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Effect of cyto/chemokine degradation in effective intercellular communication distances

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Abstract

Many complex biological processes such as cell differentiation, cell proliferation, and cell motility are governed by cell signaling. This mode of intercellular communication is of paramount importance for tissue function and ultimately for entire organism. In intercellular communication cells secrete signaling molecules such as cyto/chemokines which diffuse through the surrounding medium and eventually bind to receptors on other cells whereby the signal transduction is completed. An accurate estimation of the effective communication distances and the time scale on which signaling takes place are important for the interpretation of cell and organ physiology and ultimately in the effective and efficient chemotactically driven tissue engineering. The present study uses a solitary cell model incorporating degradation of secreted molecules to estimate the effective communication distances and the time scale on which signaling takes place. We demonstrate through our model that in presence of degradation the effective communication distances are significantly reduced.

I. INTRODUCTION

Study of biological systems to understand the macroscopic complexity arising from the microscopic cellular interactions is advancing rapidly. At the microscopic level cells interact with each other through local short-range forces such as adhesion and through long-range forces mediated via cell signaling [1]. Many complex biological processes such as cell differentiation, cell proliferation, and cell motility are governed by cell signaling [2]. This mode of intercellular communication is of paramount importance for tissue function and ultimately for entire organism. In intercellular communication cells secrete signaling molecules such as cyto/chemokines which diffuse through the surrounding medium and eventually bind to receptors on other cells whereby the signal transduction is completed [3]. Intercellular communication is dictated both by physicochemical transport processes and cellular secretion rates which in turn are determined by genetic and biochemical processes [4]. To quantitatively characterize and study the nature of intercellular signaling processes one would like to estimate the effective communication distances and the time scale on which signaling takes place [4, 5]. Estimation of these is important for the interpretation of

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cell and organ physiology and ultimately in the effective and efficient chemotactically driven tissue engineering [6, 7].

Chemotactically driven intercellular communication is a ubiquitous phenomenon in microorganisms [8]. The interpretation, estimation, and understanding of intercellular communication are crucially important in large physiological models that incorporate chemotaxis [9–11]. Chemotactically driven cell motility depends on the local concentration and concentration gradient of cell secreted molecules. Therefore, the accurate prediction of models of chemotaxis is contingent on the accurate estimation of effective communication distances over which a single cell can meaningfully propagate a soluble signal. To systematically evaluate the nature and limitations of intercellular communication Francis and Palsson [4, 5] used a solitary cell model to estimate effective communication distances over which a single cell can meaningfully propagate a soluble signal and a characteristic time required to complete this signal transduction. Francis and Palsson [4] found out that when the secretion rate is constant with time the process is governed by a single dimensionless group α which represents the ratio of biological parameters and physicochemical determinants. For physiologically relevant values of parameters contained in α , e.g. signal diffusivity and the equilibrium binding constant, Francis and Palsson [4] estimated effective communication distance approximately $250\ \mu\text{m}$ and the characteristic time 10–30 minutes. Yoshida *et al.* [12, 13] demonstrated that apart from equilibrium binding constants the time scales characterizing the periodicity of time-dependent secretion rate also influence the effective communication distance. Furthermore, Yoshida *et al.* [14] examined the dependence of effective communication distance and characteristic time on the duration of a “pulse” of secretion. Yoshida *et al.* [15] also demonstrated that the temporal non-uniformity of the secretion is more important for the intercellular communication distance than the non-uniformity of the secretion in magnitude and direction. Jabbarzadeh and Abrams [16] demonstrated that the effective communication distance increases with decreasing pulse length, but this increase is theoretically limited to approximately twice the effective communication distance in the case of steady secretion.

