Signaling between cells attached to a surface

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We present a kinetic model allowing one to classify likely scenarios of protein-mediated communication between attached cells of two distinct types. In our treatment, messenger proteins, synthesized in type-1 cells, are considered to penetrate the external membrane of these cells, diffuse in the extracellular medium, associate with the receptors in the external membrane of cells of both types, and induce intracellular signal transduction cascades, influencing the development of cells. Protein degradation inside and outside cells is taken into account as well.

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I. INTRODUCTION

Communication between cells via emitting and receiving signals is a key process in biology [1]. In particular, signaling between cells is commonly regarded as the most important factor by which cell-type differences arise in embryonic development and by which patterns in tissue organization are established [2]. The cell-cell communication is also crucial for an organism function [1]. In addition, the understanding of the mechanisms of cell signaling is important for the tissue engineering [3].

Physically, communication between cells may occur via a variety of mechanisms involving exchange of chemical messengers, electrical activity, and/or direct mechanical contacts [1]. Among these schemes, the chemical mechanism is the most universal and flexible. It may include messenger diffusion via the extracellular space [2] or via gap junctions between nearby cells [4].

Here, we are interested in the cell-cell communication occurring via messenger transport in the extracellular space. In generic kinetic models of embryonic development, this process is customarily described by employing mean-field reaction-diffusion equations, omitting the mechanistic details of the messenger-cell interaction [5]. In phenomenological mean-field kinetic models [6–8] or Monte Carlo simulations [9] focused on the tissue growth, such details are usually omitted as well. The kinetic models including the mechanistic details usually describe signal propagation between cells of one type (see, e.g., reviews by Wiley *et al.* [10] and Shvartsman [11]). In particular, Dockery and Keener [12] presented a nonlinear kinetic model of "quorum sensing" in a colony of prokaryotes in the limit when the extracellular space is well mixed and also in the case of one-dimensional (1D) messenger diffusion with mass transfer into the bulk fluid on the colony boundary. The epidermal growth factor signaling in eukaryotes was analyzed in Refs. [13–15] with emphasis on the positive feedback between various steps (a single cell is described in detail in Refs. [13,14]; signal propagation in a two-dimensional array of cells is modeled in Ref. [15]).

To complement the available models and/or to extend the physical basis for the understanding of cell-cell communication, we present an analysis of signaling between cells of two types in the case when they are attached to a surface. One motivation of this choice is its relevance for tissue and stem-cell engineering on surface templates.

Although our treatment is general and the results obtained can be applied to a variety of situations occurring *in vivo* and *in vitro*, we will use the approximations corresponding to the growth of stem cells or, more specifically, to the proliferation and differentiation of attached adult rat neural stem cells (RNSC's) (for a recent review of studies of these cells, see Ref. [16]). The corresponding kinetics are qualitatively similar to those observed in various eukaryotic cultured cells. In particular, the proliferation of the cells occurs via three phases including (i) slow initial growth, (ii) rapid exponential growth, and (iii) slowdown of the growth at high concentration of the cells [17]. During the initial phase (from seeding to approximately day one), the cells recover from the subculturing process and condition their environment by secreting substances to facilitate growth and proliferation, such as extracellular matrix and growth factors. The optimal environment for cell proliferation typically occurs between day 3 to day 5, during which the RNSC's rapidly expand their numbers, with a doubling time of approximately 10 h. After day 5, the rate of growth decreases. The experiments indicate that differentiation and termination of the growth of RNSC's are influenced by cell-cell communication [18,19]. The precise mechanistic details of the communication are, however, yet unknown.

