Chemical Engineering Science 74 (2012) 114–123

Contents lists available at SciVerse ScienceDirect

Chemical Engineering Science

journal homepage: www.elsevier.com/locate/ces

Diffusive transfer between two intensely interacting cells with limited surface kinetics

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ARTICLE INFO

Article history:
Received 6 December 2011
Received in revised form
31 January 2012
Accepted 2 February 2012
Available online 7 February 2012

Keywords:
Biomedical engineering
Cellular biology and engineering
Paracrine delivery
Mathematical modeling
Mass transfer
Diffusive interactions

ABSTRACT

The diffusive transfer, or *paracrine delivery*, of chemical factors during the interaction of an emitting cell and a receiving cell is a ubiquitous cellular process that facilitates information exchange between the cells and/or to bystander cells. In the cellular immune response this exchange governs the magnitude and breadth of killing of cellular targets, inflammation or tolerance. Paracrine delivery is examined here by solving the steady-state diffusion equation for the concentration field surrounding two intensely interacting, equi-sized cells on which surface kinetics limits the rates of factor emission and absorption. These chemical factors may be cytokines, such as Interlukins and Interferons, but the results are presented in a generic form so as to be applicable to any chemical factor and/or cell-type interaction. In addition to providing overall transfer rates and transfer efficiencies, the results also indicate that when the receiving cell is *naïve*, with few factor receptors on its surface, there may be a significant accumulation of factor in the *synaptic* region between the cells with a consequent release of factor to the medium where it can signal bystander cells. This factor accumulation may play a critical role in activating a naïve receiving cell. As the receiving cell activates and becomes more absorbent, the factor accumulation diminishes, as does potential bystander signaling.

1. Introduction

It is well known that the diffusive transfer from volatile particles/droplets is affected by the proximity of their neighbors. When the interacting particles/droplets have the same composition, transfer is lower than the single, isolated rate. The effect of these diffusive interactions has been studied extensively over the years due to their relevance to atmospheric clouds/aerosols and liquid fuel spray combustion (see, for example, Sirignano, 2010; Annamalai and Ryan, 1992; Labowsky, 1976, 1978, 1980a, 1980b; Sangiovanni and Labowsky, 1982). Diffusive interactions, however, are also important in biological systems. Cells communicate and signal through the diffusive transfer, referred to as *paracrine delivery*, of certain chemical *factors*. For example, cytokine factors such as interlukin (IL-2, IL-10, IL-12), regulate the activation, stimulation, differentiation, and proliferation of T-cells to perform their proper immune response function (Pardoll, 2002; Sharpe and Abbas, 2006). Biological interactions (Huse et al., 2006, 2008), however, differ from those of volatile droplets in at least three significant ways: first, the interactions are much more intense due to the nano-range spacing between cells; second, the cells are animate and respond to their environment; and finally, interacting cells have different emission/absorption characteristics with an emitting cell (EMC) acting as a source and a receiving cell (REC) acting as a sink whereas volatile particles with the same composition experience source/source interactions. The terms EMC and REC used here are generic and may represent, for example, a T-cell interacting with an antigen-presenting cell (APC) (Grakoui et al., 1999; Monks et al., 1998; Smith-Garvin et al., 2009) or an artificial APC (Kress et al., 2009; Steenblock and Fahmy, 2008) interacting with a T-cell (Steenblock et al., 2011). Indeed, the process of paracrine delivery is ubiquitous in cell biology and is used by other cell types such as neurons (Li et al., 2009; Robinson et al., 1996; Takeda et al., 2008) and epithelial cells (Lieblein et al., 2008; Jankowski et al., 2007; Greiff et al., 2002) for specific chemical information transfer.

Paracrine delivery has been modeled in the past by treating the cells as perfect sources and sinks (Kress et al., 2009). While this approach is reasonable and amenable to solution using classical techniques like the Method of Images, it is incomplete because it only applies to cases where the transfer is diffusion-limited. A perfect source has a uniform factor surface concentration and an infinite capacity to supply factor. A perfect sink has an

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doi:10.1016/j.ces.2012.02.001

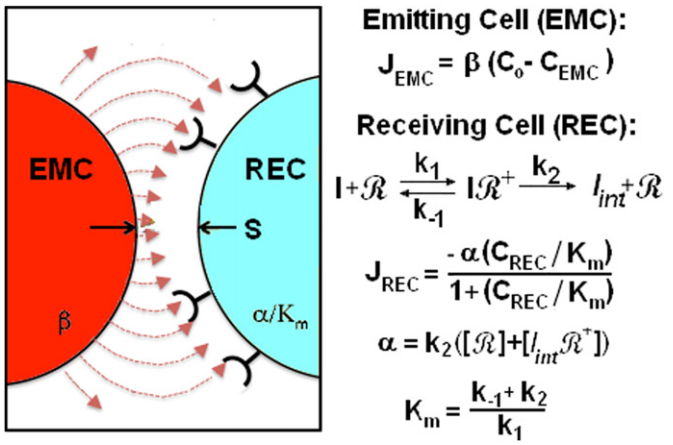

Fig. 1. A schematic of paracrine delivery interaction between an EMC and an REC with a synaptic point separation of S. Red lines are representative flux-lines of the paracrine factor emitted by a first order rate law from the EMC towards the receiving cell. Diffusing factor binds and is internalized by the REC according to Michaelis–Menten kinetics. Transfer of factor is a function of emission (β) and absorption (α/K_m, K_m) rate constants. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