In physiological conditions the secreted molecules decay in the surrounding medium with a specified rate denoted by λ which is referred to as the degradation rate [1, 17]. Pioneering work of Francis and Palsson [4, 5] in absence of degradation was extended to examine the dependence of effective communication distance both on the temporal non-uniformity of the secretion and the non-uniformity of the secretion in magnitude and direction [12–16]. In the present study we further extend the work of Francis and Palsson [4, 5] incorporating the degradation of secreted molecules. Specifically, we examine the effect of degradation of secreted molecules on the effective communication distance. We demonstrate through our extended model that in presence of degradation the effective communication distances are significantly reduced. The reduction in effective communication distance is dependent on the degradation rate. Higher the degradation rate, lower the effective communication distance. The extended model has an application in the accurate estimation of effective communication distance and ultimately in the effective and efficient chemotactically driven tissue engineering [6, 7]. The analytical solution of the fundamental model for diffusion of secreted cyto/chemokine molecules with degradation is obtained via Laplace Transform Method (see supplementary material for details). In absence of degradation we recover the

analytical solution obtained by Yoshita and Horiike [12] via Fourier Transform Method of the corresponding diffusion equation (see supplementary material for details). Solutions were obtained by evaluating the derived analytical equations such as Eqs. (5), (7), and (9) by writing a FORTRAN 90 code. Solutions to Eq. (10)–(11) were obtained using Newton-Raphson method [18].

II. ANALYSIS AND RESULTS

Cyto/Chemokine signaling by a single “solitary” cell

Consider a secreting spherical cell of radius a with its center fixed at the origin (see Fig. 1 in ref. [4]). Chemical substances (cyto/chemokine molecules) secreted from the cell surface diffuse into the surrounding medium. Considering spherical symmetry the governing diffusion equation that describes the time dependent mass transport of these molecules in presence of degradation is given by [1]

$$\frac{\partial c}{\partial t} = D \frac{1}{r^2} \frac{\partial}{\partial r} \left[r^2 \frac{\partial c}{\partial r} \right] - \lambda c, \quad (1)$$

where $c(r, t)$ is the concentration of the cyto/chemokine molecules, D is the diffusion coefficient of these molecules in the surrounding medium, r is the distance from the origin, and λ represents degradation rate of cytokine molecules. The flux $j(r, t)$ associated with $c(r, t)$ is governed by the Fick's law of diffusion [19]. According to it the diffusion flux along r -direction is proportional to the concentration gradient:

$$-D \frac{\partial c}{\partial r} = j(r, t). \quad (2)$$

The minus sign in the equation means that diffusion is down the concentration gradient. The flux of diffusing molecules is used to quantify how fast diffusion occurs.

Initially the concentration of cyto/chemokine molecules in the surrounding medium is zero. We also assume that at any time the concentration is completely diluted very far ($r \rightarrow \infty$) from the cell. At time $t = 0$ the cell starts secreting these molecules with a constant rate j_0 , which is the number of molecules uniformly secreted at the cell surface ($r = a$) per unit time and per unit cell surface area ($4\pi a^2$). These amount to the following initial (IC) and boundary (BC) conditions

$$\begin{aligned} \text{IC: } c(r, 0) &= 0 \quad \text{for } r > a, \\ \text{BC1: } c(\infty, t) &= 0 \quad \text{for } t > 0, \\ \text{BC2: } j(a, t) &= j_0 \quad \text{for } t > 0. \end{aligned}$$

The value of $j(a, t)$ at the cell surface ($r = a$) represents the secretion rate as a biological property of the cell. We obtain solution to Eq. (1) subjected to the above IC and BCs using

Laplace transform approach (see supplementary material for details). This leads to the following expression for the concentration $c(r, t)$ of the secreted molecules at any time $t > 0$ and at any given distance r from the origin

