at

$$\tau_\alpha(x) = \hat{R}_\alpha(0|x) = \lim_{s\to 0} \frac{1}{s}\left(1 - \frac{\langle \hat{G}_\alpha(x, s|x_0)\rangle}{\langle \hat{G}_\alpha(x, 0|x_0)\rangle}\right). \tag{3.9}$$

Linearizing $\langle \hat{G}_\alpha(x, s|x_0)\rangle$ with respect to s at small s, we obtain

$$\tau_\alpha(x) = -\frac{1}{\langle \hat{G}_\alpha(x, 0|x_0)\rangle} \left.\frac{\partial \langle \hat{G}_\alpha(x, s|x_0)\rangle}{\partial s}\right|_{s=0} = -\left.\frac{\partial \ln \langle \hat{G}_\alpha(x, s|x_0)\rangle}{\partial s}\right|_{s=0}. \tag{3.10}$$

It turns out that there is a general relationship between the local times $\tau_m(x)$ and $\tau_b(x)$. To derive this relationship, we use the relationship between the Laplace transforms of the components of the propagator, $\hat{G}_m(x, s|x_0)$ and $\hat{G}_b(x, s|x_0)$, which can be obtained from Eq. (3.4),

$$\hat{G}_b(x, s|x_0) = \frac{k_{on}}{k_{off} + k_e + s} \hat{G}_m(x, s|x_0). \tag{3.11}$$

This leads to

$$\left.\frac{\partial \hat{G}_b(x, s|x_0)}{\partial s}\right|_{s=0} = \frac{k_{on}}{k_{off} + k_e} \left(\left.\frac{\partial \hat{G}_m(x, s|x_0)}{\partial s}\right|_{s=0} - \frac{\hat{G}_m(x, 0|x_0)}{k_{off} + k_e}\right). \tag{3.12}$$

Averaging this over the injection point we obtain

$$-\left.\frac{\partial \langle \hat{G}_b(x, s|x_0)\rangle}{\partial s}\right|_{s=0} = \frac{k_{on}\langle \hat{G}_m(x, 0|x_0)\rangle}{k_{off} + k_e} \left(\tau_m(x) + \frac{1}{k_{off} + k_e}\right), \tag{3.13}$$

where we have used the definition of $\tau_m(x)$, Eq. (3.10).

According to Eq. (3.11), the factor $k_{on}\langle \hat{G}_m(x, 0|x_0)\rangle / (k_{off} + k_e)$, in the right-hand side of Eq. (3.13), is $\langle \hat{G}_b(x, 0|x_0)\rangle$. Using this and the definition of $\tau_b(x)$, Eq. (3.10), we arrive at one of the main results of the present paper

$$\tau_b(x) = \tau_m(x) + \frac{1}{k_{off} + k_e}, \tag{3.14}$$

which establishes the relationship between the local times $\tau_m(x)$ and $\tau_b(x)$. The relation shows that the delay time, $\tau_b(x) - \tau_m(x)$, is equal to $(k_{off} + k_e)^{-1}$, which is the mean lifetime of the morphogen-receptor complex. Earlier we obtained this result in the special case where the source of the morphogen was localized at the edge of an infinitely long interval, i.e., $p(x) = \delta(x)$ and $L \to \infty$.[19] Now, we have shown that this relationship between the local times is general. One can readily find $\tau_b(x)$ having in hand $\tau_m(x)$. In Sec. IV we will show that $\tau_m(x)$ is simply related with an effective local accumulation time in the absence of receptors, $\tau_{\rm eff}(x)$, for which we will find a general solution at arbitrary length of the interval and the injection rate density.