infinite capacity to absorb any factor that reaches its surface. Perfect/perfect interaction depends on geometric parameters such as relative size and intercellular separation. Transfer between biological cells, however, is not perfect/perfect but is limited by the finite surface kinetics. The rate at which the REC absorbs factor depends on the number and quality of the factor *receptors* on its surface. These receptors (schematically represented in Fig. 1) may be viewed in a similar light as active sites on a catalyst pellet. During the initial phase of cellular interaction, the REC is often *naïve* with few if any receptors and, thus, unable to absorb factor. The result is an accumulation of factor in the *synaptic region*, the region between the cells. It is conjectured that bathing in this accumulated factor is necessary to activate a naïve cell (Steenblock et al., 2011; Grakoui et al., 1999; Dustin, 2002, 2006). Over time, as the cell (REC) activates, more factor receptors slowly appear on its surface, resulting in increased absorption and decreased synaptic factor concentration. Further, any factor that cannot be absorbed by the kinetic limitations of the REC diffuses to the ambience and provides a chemical signal for neighboring bystander cells (Huse et al., 2006, 2008). It is important, therefore, to study cellular interactions in a more general way by including surface kinetics in the calculations. While it is desirable to examine arrays of interacting kinetically limited cells, it is fundamentally important to understand the behavior of the basic unit in such arrays: a single EMC/REC pair as considered here.

The case of a cell that emits factor at a constant rate, interacting with a non-absorbing REC was examined in Steenblock et al. (2011). The results of these calculations were used, in part, to explain the experimentally observed increase in proliferation rates of CD8 T-cells when interacting with artificial APCs. This type of analysis will be extended below to the more general (and more challenging) cases of arbitrary emission and absorption characteristics. The results will be presented in dimensionless form, so they are not limited to a specific pair of cells, but may be applied to a range of chemical factors and interacting cell-types.

2. Assumptions and method of solution

The cells are assumed to be spherical and equi-sized with R_{EMC} ($=R_{REC}$) denoting the radius of the EMC (and REC), and are separated at their *synaptic point* (*SP*), the point of closest contact, by a distance S (see Fig. 1). It is further assumed that the concentration (C) of the diffusing factor is quasi-steady (QS), implying the C-field varies slowly with time in comparison with the characteristic diffusion time. The ambient medium is assumed to be factor-free ($C_\infty=0$) and non-reactive with the factor. Under these conditions, the steady-state diffusion equation governing the C-field reduces to the Laplace Equation:

$$\nabla^{*2}C^*=0 \tag{1}$$

where the dimensionless concentration is

$$C^*=C/C_{EMCiso} \tag{2}$$

Dimensionless quantities are designated with an asterisk (*) when they have a dimensional counterpart. Distances are measured in units of R_{EMC}, thus: $R^*_{EMC}=1$($R^*_{REC}=R_{REC}/R_{EMC}=1$) and the dimensionless synaptic point separation (S^*) is S/R_{EMC}. The Laplacian operator in Eq. (1) is normalized by R^2_{EMC}. The use of dimensionless quantities allows one calculation to be applied to many situations. For example, the $S^*=0.005$ results reported here, can be applied to two interacting 8 μm diameter cells (typical of T-cells) separated by 20 nm (typical cell separation), or two 4 μm diameter cells separated by 10 nm or the interaction of any other sized cells for which the spacing is proportional.

C_{EMCiso} denotes the surface concentration of factor on the EMC if it were *isolated* (far away) from the REC. The QS field near an isolated EMC spherical cell is spherically symmetrical, with C^* decreasing inversely with distance (r^*) from the center of the cell (Fig. 2a). The transfer rate from an isolated EMC in a factor-free environment is

$$M_{EMCiso}=4\pi R_{EMC}D_{ext}C_{EMCiso} \tag{3}$$

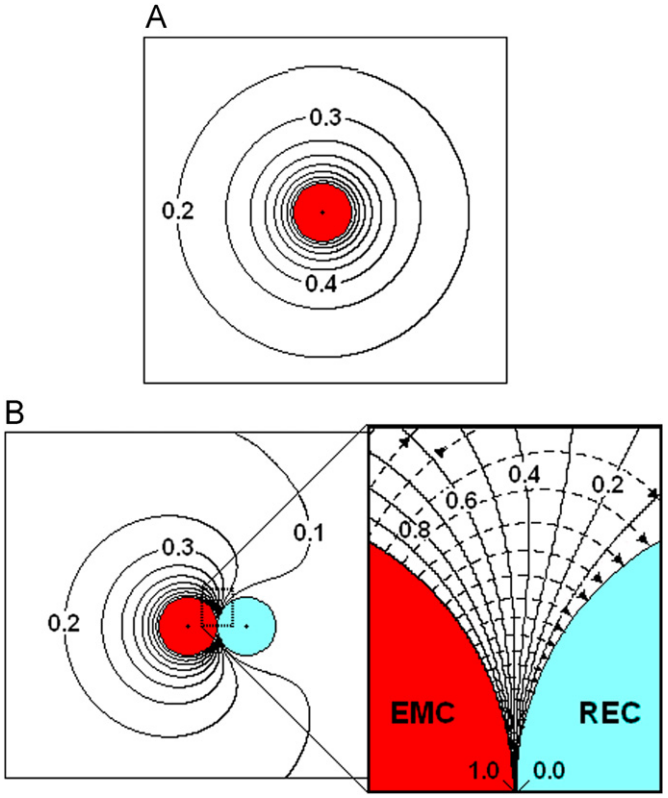

Fig. 2. The dimensionless concentration field (C^*) and flux-lines near a perfect source and perfect sink: (A) the C^*-field surrounding an isolated EMC and (B) the C^*-field (solid curves) and flux-lines (dashed curves) surrounding a perfect source and sink pair separated by $S^*=0.005$. Inset: A close up view of the synaptic region.