$$\begin{aligned} \frac{c(r,t)}{\frac{j_0 a^2}{Dr}} = & \frac{1}{2} \frac{1}{1-a\sqrt{\frac{\lambda}{D}}} \exp \left\{ \sqrt{\frac{\lambda}{D}}(r-a) \right\} \operatorname{erfc} \left(\frac{r-a}{\sqrt{4Dt}} + \sqrt{\lambda t} \right) \\ & + \frac{1}{2} \frac{1}{1+a\sqrt{\frac{\lambda}{D}}} \exp \left\{ -\sqrt{\frac{\lambda}{D}}(r-a) \right\} \operatorname{erfc} \left(\frac{r-a}{\sqrt{4Dt}} - \sqrt{\lambda t} \right) \\ & - \frac{1}{1-a^2 \frac{\lambda}{D}} \exp \left\{ \frac{r-a}{a} + \frac{Dt}{a^2} \left(1-a^2 \frac{\lambda}{D} \right) \right\} \operatorname{erfc} \left(\frac{r-a}{\sqrt{4Dt}} + \frac{1}{a} \sqrt{Dt} \right), \quad (3) \end{aligned}$$

where $\operatorname{erfc}(x) \equiv \frac{2}{\sqrt{\pi}} \int_x^\infty \exp(-t^2) dt$ is the complementary error function [20]. Note that in absence of degradation ($\lambda = 0$) the above expression for $c(r, t)$ is the same as listed equation 9.10 (4) in ref. [21] and also as obtained by Yoshida and Horike (Eq. (10) in ref. [12]) via Fourier transformation of the corresponding governing diffusion equation (see supplementary material for details). We non-dimensionalize the above equation using the reference length scale chosen to be the cell radius a and the reference time scale chosen to be the corresponding diffusion time $t_{\text{diff}} = a^2/4D$. Thus the dimensionless length and time variables are:

$$\zeta = \frac{r}{a}, \quad \tau = \frac{4Dt}{a^2}, \quad \text{and} \quad \bar{\lambda} = \frac{a^2 \lambda}{4D}.$$

Thus Eq. (3) can be written as:

$$c(\zeta, \tau) = \frac{j_0 a}{D} \Psi_{\bar{\lambda}}(\zeta, \tau), \quad (4)$$

where $\Psi_{\bar{\lambda}}(\zeta, \tau)$, a dimensionless function of length, time and $\bar{\lambda}$, is given by

$$\begin{aligned} \Psi_{\bar{\lambda}}(\zeta, \tau) = & \frac{1}{2\zeta} \frac{1}{1-2\sqrt{\bar{\lambda}}} \exp \left\{ 2\sqrt{\bar{\lambda}}(\zeta-1) \right\} \operatorname{erfc} \left(\frac{\zeta-1}{\sqrt{\tau}} + \sqrt{\bar{\lambda}\tau} \right) \\ & + \frac{1}{2\zeta} \frac{1}{1+2\sqrt{\bar{\lambda}}} \exp \left\{ -2\sqrt{\bar{\lambda}}(\zeta-1) \right\} \operatorname{erfc} \left(\frac{\zeta-1}{\sqrt{\tau}} - \sqrt{\bar{\lambda}\tau} \right) \\ & - \frac{1}{\zeta} \frac{1}{1-4\bar{\lambda}} \exp \left\{ \zeta-1 + \frac{\tau}{4}(1-4\bar{\lambda}) \right\} \operatorname{erfc} \left(\frac{\zeta-1}{\sqrt{\tau}} + \frac{1}{2}\sqrt{\tau} \right) \quad (5) \end{aligned}$$

Definition and Estimation of a Characteristic Time Constant

From above Eq. (1) we can easily obtain the steady state concentration profile by setting $\frac{\partial c}{\partial t} = 0$. Alternatively, the same can be obtained by taking the limit $\tau \rightarrow \infty$ in above Eqs. (4)–(5). This leads to the following expression for the steady state concentration profile

$$c(\zeta, \infty) = \frac{j_0 a}{D} \frac{1}{\zeta} \frac{1}{1 + 2\sqrt{\lambda}} \exp \left\{ -2\sqrt{\lambda}(\zeta - 1) \right\}. \quad (6)$$

