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Comment on Temporal Non-uniformity Effects of the Secretion Rate on the Effective Communication Distance

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The effective communication distance was investigated in the physicochemical process of signaling. It was found to exhibit a marked dependence on the secretion time under certain conditions.

Keywords: effective communication distance, secretion rate, diffusion, intercellular signaling

Introduction

Intercellular signaling is a major current topic in bioscience.[1-3] We have recently discussed the concept of the effective communication distance and characteristic time.[4-7] In our independent cell model, a primary cell secretes chemical substances (molecules) on its spherical cell surface. The molecules diffuse in the surrounding medium, until a chemical reaction takes place with receptors. The effective communication distance indicates how far the signal can be transferred from the primary cell to the receptor. Qualitatively, if the secretion rate is assumed to be temporally uniform (or time-independent), it is proportional to $aj_0/(DK)$, with the radius of secreting cell a, the secretion rate j_0, the dissociation constant of the signaling ligand K, and the self-diffusion constant of a ligand D.[4-9] We pointed out that the temporal non-uniformity of the secretion rate is necessary for modeling non-saturation phenomena, and demonstrated the usefulness of the model[5,6] in a realistic estimation of the effective communication distance and characteristic time for human cytokines.

In this paper, we make a further investigation of the effective communication distance (r_c) based on our previous paper.[5] It is necessary to take into account temporal non-uniformity effects to understand signaling characteristics from the properties of the component proteins participating in the process, but this point was not necessarily fully discussed previously. We investigated the behavior of r_c by varying the secretion time under the condition that the magnitude of the enhanced secretion rate or the total amount of secretion is kept constant.

Communication Distance

We considered a secreting spherical cell of radius a with its center fixed at origin. It releases chemical substances (molecules) at a spatially uniform rate from the cell surface to the surrounding medium. When there are no sources or sinks in the surrounding medium, the concentration (or density) of molecules, $c(r, t)$, obeys the diffusion equation given by

$$\left(\frac{D}{r^2}\frac{\partial}{\partial r}r^2\frac{\partial}{\partial r}-\frac{\partial}{\partial t}\right)c(r,t)=0 \qquad (1)$$

in the surrounding medium ($r>a$), for $t>0$ with r being the distance from the origin.[11,12] The flux or current associated with $c(r, t)$ is defined by

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

The value of this quantity $j(a, t)$ at the cell surface ($r=a$) is the secretion rate. It is the number of molecules secreted per unit area per unit time, and represents a biological property of the cell.[6] The boundary conditions for eq. (1) in which there are initially no molecules, and the concentration is completely diluted very far from the cell are given by

$$c(r, 0) = 0 \text{ for } r>a, \text{ and } c(\infty, t) = 0 \text{ and } j(a, t) = p(t) \text{ for } t = 0. \tag{3}$$

We assume the rectangular time-dependence of the secretion rate[5,10], i.e., the primary cell releases the molecules with a constant enhanced rate during the secretion time of t_s;

$$\begin{aligned} p(t) &= p_1 \qquad \text{for } 0 \leq t \leq t_s \\ &= p_0 \qquad \text{for } t_s \leq t \end{aligned} \tag{4}$$

where the value of p_1 is larger than that of p_0 at the basal level, as shown in Fig. 1. The solution of the diffusion equation corresponding to the secretion rate given by eq. (4) is expressed as the reduced (or dimensionless) concentration $\varphi(x, y)=a^3c(r, t)$ in terms of the reduced distance $x=r/a$ and the reduced time $y=tD/a^2$ as

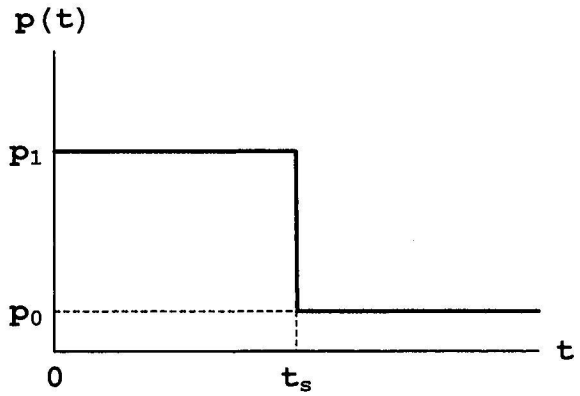

Figure 1 Time-dependence of the secretion rate $p(t)$ given by eq. (2). The value p_1 shows the enhanced rate during the time interval of t_s, and p_0 is the basal secretion rate ($0 < p_0 < p_1$).

$$\varphi(x,y) = \frac{\beta_1}{x} f(x,y) + \theta(y - y_s)\frac{(\beta_0 - \beta_1)}{x} f(x, y - y_s) \tag{5}$$

$$f(x,y) = \operatorname{erfc}\left(\frac{x-1}{2\sqrt{y}}\right) - \exp(x-1+y)\operatorname{erfc}\left(\frac{x-1}{2\sqrt{y}} + \sqrt{y}\right) \tag{6}$$

where the quantities $\beta_0=p_0a^4/D$, $\beta_1=p_1a^4/D$, and $y_s=t_sD/a^2$ are all reduced values of p_0, p_1, and t_s, respectively. The quantity $\theta(y-y_s)$ represents the step function; $\theta(y-y_s)=1$ for $y>y_s$, and $\theta(y-y_s)=0$ otherwise. Also, the complementary error function is represented by erfc.