IV. GENERAL SOLUTIONS FOR THE TIMES $\tau_m(x)$ AND $\tau_{\rm eff}(x)$

According to the definition in Eq. (3.10), the local time $\tau_m(x)$ is given by

$$\tau_m(x) = -\frac{1}{\langle \hat{G}_m(x, 0|x_0)\rangle} \left.\frac{\partial \langle \hat{G}_m(x, s|x_0)\rangle}{\partial s}\right|_{s=0}. \tag{4.1}$$

The Laplace transform $\hat{G}_m(x, s|x_0)$ satisfies the equation, which can be obtained by Laplace transforming Eq. (3.3) and substituting into the resulting equation $\hat{G}_b(x, s|x_0)$ given in

Eq. (3.11). This leads to

$$D\frac{d^2\hat{G}_m}{dx^2} - \left[k_{\rm deg} + s + \frac{k_{on}(k_e+s)}{k_{off}+k_e+s}\right]\hat{G}_m = -\delta(x-x_0), \tag{4.2}$$

with reflecting boundary conditions at the ends of the interval, $\partial\hat{G}_m / \partial x|_{x=0,\,L} = 0$. An approximate small-$s$ solution to this equation is given by

$$\hat{G}_m(x,s|x_0) \approx G_m^{(0)}(x|x_0) - sG_m^{(1)}(x|x_0), \quad s \to 0, \tag{4.3}$$

where

$$G_m^{(0)}(x|x_0) = \hat{G}_m(x,0|x_0), \tag{4.4}$$

and

$$G_m^{(1)}(x|x_0) = -\left.\frac{\partial\hat{G}_m(x,s|x_0)}{\partial s}\right|_{s=0}. \tag{4.5}$$

Using $G_m^{(0)}(x|x_0)$ and $G_m^{(1)}(x|x_0)$ we can write Eq. (4.1) as

$$\tau_m(x) = \frac{\langle G_m^{(1)}(x|x_0)\rangle}{\langle G_m^{(0)}(x|x_0)\rangle}. \tag{4.6}$$

Linearizing Eq. (4.2) with respect to s, we find that functions $G_m^{(0)}(x|x_0)$ and $G_m^{(1)}(x|x_0)$ satisfy

$$D\frac{d^2G_m^{(0)}}{dx^2} - k_{\rm deg}^{eff}G_m^{(0)} = -\delta(x-x_0), \tag{4.7}$$

$$D\frac{d^2G_m^{(1)}}{dx^2} - k_{\rm deg}^{eff}G_m^{(1)} = -\left[1 + \frac{k_{on}k_{off}}{(k_{off}+k_e)^2}\right]G_m^{(0)}, \tag{4.8}$$

subject to reflecting boundary conditions at the ends of the interval, $\partial G_m^{(0,1)} / \partial x|_{x=0,\,L} = 0$. The rate constant $k_{\rm deg}^{eff}$ here is given by

$$k_{\rm deg}^{eff} = k_{\rm deg} + \frac{k_{on}k_e}{k_{off}+k_e}. \tag{4.9}$$

It can be interpreted as an effective degradation rate constant.

In our earlier works,[18,19,21,22] we studied the local accumulation time that characterizes the formation kinetics of the morphogen steady-state concentration profile in the absence of receptors. This is formally equivalent to irreversible morphogen binding to the receptors. The theory developed in the present paper reduces to this special case if we take $k_{on} = 0$ and/or $k_{off} \to \infty$. As a result, $k_{\rm deg}^{eff} = k_{\rm deg}$, Eq. (4.9), and the square brackets in Eq. (4.8) reduce to unity, so that Eqs. (4.7) and (4.8) take the form

$$D\frac{d^2G_m^{(0)}}{dx^2} - k_{\rm deg}G_m^{(0)} = -\delta(x-x_0), \tag{4.10}$$

$$D\frac{d^2G_m^{(1)}}{dx^2} - k_{\rm deg}G_m^{(1)} = -G_m^{(0)}, \tag{4.11}$$

with the same reflecting boundary conditions at the ends of the interval, $\partial G_m^{(0,1)} / \partial x|_{x=0,\,L} = 0$. It turns out that time $\tau_m(x)$, Eq. (4.6), in the general case is proportional to the local accumulation time $\tau_{\mathit{eff}}(x)$, which characterizes the formation of the steady-state concentration profile in the absence of receptors, assuming that the degradation rate constant is $k_{\rm deg}^{eff}$ given in Eq. (4.9).