The above expression represents the maximum concentration buildup after a long time ($\tau \rightarrow \infty$) at a given distance from the secreting cell. However, reaching the steady state (maximum) concentration at a given distance requires an infinite amount of time ($\tau \rightarrow \infty$). We can therefore define a time constant similar to Francis and Palsson [4] that characterizes the concentration buildup in relation to physiologically relevant events. We define a characteristic time constant, τ_f , as the time at which the concentration $c(\zeta, \tau_f)$ will be some fraction, f , of the steady state (maximum) concentration $c(\zeta, \infty)$ at a given distance as:

$$\Psi_{\bar{\lambda}}(\zeta, \tau_f) = f \Psi_{\bar{\lambda}}(\zeta, \infty). \quad (7)$$

One can easily obtain a numerical solution to above Eq. (7). This is shown in Fig. 1 at $f = 0.5$, $a = 0.001$ cm, $D = 10^{-6}$ cm²/s for $\lambda = 0, 0.00018$ s⁻¹, and 0.00028 s⁻¹ ($\bar{\lambda} = 0, 0.000045$, and 0.000070). It is apparent from this figure that for $\lambda = 0$ there is a parabolic relation between τ_f and ζ of the type: $\tau_f = (b\zeta)^2$ for large ζ ($\zeta > \approx 4 - 5$). Hence, substituting $\tau_f = (b\zeta)^2$ in above Eq. (7), expanding Ψ in a series, and evaluating the limit for large ζ (see supplementary material for details), a relationship between b and f is found for $\lambda = 0$:

$$\operatorname{erfc} \left(\frac{1}{b} \right) = f. \quad (8)$$

Therefore, for $\lambda = 0$ we can determine b from above Eq. (8) for a chosen value of f . Then a characteristic time constant τ_f can be directly determined using $\tau_f = (b\zeta)^2$ at any distance ζ from the secreting cell for $\lambda = 0$. We chose $\tau_{0.5}$ as a characteristic time constant, i.e., the time it takes for the signal to reach half of its maximum strength [4]. However, for $\lambda \neq 0$ there is a parabolic and a linear relation between τ_f and ζ for small ζ ($\zeta < \approx 5$) and for large ζ ($\zeta > \approx 5$), respectively (see inset in Fig. 1). Therefore, for $\lambda \neq 0$ we were unable to reach a unique relationship between b and f similar to Eq. (8) for $\lambda = 0$. One might anticipate an additional parameter $\bar{\lambda}$ in this relationship. Nevertheless, it is apparent from Fig. 1 that there is a significant reduction in $\tau_{0.5}$ due to degradation of secreted cyto/chemokine molecules. We chose diffusion coefficient $D = 10^{-7} - 10^{-6}$ cm²/s for signaling molecules in the 10–100 kDa range [22]. Using these values for D , dimensional values of characteristic time constant $\tau_{0.5}$ at specified locations are listed in Table 1. The chosen locations r are the same as those chosen by Francis and Palsson [4] to make a direct comparison between $\tau_{0.5}$ obtained in absence and in presence of degradation of secreted cyto/chemokine molecules. It is seen from Table 1 that for a given D at any location $\tau_{0.5}$ is reduced due to degradation. The percent reduction in $\tau_{0.5}$ increases with distance from the secreting cell. Furthermore at a given location as D decreases the percentage reduction in $\tau_{0.5}$ increases.

Definition and Estimation of Effective Signal Propagation Distance

Above we defined a characteristic time constant, the time it takes to reach a given concentration at a given distance away from the secreting cell. Now we are interested in knowing how far a meaningful signal can be propagated. It is the critical concentration of molecules (K_m) that determines if the signal is meaningful at a given location. Specifically, at a given location if concentration of secreted molecules is higher than K_m then the signal is meaningful to the responding cell. We can therefore determine how a meaningful signal propagates with time simply by substituting this critical concentration K_m for $\alpha(\zeta, \tau)$ in Eq. (4):

$$K_m = \frac{j_0 a}{D} \Psi_{\lambda}(\zeta, \tau) \text{ or } 1 = \alpha \Psi_{\lambda}(\zeta, \tau) \text{ where: } \alpha = \frac{j_0 a}{D K_m}. \quad (9)$$

