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Effect of cyto/chemokine degradation in effective intercellular communication distances

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HIGHLIGHTS

- 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.

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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.

1. 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

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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 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 μm and the characteristic time 10–30 min. 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 (Appendix A) for details). In absence of degradation we recover the analytical solution obtained by Yoshida 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 Eqs. (10)–(11) were obtained using Newton–Raphson method [18].

2. 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]

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

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:

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

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 ($r \to \infty$) from the cell. At time $t = 0$ the cell starts secreting these