To show this, we introduce function $\tilde{G}_m^{(1)}(x|x_0)$ defined by

$$G_m^{(1)}(x|x_0) = \left[1 + \frac{k_{on}k_{off}}{(k_{off}+k_e)^2}\right]\tilde{G}_m^{(1)}(x|x_0). \tag{4.12}$$

Substituting this into Eq. (4.8), we find that $\tilde{G}_m^{(1)}(x|x_0)$ satisfies

$$D\frac{d^2\tilde{G}_m^{(1)}}{dx^2} - k_{\rm deg}^{eff}\tilde{G}_m^{(1)} = -G_m^{(0)}, \tag{4.13}$$

subject to reflecting boundary conditions at the ends of the interval, $\partial\tilde{G}_m^{(1)} / \partial x|_{x=0,\,L} = 0$. One can see that Eqs. (4.7) and (4.13) are identical to Eqs. (4.10) and (4.11) with $k_{\rm deg} = k_{\rm deg}^{eff}$. Based on this identity, we introduce time $\tau_{\mathit{eff}}(x)$ defined as

$$\tau_{\mathit{eff}}(x) = \frac{\langle\tilde{G}_m^{(1)}(x|x_0)\rangle}{\langle G_m^{(0)}(x|x_0)\rangle}. \tag{4.14}$$

This time is the local accumulation time of the formation of the steady-state concentration profile in the absence of receptors on condition that the degradation rate constant is given by $k_{\rm deg}^{eff}$, Eq. (4.9). Finally substituting $G_m^{(1)}(x|x_0)$ given in Eq. (4.12) into Eq. (4.6), we obtain

$$\tau_m(x) = \left[1 + \frac{k_{on}k_{off}}{(k_{off}+k_e)^2}\right]\tau_{\mathit{eff}}(x). \tag{4.15}$$

This simple relationship between times $\tau_m(x)$ and $\tau_{\mathit{eff}}(x)$ is the second main result of this paper.

Now we find a general solution for $\tau_{\mathit{eff}}(x)$. To do this, we use the fact that the solution to Eq. (4.13) can be written as

$$\tilde{G}_m^{(1)}(x|x_0) = \int_0^L G_m^{(0)}(x|x')G_m^{(0)}(x'|x_0)dx'. \tag{4.16}$$

Substituting this into Eq. (4.14), we obtain

$$\tau_{\mathit{eff}}(x) = \frac{1}{\langle G_m^{(0)}(x|x_0)\rangle}\int_0^L G_m^{(0)}(x|x')\langle G_m^{(0)}(x'|x_0)\rangle dx', \tag{4.17}$$

which gives $\tau_{\mathit{eff}}(x)$ in terms of the function $G_m^{(0)}(x|x_0)$. Finally, we find this function solving Eq. (4.7),

$$G_m^{(0)}(x|x_0) = A\left[\cosh\left(\frac{x}{\lambda_{\mathit{eff}}}\right)\cosh\left(\frac{L-x_0}{\lambda_{\mathit{eff}}}\right)H(x_0-x) + \cosh\left(\frac{L-x}{\lambda_{\mathit{eff}}}\right)\cosh\left(\frac{x_0}{\lambda_{\mathit{eff}}}\right)H(x-x_0)\right], \tag{4.18}$$

where A and λ_{eff} are given by

$$A = \frac{1}{k_{\rm deg}^{eff}\lambda_{\mathit{eff}}\sinh\left(\frac{L}{\lambda_{\mathit{eff}}}\right)}, \tag{4.19}$$

$$\lambda_{\mathit{eff}} = \sqrt{\frac{D}{k_{\rm deg}^{eff}}} = \sqrt{\frac{D(k_{off}+k_e)}{k_{\rm deg}k_{off} + k_{\rm deg}k_e + k_{on}k_e}}. \tag{4.20}$$

Expressions in Eqs. (4.17)–(4.19) provide a general solution for $\tau_{\mathit{eff}}(x)$ at arbitrary length L of the interval and the injection rate density $p(x_0)$. This is the third main result of the present paper. Having in hand this general solution, one can find a general solution for $\tau_m(x)$ using Eq. (4.15).