II. BIOCHEMICAL BACKGROUND

In our model, two types of cells (types 1 and 2) are considered to be attached to a flat surface in the solution of thickness L (Fig. 1). The cell-cell communication is assumed to occur via the conventional mechanism involving messenger protein diffusion in the extracellular medium [2]. The initiation of signaling activity includes the mRNA synthesis via transcription of the corresponding genes and the messenger-protein synthesis by mRNA on ribosomes. These processes are considered to occur only in the type-1 cells (in the type-2 cells, the messenger-protein synthesis is assumed

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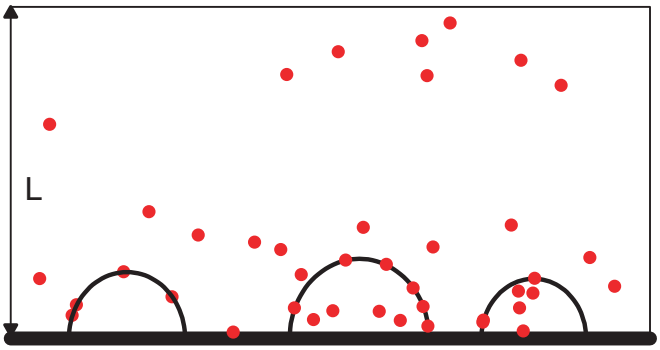

FIG. 1. (Color online) Schematic arrangement of cells on the surface. Small solid circles show messenger proteins. L is the thickness of the solution.

to be negligible). The messenger proteins are considered to penetrate the external membrane of cells, to diffuse in the solution, to associate with the receptors incorporated into the external membrane of cells of both types (due to this process, the messenger proteins are often called "ligands"), and to induce intracellular signal transduction cascades. These cascades result in the formation of other proteins, which may, e.g., inhibit or activate transcription of the genes governing the cell proliferation and differentiation (for a review of generic models of gene regulation and signaling networks, see Refs. [20,21], respectively). In addition, the messenger proteins are assumed to degrade at all the steps of the signaling activity. Our goal is to calculate the number of protein-receptor complexes inducing signal cascades inside the cells.

III. PROTEIN DIFFUSION IN THE EXTRACELLULAR SPACE

To mathematically formalize the scheme outlined above, we start from the analysis of protein diffusion in the extracellular medium. As usual, this process is described by Fick's second law as

$$\frac{\partial u}{\partial t} = D\nabla^2 u - k_s u, \tag{1}$$

where u is the protein concentration, D the diffusion coefficient, and k_s the rate constant of protein degradation in the solution outside the cells.

The rate constant k_s depends on the concentration(s) of species reacting with messenger protein. *In vivo*, the extracellular medium is usually believed to have sequestrating effect on protein factors and, in addition, contain proteinases that degrade them. Thus, the signal-mediating species may degrade outside the cells. We are primarily interested in cell signaling during proliferation and differentiation of stem cells *in vitro*. In this case, the medium used to cultivate cells typically contains a lot of various ingredients including enzymes or those related to enzymes and accordingly the signal-mediating species may degrade outside the cells as well. In practice, the medium composition is usually balanced in order to optimally feed cells and the detailed information on the effect of the medium on signal-mediating species is lacking. Alternatively, the extracellular enzymes can be excreted by the cells [22]. In our analysis, we assume that the former channel of the enzyme supply is dominating and accordingly the rate constant k_s is considered to be independent of the cell density.

To validate Eq. (1), we may note in addition that in reality the concentration of signal-mediating proteins is typically low [2] and accordingly the nonlinear features of the protein degradation kinetics are negligible. For this reason, the reaction kinetics in Eq. (1) is considered to be first order. (For a discussion of some of the consequences of the introduction of nonlinear degradation kinetics, see Ref. [23].)