As the primary cell secretes signaling molecules during a finite time interval of t_s, the concentration of signaling molecules at some fixed distance from the cell does not reach the saturation value given by the stationary solution of the diffusion equation. It exhibits instead a peak as a function of time. The effective communication distance is conventionally introduced by the criteria of the fractional critical concentration, i.e., the distance at which the peak concentration value is equal to twice the critical value determined from the dissociation constant of the signaling ligand for its receptor.[6,10] Namely, in reduced units, the effective communication distance $x_c = r_c/a$ is given by the value of $x=r/a$, at which the maximum value of $\varphi(x,y)$ as a function of $y = tD/a^2$ is equal to $2\varphi_c = 2Ka^3$, as schematically depicted in Fig. 2. The characteristic time may be estimated as a representative value in the time interval satisfying $\varphi(x_c,y) \geq \varphi_c$, at $x = x_c$, if the width is not so large.

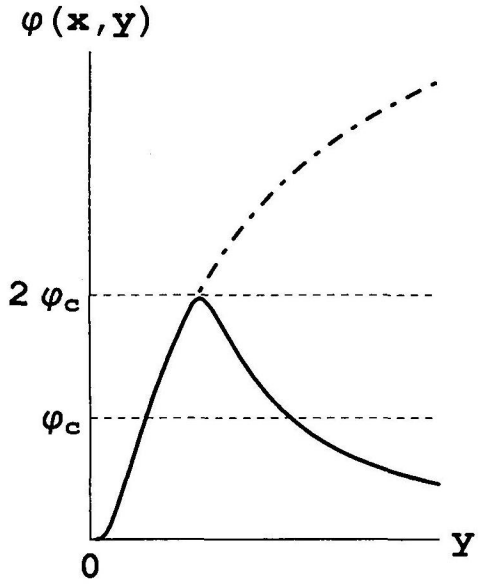

Figure 2 Criteria of fractional critical concentration to determine the effective communication distance. The solid curve schematically shows the reduced concentration $\varphi(x,y)$ as a function of the reduced time y for a finite value of x. For $x=x_c$, the peak value of $\varphi(x,y)$ is equal to $2\varphi_c$. The dash-dotted curve represents $\varphi(x,y)$ for $y_s=\infty$.

Results and Discussion

Experimental results are available for human cytokines, i.e., $a=10$ μm, $D=5\times10^{-6}$ cm^2 s^{-1}, $K=10$ pM$= 6\times10^{15}$ molecules m^{-3}, given by Savinell *et al.*[13] and Francis and Palsson.[8,9] For these input data values, the unit of time a^2/D is equal to 0.2 s, and $\varphi_c \equiv Ka^3=6$ as the reduced critical concentration. Previously, we had taken $\beta_1 = p_1a^4/D = 4800$ and $y_s=170$ as reasonable values, and found by using the criteria of the fractional critical concentration that reduced values of the effective communication distance and characteristic time are $x_c=40$ and $y_c=360$, respectively, (or $r_c=400$ μm and $t_c=72$ s).

We consistently adopted the same values for a, D, K and β_1 as in ref. 5 (or $a=10$ μm, $D=5\times10^{-6}$ cm^2 s^{-1}, $K=10$ pM, and $\beta_1=4800$). Firstly, we investigated the dependence of the effective communication distance by varying the secretion time, but keeping the magnitude of the enhanced secretion rate as constant : For simplicity, we set $\beta_0 = p_0a^4/D$ as zero. Figure 3 shows the results of $\varphi(x,y)$ as a function of y, for the five values of $y_s = t_sD/a^2$, or $y_s/171 = 0.05$, 0.2, 1, 2, 4. The variation in $\varphi(x,y)$ with y_s for a fixed value of x had been presented in Fig. 3 in ref. 5. We calculated the value of x for each curve so that the peak value was just equal to $2\varphi_c$, as in Fig. 2, and obtained $x=14.7$, 23.2, 39.5, 49.5, 62.0, respectively, for $y_s/171=0.05$, 0.2, 1, 2, 4. These values are adopted in Fig. 3, and thus the value of x is different for each curve. By definition, these have the meaning of the reduced effective communication distance x_c corresponding to the given secretion time. The value of x_c is found to increase