A. Illustrative example

As an illustrative example consider the situation where the source of the morphogen is localized at the edge of the interval, $p(x) = \delta(x)$. In this case Eq. (3.2) leads to

$$\left\langle G_m^{(0)}(x|x_0)\right\rangle = G_m^{(0)}(x|0) = \frac{\cosh\left(\frac{L-x}{\lambda_{eff}}\right)}{\sqrt{Dk_{\rm deg}^{eff}}\sinh\left(\frac{L}{\lambda_{eff}}\right)}. \quad (4.21)$$

Substituting this into Eq. (4.17), we find that $\tau_{eff}(x)$ is given by

$$\tau_{eff}(x) = \frac{1}{G_m^{(0)}(x|0)}\int_0^L G_m^{(0)}(x|x')G_m^{(0)}(x'|0)dx'. \quad (4.22)$$

Using the expression for $G_m^{(0)}(x|x_0)$ in Eq. (4.18) and carrying out the integration, we obtain

$$\tau_{eff}(x) = \frac{1}{2k_{\rm deg}^{eff}}\left[1 + \frac{L}{\lambda_{eff}}\coth\left(\frac{L}{\lambda_{eff}}\right) - \frac{L-x}{\lambda_{eff}}\tanh\left(\frac{L-x}{\lambda_{eff}}\right)\right]. \quad (4.23)$$

When $k_b = 0$ and/or $k_{dis} \to \infty$, $k_{\rm deg}^{eff}$ and λ_{eff} are replaced by $k_{\rm deg}$ and $\lambda = \sqrt{D/k_{\rm deg}}$, and we recover the result for the local accumulation time obtained in Refs. 19 and 21.

Finally, we can use $\tau_{eff}(x)$ given in Eq. (4.23) to find the local times $\tau_m(x)$ and $\tau_b(x)$ associated with the formation of the steady-state concentrations of diffusing morphogen molecules and morphogen-receptor complexes at point x of the patterned tissue by means of Eqs. (4.15) and (3.14), respectively. The results are

$$\tau_m(x) = \frac{1}{2k_{\rm deg}^{eff}}\left[1 + \frac{k_{on}k_{off}}{(k_{off}+k_e)^2}\right] \times \left[1 + \frac{L}{\lambda_{eff}}\coth\left(\frac{L}{\lambda_{eff}}\right) - \frac{L-x}{\lambda_{eff}}\tanh\left(\frac{L-x}{\lambda_{eff}}\right)\right] \quad (4.24)$$

and

$$\tau_b(x) = \frac{1}{2k_{\rm deg}^{eff}}\left[1 + \frac{k_{on}k_{off}}{(k_{off}+k_e)^2}\right] \times \left[1 + \frac{L}{\lambda_{eff}}\coth\left(\frac{L}{\lambda_{eff}}\right) - \frac{L-x}{\lambda_{eff}}\tanh\left(\frac{L-x}{\lambda_{eff}}\right)\right] + \frac{1}{k_{off}+k_e}. \quad (4.25)$$

As $L \to \infty$, Eq. (4.23) takes the form

$$\tau_{eff}(x) = \frac{1}{2k_{\rm deg}^{eff}}\left(1 + \frac{x}{\lambda_{eff}}\right). \quad (4.26)$$

$\tau_m(x)$ and $\tau_b(x)$, Eqs. (4.24) and (4.25), in this limiting case reduce to

$$\tau_m(x) = \frac{1}{2k_{\rm deg}^{eff}}\left(1 + \frac{x}{\lambda_{eff}}\right)\left[1 + \frac{k_{on}k_{off}}{(k_{off}+k_e)^2}\right] \quad (4.27)$$

and

$$\tau_b(x) = \frac{1}{2k_{\rm deg}^{eff}}\left(1 + \frac{x}{\lambda_{eff}}\right)\left[1 + \frac{k_{on}k_{off}}{(k_{off}+k_e)^2}\right] + \frac{1}{k_{off}+k_e}, \quad (4.28)$$

which are identical to the results for $\tau_m(x)$ and $\tau_b(x)$ obtained in Ref. 19 for the particular case of infinitely long interval ($L \to \infty$) and the localized source of the morphogen ($p(x) = \delta(x)$).