In the *in vitro* experiments, there are four time scales characterizing, respectively, (i) intracellular biochemical reactions, (ii) signal propagation in the extracellular space, (iii) proliferation and differentiation, and (iv) the change of the medium. For stem cells, the medium is typically changed every other day or every day. The time scale characterizing proliferation and differentiation is usually somewhat shorter (e.g., about or longer than 10 h in the RNSC case). The intracellular biochemical reactions and signal propagation are usually much faster. [For example, the coefficient of diffusion of large biological molecules in the extracellular space, given by $D=k_BT/(6\pi\eta r)$ (r is the molecular radius, and η is the viscosity), is usually comparable to or larger than 2×10^{-7} cm^2/s. The cell size R is comparable to or smaller than 10^{-2} cm. The time, corresponding to diffusion on the distance R, is accordingly estimated as $\tau=(R/D)^{-1/2} \leqslant 200$ s.] Under such circumstances, we can use the steady-state approximation for describing all the processes related to signaling. This approximation is of course not always applicable. For example, the pattern formation during embrionic development is often believed to include unsteady-state signal propagation [11].

In the the steady-state case, Eq. (1) can be rewritten as

$$D\nabla^2 u - k_s u = 0. \tag{2}$$

The characteristic inverse length scale corresponding to this equation is given by $\kappa=(k_s/D)^{1/2}$. The way one can solve it depends on the relationship between κ and three natural length scales L, l, and R, characterizing, respectively, the thickness of the medium, the distance between cells, and the cell size. Our analysis is performed for

$$\kappa l \ll 1. \tag{3}$$

Physically, condition (3) means that the diffusion length scale characterizing the concentration gradients is much larger than the distance between cells and also much larger than the thickness of the layer formed by cells. In this case, the protein-concentration gradients along the surface are usually negligible, and accordingly we need to solve the 1D version of Eq. (2)—i.e.,

$$D\frac{\partial^2 u}{\partial z^2} - k_s u = 0, \tag{4}$$

where z is the coordinate perpendicular to the surface. In addition, the cellular processes can be taken into account by using the appropriate boundary condition near the surface

carrying the cells (at $z=0$). Specifically, the protein diffusion flux should be equal at $z=0$ to the net protein flux, generated by the cells. At the liquid-gas interface (at $z=L$), the diffusion flux has to be equal to zero. Thus, we have

$$-D\frac{\partial u}{\partial z}\bigg|_{z=0} = J_{net}, \qquad \frac{\partial u}{\partial z}\bigg|_{z=L} = 0.$$

The solution to Eq. (4) with these boundary conditions is

$$u(z) = u_s \cosh[\kappa(L-z)]/\cosh(\kappa L), \tag{5}$$

where

$$u_s = J_{net}/[D\kappa \tanh(\kappa L)] \tag{6}$$

is the protein concentration near the surface.

Concerning the validity of the equations above, it is appropriate to notice that in reality, the size of cells is relatively small (for example, the RNSC size is about 10^{-2} mm), and accordingly the gradients of the protein concentration inside cells are well known to usually be negligible. This means that

$$(k_c/D)^{1/2}R \ll 1, \tag{7}$$

where k_c is the rate constant of protein degradation inside the cells. In the extracellular medium, the concentration of species which may result in protein degradation is much lower than that inside the cells, and accordingly we have $k_s \ll k_c$. In addition, the cell-cell communication usually becomes important when the densitiy of cells is appreciable (in the RNSC case, e.g., at $l \simeq R$). Combining these two conditions with Eq. (7), one can easily show that as a rule condition (3) safely holds.

On the late stage of the growth, the RNSC's form islands and/or hemispheres containing a few (typically up to five) layers of cells [17]. In this case, condition (3) should be replaced by $\kappa h \ll 1$, where h is the typical thickness of islands or hemispheres. The latter condition safely holds as well.

In addition, one could expect that the applicability of Eq. (4) and the corresponding boundary conditions requires that $L \gg R$. For the RNSC growth *in vitro*, this condition is fulfilled. In the *in vivo* cases, L and R may be comparable (e.g., L may be 2 or 3 times larger than R). In such cases, the results presented below may, however, still be applicable provided that condition (3) is satisfied. For $L \simeq R$, the latter condition guarantees that the protein-concentration gradients are negligible both along and perpendicular to the surface (in particular, the results are independent of the protein diffusion coefficient), and accordingly, all the balance equations needed for our analysis remain valid.