From above Eq. (9) we can determine how far a meaningful signal has propagated at any instant of time. Specifically, for a given value of α , Eq. (9) can be numerically solved for ζ , the distance from the center of the secreting cell that the leading edge of the signal has propagated to as a function time τ (see Fig. 2). The maximal distance ζ_{∞} that a signal can propagate is at steady state ($\tau \rightarrow \infty$). Taking the limit as $\tau \rightarrow \infty$ in Eq. (9) we get

$$\zeta_{\infty} \exp \left\{ 2 \sqrt{\lambda} (\zeta_{\infty} - 1) \right\} = \frac{\alpha}{1 + 2 \sqrt{\lambda}}. \quad (10)$$

It is apparent from above Eq. (10) that in absence of degradation ($\lambda = 0$) the maximum meaningful signal propagation distance ζ_{∞} is equal to the parameter α [4]. However, in presence of degradation ($\lambda > 0$) the corresponding maximum meaningful signal propagation distance would be lower (see Fig. 2 and supplementary material for details). The reduction in maximum meaningful signal propagation distance is dictated by the degradation rate at a given value of α . Higher the degradation rate, lower the maximum meaningful signal propagation distance. One might therefore anticipate a corresponding reduction in “effective” communication distance as well [4]. Nevertheless we first formally define “effective” communication distance similar to that defined by Francis and Palsson [4].

The above Eq. (10) is valid only at steady state ($\tau \rightarrow \infty$). However, in physiological conditions cells do not have an infinite amount of time ($\tau \rightarrow \infty$) to propagate a signal. Hence, we define an “effective” communication distance similar to Francis and Palsson [4]. We define the effective communication distance $\zeta_{0.5}$ as the distance that a meaningful signal can propagate in one characteristic time constant, $\tau_{0.5}$ [4]. Using Eq. (7) and Eq. (9) we arrive at the following governing equation for $\zeta_{0.5}$

$$\zeta_{0.5} \exp \left\{ 2 \sqrt{\lambda} (\zeta_{0.5} - 1) \right\} = \frac{1}{2} \frac{\alpha}{1 + 2 \sqrt{\lambda}}. \quad (11)$$

It is apparent from above Eq. (11) that in absence of degradation ($\lambda = 0$) the “effective” communication distance $\zeta_{0.5}$ is equal to $\frac{1}{2}\alpha$ [4]. However, in presence of degradation ($\lambda \neq 0$) the corresponding effective communication distance would be lower (see Fig. 3 and Table 2). The reduction in effective communication distance is dictated by the degradation rate. Higher the degradation rate, lower the effective communication distance. It is apparent from Table 2 that for a given α the effective communication distance $\zeta_{0.5}$ decreases due to degradation. Moreover, for a given λ the percentage reduction in $\zeta_{0.5}$ increases with α .

III. DISCUSSION

In absence of degradation ($\lambda = 0$) when the secretion rate is constant with time the process is governed by a single dimensionless group α which represents the ratio of biological parameters and physicochemical determinants [4]. Specifically, α is proportional to the ratio of cyto/chemokine diffusion time scale and secretion time constant [4]:

$$\alpha = \frac{4}{3} \frac{t_{\text{diff}}}{t_{\text{sec}}} \text{ where } t_{\text{diff}} = \frac{a^2}{4D}, t_{\text{sec}} = \frac{K_m a}{3j_0} \text{ with } j_0 = \frac{F_0}{4\pi a^2}. \quad (12)$$

The dimensionless property α measures the relative rates at which the concentration of secreted cyto/chemokine molecules builds up close to the membrane of the secreting cell vs. how quickly it diffuses away from the cell surface [4]. If the time constant for secretion is slow compared with diffusion, then no effective signaling will take place because in this case insignificant concentration of secreted cyto/chemokine molecules will build up near the signaling cell [4]. On the other hand, if the diffusion process is slow compared with the secretion of the cyto/chemokine molecules then effective signaling will take place because in this case significant concentration of secreted cyto/chemokine molecules will build up near the signaling cell [4]. The effective signaling therefore depends on the cell's ability to rapidly secrete the signaling molecules given the diffusion times are determined by physics [4].