V. CONCLUDING REMARKS

The present paper is devoted to the two local times $\tau_m(x)$ and $\tau_b(x)$, which provide time scales characterizing the formation of steady-state concentration profiles of the diffusing morphogen molecules and morphogen-receptor complexes at point x of the patterned tissue, respectively. At $t = 0$ the concentrations of both diffusing morphogen molecules and morphogen-receptor complexes are zero, $C_{m,b}(x, 0) = 0$. As time goes from zero to infinity, these concentrations monotonically increase from zero to their steady-state values, $C_{m,b}^{ss}(x)$. Local kinetics of the formation of the steady-state concentrations are described by the time-dependent concentration profiles $C_{m,b}(x, t)$. One can use the local times to construct a single-exponential approximation for $C_{m,b}(x, t)$.

$$C_{m,b}(x,t) = C_{m,b}^{ss}(x)\{1 - \exp[-t/\tau_{m,b}(x)]\}. \quad (5.1)$$

The accuracy of this approximation is illustrated in Fig. 2 in the special case of infinite interval ($L \to \infty$) and localized source of the morphogen molecules ($p(x) = \delta(x)$). In this case the steady-state concentration profiles are single exponential, $C_{m,b}^{ss}(x) = C_{m,b}^{ss}(0)\exp(-x/\lambda_{eff})$, with λ_{eff} given by Eq. (4.20).

Two main results of our analysis are given in Eqs. (3.14) and (4.15). The former establishes a simple relationship between the two local times. It shows that the delay time, $\tau_b(x) - \tau_m(x)$, is equal to $(k_{off} + k_e)^{-1}$, which is the mean lifetime of the morphogen-receptor complex. Our second main result, given in Eq. (4.15), shows that one can find the local time $\tau_m(x)$ in the presence of receptors, using the local accumulation time $\tau_{eff}(x)$ describing the formation of the steady-state concentration profile in the absence of receptors. For the latter time we have obtained a general solution, Eqs. (4.17)–(4.19), which gives $\tau_{eff}(x)$ at arbitrary length L of the interval and the injection rate density $p(x_0)$. This is the third main result of the present paper.

Both the relationship between the two local times and the relationship between $\tau_m(x)$ and the local accumulation time $\tau_{eff}(x)$ are universal in the sense that they are independent of the location of the observation point x, the injection rate density $p(x_0)$, and the length L of the interval. The only model parameters involved in these relationships are the rate constants k_{on}, k_{off}, k_e, and $k_{\rm deg}$. This suggests that the relationships in Eqs. (3.13) and (4.15) may be applicable beyond the one-dimensional model of a patterned tissue analyzed in the present paper. Finally, we note that the formalism developed above can be generalized to the case of subdiffusive motion of the morphogen discussed in recent papers.[27,28]