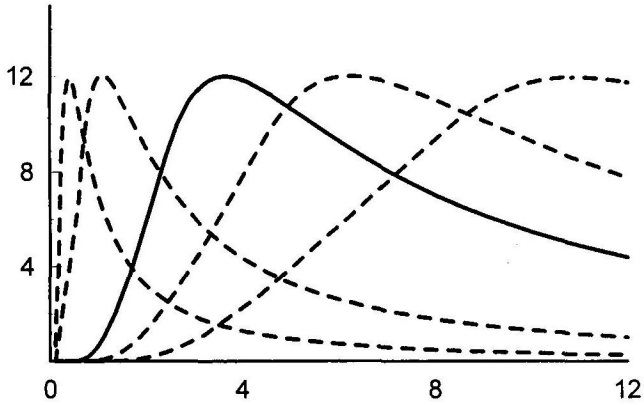

Figure 3 The y_s -dependence of $\varphi(x,y)$ for a constant value of p_1. The vertical and horizontal axes are $\varphi(x,y)$ and $y/100$, respectively. Five curves are for $y_s/171=0.05$, 0.2, 1, 2, 4 from left to right, where the reference curve for $y_s/171=1$ is shown as a solid line. The value of x is different for each curve (See the text for details).

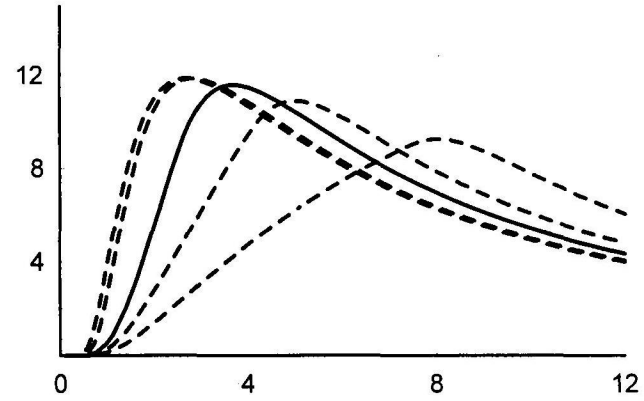

Figure 4 The y_s -dependence of $\varphi(x,y)$, with the total amount of secreted molecules kept constant. The vertical and horizontal axes are $\varphi(x,y)$ with $x=40$ and $y/100$, respectively. Five curves are for $y_s/171=0.05$, 0.2, 1, 2, 4 from left to right, and the solid line has the same meaning as in Fig. 3.

rather smoothly with t_s. It is noted for Fig. 3 that the reduced characteristic times satisfying $\varphi(x_c,y)=\varphi_c$ are obtained as $y=19.7$, 56.4, 201, 350, 616, respectively, for $y_s/171=0.05$, 0.2, 1, 2, 4. When t_s increases further, the value of x_c approaches $aj_0/(2DK)$, corresponding to the constant secretion rate $j_0=p_1$: For the values of D, K and β_1 given above, $x_c=r_c/a=400$.

Secondly, we investigated the behavior of r_c by varying t_s, but keeping the total amount of chemical substances secreted from the primary cell, or the product of p_1 and t_s , constant. Figure 4 shows $\varphi(x,y)$ at a fixed distance of $x=40$ from the cell, as a function of y by adopting the same values of y_s as in Fig. 3. It was found that $\varphi(x,y)$ remains almost unchanged when t_s is very small. This means that r_c approaches a constant value in the limit of small t_s . On the other hand, when t_s becomes sufficiently large, or roughly comparable to $r^2/6D$ expected from the diffusion, $\varphi(x,y)$ is clearly dependent on t_s,

and has a peak at a larger value of y, with the peak value decreasing. This indicates that r_c decreases with t_s in this regime. In fact, we obtained x_c=39.8, 39.8, 39.5, 38.5, 35.6 for $y_s/171$=0.05, 0.2, 1, 2, 4, respectively.

In summary, we discussed the dependence of the effective communication distance r_c on the secretion time t_s. For a given magnitude of enhanced secretion rate, the value of the effective communication distance shows a smooth dependence on the secretion time, as found from Fig. 3. When the secretion time was varied under the condition that the total amount of secreted molecules, or the integrated value of the secretion rate $p(t)$ is kept constant, the effective communication distance was found to be almost constant for a sufficiently small value of t_s, and gradually decreased with increasing t_s. The situation in which p_1 goes to infinity and t_s goes to zero with their products kept constant, contrasts with the case of the temporally uniform secretion rate (or p_1 is constant, and t_s goes to infinity). If this regime was relevant to signaling, the effective communication distance would not largely depend on the secretion time, but would be governed by the total amount of secretion.

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