The diffusion coefficient, D , is purely a physicochemical property which has been shown to range between $10^{-7} - 10^{-6} \text{ cm}^2/\text{s}$ for signaling molecules in the 10–100 kDa range [22]. The secretion rates F_0 have been experimentally shown to fall into the range of 2300–8000 molecules/cell/s [23]. The binding constant K_m has a minimum value for the signal to be meaningful to the responding cell. This has been shown to fall into the range of 10–50 pM [24]. Thus the secretion time constant t_{sec} has a minimum value due to the minimum values for the binding constant of the responding cell and the maximal constraints on the achievable secretion rate. Based on these values and taking cell radius as $a = 0.001 \text{ cm}$, the maximum value for α is estimated to be on the order of 100. For example at $D = 10^{-6} \text{ cm}^2/\text{s}$, $K_m = 6.023 \times 10^9 \text{ molecules/cm}^3$, and $F_0 = 8000 \text{ molecules/cell/s}$ the value of α is 105.70. Therefore, in absence of degradation ($\lambda = 0$) the effective communication distance is $\zeta_{0.5} = 52.85$ at $\alpha = 105.70$. The corresponding characteristic time constants obtained from Eq. (7) or Table 1 are approximately 12.8 min and 51.17 min at $a = 0.0005 \text{ cm}$ and $a = 0.001 \text{ cm}$, respectively. Note that Francis and Palsson [4, 5] have used $a = 0.0005 \text{ cm}$ in their work. Therefore, in absence of degradation ($\lambda = 0$) the findings of the present study that at $\alpha =$

105.70 the effective communication distance is $\zeta_{0.5} = 52.85$ and the corresponding characteristic time constant is 12.8 min at $a = 0.0005$ cm are in agreement with the corresponding findings of Francis and Palsson [4, 5], although their concentration profile [eq. 2 in ref. 4] for the same initial and boundary conditions is incorrect as pointed out both by Yoshida and Horiike [12] and by Jabbarzadeh and Abrams [16]. The correct concentration profile is given by equation 9.10 (4) in ref. [21] (see Supplementary Material for details).

However, in presence of degradation ($\lambda \neq 0$) both the characteristic time constant and the effective communication distance are reduced. In the present study the chosen values for the degradation rate $\lambda = 0.00018 \text{ s}^{-1}$ and 0.00028 s^{-1} are physiologically relevant [11, 25]. Based on these values for the degradation rate we demonstrated that for a given D at any location the characteristic time constant is reduced due to degradation of secreted cyto/chemokine molecules. The percent reduction in the characteristic time constant increases with distance from the secreting cell. For example at $\lambda = 0.00018 \text{ s}^{-1}$ the percentage reduction in the characteristic time constant are 41.3% and 50.4% at $r = 235 \text{ }\mu\text{m}$ and $r = 330 \text{ }\mu\text{m}$, respectively. Furthermore at a given location as D decreases the percentage reduction in the characteristic time constant increases. For example at $r = 235 \text{ }\mu\text{m}$ the percentage reduction in the characteristic time constant are 41.3% and 68.9% at $\lambda = 0.00018 \text{ s}^{-1}$ and $\lambda = 0.00028 \text{ s}^{-1}$, respectively. Based on these values for the degradation rate we also demonstrated that in presence of degradation the effective communication distances are reduced. The reduction in the effective communication distance is dictated by the degradation rate. Higher the degradation rate, lower the effective communication distance. We have shown that for a given a the effective communication distance decreases due to degradation. Moreover, for a given degradation rate the percentage reduction in the effective communication distance increases with a . For example at $\lambda = 0.00018 \text{ s}^{-1}$ the percentage reduction in the effective communication distance are 36.3% and 57.4% at $a = 105.70$ and $a = 211.40$, respectively.