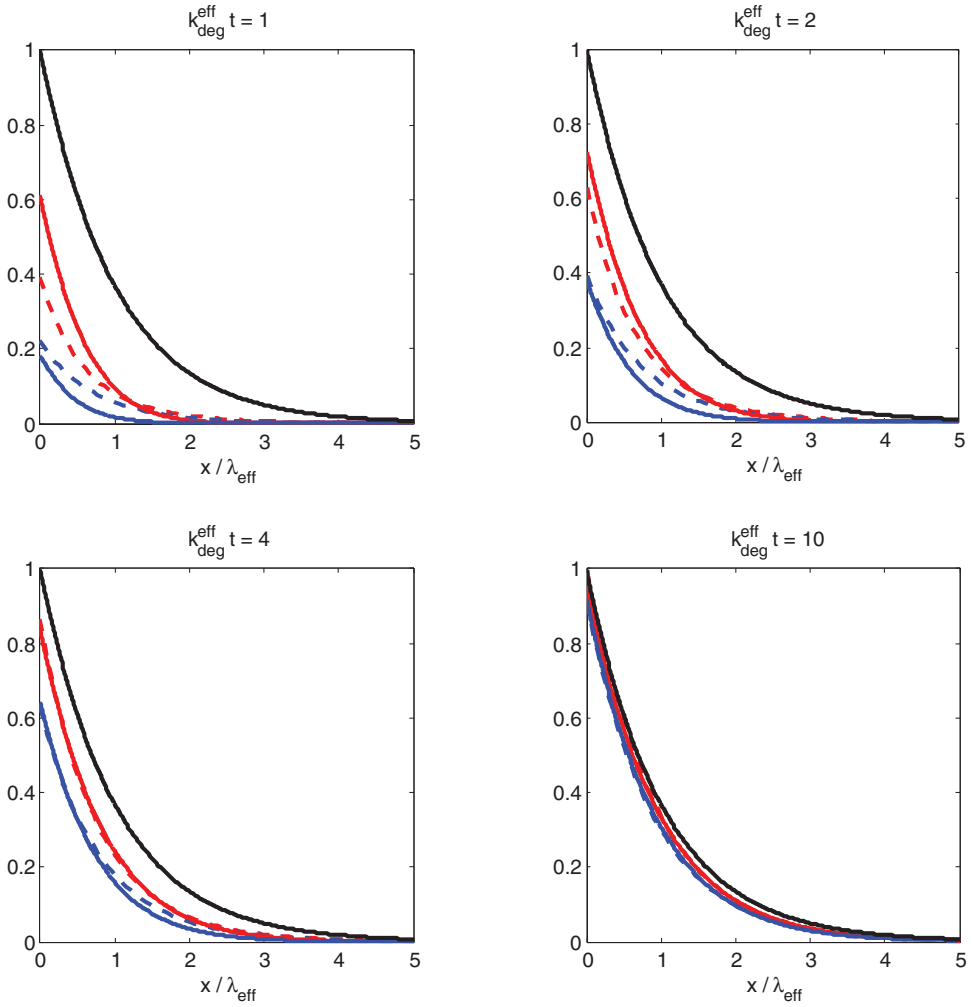

FIG. 2. Single-exponential approximation of the concentration dynamics. The four panels present concentration profiles of mobile and immobile species at different times: $tk_{\mathrm{deg}}^{eff} = 1$, 2, 4, and 10, where k_{deg}^{eff} is given in Eq. (4.9). The profiles are normalized to the corresponding steady-state values at $x = 0$. The red and blue lines represent the mobile and immobile species, respectively. The black lines are the normalized steady-state profile profiles, $\exp(-x/\lambda_{eff})$, where λ_{eff} is given in Eq. (4.20). Solid and dashed curves are exact solutions for the concentration profiles obtained numerically and their single-exponential counterparts, Eq. (5.1), respectively. The quality of the single-exponential approximation improves with time. The plots show the dependences for the following choice of the problem parameters: $D = Q = 1$, $k_{on} / k_{\mathrm{deg}}^{eff} = 1$, and $k_{off} / k_{\mathrm{deg}}^{eff} = k_e / k_{\mathrm{deg}}^{eff} = 0.25$.

Our analysis is based on the assumption that the receptor is present in excess. This makes the model linear that allows us to find the analytical solutions mentioned above. The question naturally arises how the obtained results will change for non-linear models. In Ref. 20, a formalism is developed which can be used to evaluate the local accumulation time for non-linear models in one-component systems. Generalization of this formalism to two-component systems discussed above is not an easy task. This is an issue we hope to tackle in the future.

ACKNOWLEDGMENTS

A.M.B. was supported by the Intramural Research Program of the NIH, Center for Information Technology. S.Y.S. acknowledges partial support by the National Science Foundation [grants DMS-1119714 and DMS-0718604]. The authors thank Bomyi Lim (Princeton) for preparing the figure used in this paper.

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