IV. CELLULAR PROCESSES

In our model, the messenger proteins are considered to be produced in the type-1 cells. Inside a cell of this type, the steady-state balance of the protein production and removal is described as

$$j_p = k_c u_c + r_t(u_c - u_s), \tag{8}$$

where j_p is the protein-synthesis rate, u_c the intracellular protein concentration, k_c the rate constant of protein degradation in cells (this process usually occurs in special compartments called lysosomes [1]), and r_t the coefficient of protein transport through the external membrane (proteins usually leave and enter the cell by exocytosis and endocytosis—i.e., with a rearrangement and/or redistribution of lipids [1]). With appropriate specification of the rate constants in Eq. (8), it can describe the average balance of the rates either per unit volume or per the whole cell (in the latter case, for example, the rate constant k_c should be proportional to the cell volume). In our treatment, we assume that Eq. (8) describes the whole cell. Note also that phenomenologically the second term on the right-hand part of Eq. (8) corresponds to the linear-response theory and accordingly it is valid (provided that the difference $u_c - u_s$ is not large) irrespective of the mechanistic details of the protein diffusion via the membrane.

The messenger proteins diffusing in the solution outside the cells may associate with the receptors incorporated into the external membrane of the type-1 cells. For a single cell, this process is described as

$$r_a u_s = (r_d + k_a)u_a, \tag{9}$$

where u_a is the number of bound proteins, r_a and r_d are the association and dissociation rate constants (r_a is proportional to the number of the receptors), and k_a is the rate constant of degradation of attached proteins. Using Eq. (9), we assume that the probability that a receptor binds a messenger protein is low—i.e., the quantity of bound receptors is low compared to the total number of receptors. In reality, the dissociation process is relatively slow and nevertheless this condition is usually fulfilled, because u_s is low [2].

Employing Eqs. (8) and (9), we get

$$u_c = \frac{j_p + r_t u_s}{r_t + k_c}, \quad u_a = \frac{r_a u_s}{r_d + k_a}. \tag{10}$$

The contribution of a cell of type 1 to the net protein flux near the surface is given by

$$J_1 = r_t(u_c - u_s) + r_d u_a - r_a u_s \tag{11}$$

or, after substituting expressions (10) for u_c and u_a,

$$J_1 = \frac{r_t j_p}{r_t + k_c} - \left(\frac{r_t k_c}{r_t + k_c} + \frac{r_a k_a}{r_d + k_a}\right)u_s. \tag{12}$$

The equations for a cell of type 2 are similar to those presented above. The only difference is that in this case there is no term describing the protein synthesis; i.e., we have

$$K_c U_c + R_t(U_c - u_s) = 0, \quad R_a u_s = (R_d + K_a)U_a, \tag{13}$$

$$U_c = \frac{R_t u_s}{R_t + K_c}, \quad U_a = \frac{R_a u_s}{R_d + K_a}, \tag{14}$$

$$J_2 = R_t(U_c - u_s) + R_d U_a - R_a u_s, \tag{15}$$

or

$$J_2 = -\left(\frac{R_t K_c}{R_t + K_c} + \frac{R_a K_a}{R_d + K_a}\right) u_s. \tag{16}$$

All the symbols are here defined like those in Eqs. (8)–(12). To get a one-to-one correspondence of the symbols, we have simply replaced lowercase letters by uppercase letters.