For physiologically relevant values of parameters contained in a , e.g. signal diffusivity, secretion rate, and the equilibrium binding constant and the degradation rate λ , we have demonstrated that both the effective communication distance and the time scale on which signaling takes place are reduced up to 50% compared with those in absence of degradation of secreted cyto/chemokine molecules. The definition, an accurate estimation, and understanding of the effective communication intercellular communication distances are of fundamental importance to the area of organ physiology, signaling pathways, and for the effective and efficient chemotactically driven tissue engineering. The presented study has demonstrated that not only the dimensionless property a but also the degradation rate λ are fundamentals to these endeavors. The presented model has an application in the accurate estimation of effective communication distance and ultimately in the effective and efficient chemotactically driven tissue engineering [7].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights (for review)

We examine the effect of degradation of secreted molecules on the effective communication distance.

We demonstrate that in presence of degradation the effective communication distances are significantly reduced.

The reduction in effective communication distance is dependent on the degradation rate.

Higher the degradation rate, lower the effective intercellular communication distance.

FIG. 1.

Location-dependent time constant obtained from the numerical solution to Eq. (7) at $\lambda = 0, 0.00018, 0.00028 \text{ s}^{-1}$. The time constant is defined as the time it takes to reach half of the steady-state concentration at a particular distance from the secreting cell.

FIG. 2.

The propagation distance ζ of soluble cyto/chemokine signal over time obtained from the numerical solution to Eq. (9) at $D = 10^{-6} \text{ cm}^2/\text{s}$, $a = 0.001 \text{ cm}$, $K_m = 6.023 \times 10^9 \text{ cm}^3/\text{s}$, $F_0 = 8000 \text{ molecules/cell/s}$, and $\lambda = 0, 0.00018, 0.00028 \text{ s}^{-1}$. The corresponding value of $\alpha = \frac{j_0 a}{DK_m}$ with $j_0 = \frac{F_0}{4\pi a^2}$ is 105.70. As indicated the propagation distance is defined as the location where c/K_m is unity. The corresponding values of maximum meaningful signal propagation distance ζ_∞ obtained from the numerical solution to Eq. (10) at $\lambda = 0, 0.00018$, and 0.00028 s^{-1} are 105.70, 52.37, and 47.64, respectively.

FIG. 3. Effect of degradation on the effective communication distance $\zeta_{0.5}$ at (a) $\alpha = 105.70$ (b) $\alpha = 211.40$. Eq. (9) is plotted for the steady state ($\tau \rightarrow \infty$) solution (solid lines) as well as using the definition for the location dependent time constant $\tau_{0.5}$ (dashed lines).

TABLE I

Characteristic time constants $\tau_{0.5}$ for intercellular communication at different distances from the secreting cell

$r \text{ } \mu\text{m}$	$t \text{ min}$			
	$D = 10^{-6} \text{ cm}^2/\text{s}$ $\lambda = 0$	$D = 10^{-6} \text{ cm}^2/\text{s}$ $\lambda = 0.00018 \text{ s}^{-1}$	$D = 10^{-7} \text{ cm}^2/\text{s}$ $\lambda = 0$	$D = 10^{-7} \text{ cm}^2/\text{s}$ $\lambda = 0.00018 \text{ s}^{-1}$
75	1	0.83	10	5.90
150	4	2.81	40	16.82
235	10	5.87	100	31.10
330	20	9.92	200	48.11
570	60	21.80	600	93.07

TABLE IIEffect of degradation on effective communication distance $\zeta_{0.5}$

α	$\zeta_{0.5}$		
	$\lambda = 0$	$\lambda = 0.00018 \text{ s}^{-1}$	$\lambda = 0.00028 \text{ s}^{-1}$
39.64	19.82	16.00	15.34
66.06	33.03	23.96	22.62
105.70	52.85	33.66	31.31
211.40	105.70	45.00	40.53