The net protein flux generated near the surface is given by

$$J_{net} = J_1 N_1 + J_2 N_2, \tag{17}$$

where N_1 and N_2 are the surface densities of the cells of types 1 and 2, respectively. Substituting Eqs. (12) and (16) into this expression yields

$$J_{net} = \frac{r_t j_p N_1}{r_t + k_c} - \Phi(N_1, N_2) u_s, \tag{18}$$

where

$$\Phi(N_1, N_2) \equiv \left(\frac{r_t k_c}{r_t + k_c} + \frac{r_a k_a}{r_d + k_a}\right) N_1 + \left(\frac{R_t K_c}{R_t + K_c} + \frac{R_a K_a}{R_d + K_a}\right) N_2. \tag{19}$$

V. GENERAL RESULTS

Using Eqs. (6) and (18), we obtain the following general expression for the protein concentration near the surface:

$$u_s = \frac{r_t j_p N_1}{(r_t + k_c)[D\kappa \tanh(\kappa L) + \Phi(N_1, N_2)]}. \tag{20}$$

Substituting this expression into Eqs. (10) and (14) yields the numbers of proteins, associated with the receptors of the cells of types 1 and 2,

$$u_a = \frac{r_a r_t j_p N_1}{(r_d + k_a)(r_t + k_c)[D\kappa \tanh(\kappa L) + \Phi(N_1, N_2)]}, \tag{21}$$

$$U_a = \frac{R_a r_t j_p N_1}{(R_d + R_a)(r_t + k_c)[D\kappa \tanh(\kappa L) + \Phi(N_1, N_2)]}. \tag{22}$$

The rates of generation of signal transduction cascades inside the cells are proportional to u_a and U_a. Thus, expressions (21) and (22) for u_a and U_a make it possible to clarify the dependence of cell signaling on the surface concentration of cells.

The simplest and perhaps most important situation (especially for the *in vivo* conditions) is realized in the case when the protein degradation outside the cells is relatively rapid so that

$$D\kappa \tanh(\kappa L) \gg \Phi(N_1, N_2). \tag{23}$$

In this case, Eqs. (21) and (22) can be simplified as

$$u_a \simeq \frac{r_a r_t j_p N_1}{(r_d + k_a)(r_t + k_c) D\kappa \tanh(\kappa L)}, \tag{24}$$

$$U_a \simeq \frac{R_a r_t j_p N_1}{(R_d + R_a)(r_t + k_c) D\kappa \tanh(\kappa L)}. \tag{25}$$

According to these equations, u_a and U_a are proportional to the surface concentration of the type-1 cells and independent of the surface concentration of the type-2 cells. Physically, this regime occurs when the synthesis of messenger protein inside cells of type 1 is balanced primarily by their degradation in the extracellular medium.

In the opposite case [compared to condition (23)], Eqs. (21) and (22) are reduced to

$$u_a \simeq \frac{r_a r_t j_p N_1}{(r_d + k_a)(r_t + k_c)\Phi(N_1, N_2)}, \tag{26}$$

$$U_a \simeq \frac{R_a r_t j_p N_1}{(R_d + R_a)(r_t + k_c)\Phi(N_1, N_2)}. \tag{27}$$

According to these equations, the dependence of u_a and U_a on N_1 and N_2 is in general nonlinear.

Looking at expression (19) for $\Phi(N_1, N_2)$, one can notice that it contains two parts related to the cells of types 1 and 2, respectively. Depending on the ratio of those parts, there are two situations when expressions (26) and (27) can further be simplified. In particular, if the terms related to the type-1 cells dominate, i.e.,

$$\left(\frac{r_t k_c}{r_t + k_c} + \frac{r_a k_a}{r_d + k_a}\right) N_1 \gg \left(\frac{R_t K_c}{R_t + K_c} + \frac{R_a K_a}{R_d + K_a}\right) N_2 \tag{28}$$

and, accordingly,

$$\Phi(N_1, N_2) \simeq \left(\frac{r_t k_c}{r_t + k_c} + \frac{r_a k_a}{r_d + k_a}\right) N_1, \tag{29}$$

we have

$$u_a \simeq \frac{r_a r_t j_p}{r_t k_c (r_d + k_a) + r_a k_a (r_t + k_c)}, \tag{30}$$

$$U_a \simeq \frac{R_a r_t j_p (r_d + k_a)}{(R_d + R_a)[r_t k_c (r_d + k_a) + r_a k_a (r_t + k_c)]}. \tag{31}$$

In this case, u_a and U_a are independent of N_1 and N_2. Physically, this regime occurs when the type-1 cells are responsible both for the protein synthesis and degradation.

In the opposite case [compared to condition (28)] when

$$\Phi(N_1, N_2) \simeq \left(\frac{R_t K_c}{R_t + K_c} + \frac{R_a K_a}{R_d + K_a}\right) N_2, \tag{32}$$

we obtain

$$u_a \simeq \frac{r_a r_t j_p N_1}{N_2 (r_d + k_a)(r_t + k_c)} \Bigg/ \left(\frac{R_t K_c}{R_t + K_c} + \frac{R_a K_a}{R_d + K_a}\right), \tag{33}$$

$$U_a \simeq \frac{R_a r_t j_p N_1}{N_2 (R_d + R_a)(r_t + k_c)} \Bigg/ \left(\frac{R_t K_c}{R_t + K_c} + \frac{R_a K_a}{R_d + K_a}\right). \tag{34}$$

In this case, u_a and U_a are proportional to N_1/N_2, because the synthesis of proteins in the type-1 cells is balanced by their

degradation due to interaction with the type-2 cells.

Using Eqs. (23)–(34), we have classified various situations depending on the relative role of the messenger-protein diffusion in the extracellular medium and protein degradation in different regions. In addition, these equations make it possible to scrutinize the relative role of various cellular processes. For example, Eqs. (24) and (25) indicate that the protein transport through the external membrane of the type-1 cell limits signaling provided that $r_t \ll k_c$. Equation (25) shows that the signaling to the type-2 cells is limited by degradation of the proteins bound to the receptors of these cells provided that $R_a \ll R_d$. Many other similar conditions can be obtained from Eqs. (26)–(34).

VI. CONCLUSION

In summary, we have constructed a generic kinetic model describing protein-mediated signaling between cells attached to a surface. The results obtained have allowed us to classify likely scenarios of cell-cell communication:

(i) In the simplest case, the rates of generation of signal transduction cascades inside the cells are proportional to concentration of the cells emitting signals. The assumptions of this type are often used in the mean-field and Monte Carlo models of the tissue growth [6,9].

(ii) The signal intensity may be independent of concentration of cells. In this case, the cell-cell communication may, e.g., influence the rate of proliferation and differentiation of cells but does not change a type of the growth kinetics. Thus, the communication may be kinetically hidden.

(iii) The rates of generation of signal transduction cascades may be proportional to concentration of the cells emitting signals and inversely proportional to concentration of the cells receiving signals. In this case, the role of the cell-cell communication may diminish with increasing concentration of the cells receiving signals.

The results obtained extend the conceptual basis of the biophysical studies of cell signaling, stem-cell research, and biological surface science (for a review of the latter field, see Ref. [24]). In addition, the model proposed can be used beyond the cases treated above or as an ingredient of more global models of genetic networks (for the perspectives in this area, see Ref. [25]). In our analysis, for example, the protein-synthesis rate j_p is considered to be a free parameter. In reality, as mentioned in the Introduction, j_p may depend on u_a due to the feedback between the protein synthesis and signal propagation. In this case, our main final equations (20)–(22) are valid as well. The analysis below Eqs. (20)–(22) should, however, be slightly modified, taking into account the specifics of the feedback. Due to the feedback, the dependence of the protein concentrations u_s, u_a, and U_a on the governing parameters may be sigmoidal.

Concerning applications of the model to specific systems, we may note that at present the proteins mediating communication between stem cells are usually not well established and as a rule the sets of the corresponding rate constants are far from complete. For these reasons, an analysis of specific systems is beyond our present goals. We may only mention that our interest to the subject under consideration is related to experimental studies of proliferation and differentiation of attached adult rat neural stem cells [17,26]. The corresponding kinetics can be explained [26] assuming the concentration of the signal-mediating species to be proportional to concentration of the cells [like in item (i) above]. Identification of more complex situations in real systems needs additional studies.

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