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# Directional migration: a prototypical cellular control system

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*Abstract*— **Chemotaxis, the ability to move directionally in response to external chemical gradients, is a process found in many cell types. Individual bacteria and amoebae rely on chemotaxis to hunt for food. In mammalian cells, chemotaxis is crucial during development and as part of the immune system. In this paper we show how control theory can be instrumental towards the understanding of chemotaxis.**

## I. Introduction

Cellular signaling pathways are networks of interacting biochemical compounds that form the circuitry regulating cellular function. There are close analogs between many of the systems found in biology and those classically studied by control engineers. Our goal in this paper is to illustrate how some of these concepts arise in one of the best-studied forms of cellular function: directed cell migration.

Chemotaxis is the movement of cells guided by concentration gradients of a diffusible chemical. These chemicals can act as either attractants or repellents. Single-cell organisms, including bacteria and amoebae use chemotaxis as a way of seeking food.

In higher organisms, including mammalians, chemotaxis is employed by different cell types. Perhaps the best understood chemotactic system in humans is the movement of a type of white blood cell known as a *polymorphonuclear neutrophil*. These cells sense N-formylated peptides secreted by bacteria. (These peptides are specific to bacteria because only they use them to synthesize proteins [1]). Neutrophils are able to interpret extracellular concentrations of these peptides and move towards the source of the bacterial infection.

There are cells which, though normally stationary, can also migrate in response to external cues. These include so-called border cells. During development of the *Drosophila* (the common fruit fly) egg, a single layer of approximately 1000 follicle cells comprise the ephithelium [2]. A pair of specialized cells, known as polar cells, differentiate at the anterior end of the egg chamber. These cells, recruit four to eight additional cells which form a border cell cluster. They then migrate along the length of the egg ($\sim 150\,\mu$m). This migration is guided by chemoattractants that are secreted from the developing egg.

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A similar transition from a usually-stationary cell to a migratory cell is also observed, to deadly consequences, in tumor cells. Cancer that has not spread can often be treated successfully by the removal of the primary tumor; once it has metastasized, however, treatment is considerably more difficult. In fact, it is now appreciated that local invasion and distant metastasis are lethal [3]; more than 90% of cancer deaths can be attributed to the development of metastases [4].

It follows that there is considerable medical interest in the study of chemotaxis. However, directed cell migration is a process in which control theory plays a fundamental role.

## II. Required components

Cell migration involves the coordinated operation of several subsystems.

### A. Accurate sensors

To detect extracellular stimuli requires sensors for these chemicals. Cells posses a variety of surface receptors, specific for individual chemicals, that are connected across the cellular membrane to intracellular signaling molecules. When bound to extracellular molecules, these occupied receptors trigger pathways that lead to a cellular response. An excellent reference for the analysis of receptor interactions is the monograph by Lauffenburger and Linderman [5]. See also [6]. In this section we introduce some basics.

Receptor-ligand binding is typically represented by a deterministic differential equation

$$\frac{dC}{dt} = -k_{-r}C + k_f RL \tag{1}$$

Here $C$ and $R$ represent the concentration of bound and unbound receptors, respectively, and $L$ the concentration of free chemoattractant, or ligand. Conservation requires that $R_T = C + R$ be constant, so that

$$\frac{dC}{dt} = -\left[k_{-r} + k_f L\right] C + k_f R_T L$$

more accurately represents the system. This equation clearly shows how the cellular sensor can saturate for sufficiently large concentrations of chemoattractant. Strictly speaking, the ligand molecules are also conserved, so that $L$ should

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be replaced by $L_0 - C$. The resulting equation

$$\frac{dC}{dt} = -k_{-r}C + k_f[R_T - C][L_0 - C]$$

is a Riccati differential equation for which analytic solutions are possible [5]. Typically, however, the number of bound ligand molecules is low relative to the concentration of free ligand, ligand depletion plays little role, and Equation (1) is sufficient to describe most systems.

*1) Spatial considerations:* Equation (1) is ubiquitous in models describing cell surface binding, where concentrations are typically represented in fractions of a Molar (abbreviated M). This is the concentration equivalent to Avogadro's number of molecules ($6.02 \times 10^{23}$) in a liter (moles/liter). It is useful to keep in mind, however, that this volumetric concentration is not accurate for representing the cell surface receptors. The binding process described by (1) represents the "capture" of a diffusible molecule in 3-D by an immobile (or mostly immobile) receptor which is constrained to reside on the two-dimensional cell surface. Thus, their concentration is properly represented in terms of numbers/area. To represent this reaction accurately requires that we compute the flux of the ligand through a given area.

The analysis for this type of reaction goes back to the work of Berg and Purcell [7]; our exposition follows [5]. Specifically, assume that a cell of radius $a$ is centered at the origin and that $L(r)$, $r \geq a$, represents the concentration of free ligand. At steady-state, the distribution of $L$ obeys the diffusion equation

$$D\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dL}{dr}\right) = 0 \tag{2}$$

One boundary condition is obtained by noting that as $r \uparrow \infty$, $L(r) \to L_0$.

Following Fick's law of diffusion, there is a flux of ligand molecules to the receptor at the surface of the cell equal to $4\pi a^2 D(dL/dr)$. This number must equal the rate at which the ligand is absorbed by receptors and is given by the association rate for each free receptor ($k_{\text{on}}$) times the number or free receptors on the cell surface ($\hat{R}$; the surface concentration $R$ times the surface area $4\pi a^2$) times the concentration of ligand at the cell surface. This leads to the second boundary condition:

$$4\pi a^2 D \left.\frac{dL}{dr}\right|_{r=a} = k_{\text{on}}\hat{R}L(a)$$

The solution to (2) with the two boundary conditions is

$$L(r) = \frac{4\pi Da + k_{\text{on}}\hat{R}(1 - a/r)}{4\pi Da + k_{\text{on}}\hat{R}}L_0$$

From this we obtain the equivalent forward reaction rate for the cell

$$(k_f)_{\text{cell}} = k_{\text{on}}\hat{R}\frac{L(a)}{L_0} = \frac{4\pi Dsk_{\text{on}}\hat{R}}{4\pi Da + k_{\text{on}}\hat{R}}$$

which can be normalized, on the usual per-receptor level by dividing by $\hat{R}$. Note that the "constant" in (1) is actually a function of the free receptor concentration.

*2) Stochastic effects:* A second way in which (1) is an idealization is by ignoring the stochastic nature of receptor-ligand interactions. The effect of these fluctuations in experiments has been an important area of research in systems biology recently and has led to considerable theoretical work; see [8]–[10] and the references therein.

Stochastic deviations arise from the fact that reactions represent the interaction of individual molecules. The state of the system $x = [x_1, \ldots, x_n]$ is a random variable describing the number of the "$i$" molecules in the system. For each reaction $j \in \{1, \ldots, m\}$, there is an associated propensity function $a_j(x)$, which may be a function of the state, that when multiplied by $dt$ describes the probability that given $x(t) = x$, reaction $j$ will occur in the time interval $[t, t + dt)$.

If we denote by $P(x, t)$ the probability that the system is at state $x$, then

$$\frac{\partial P(x,t)}{\partial t} = \sum_{j=1}^{m}[a_j(x - v_j)P(x - v_j) - a_j(x)P(x,t)]$$

where $v_j$ denotes a stoichiometric vector that describes the number of molecules created/destroyed by reaction $j$. By multiplying this equation by $x$, and averaging, we obtain the following equation for the mean of $x_i$:

$$\frac{d\langle x_i(t)\rangle}{dt} = \sum_{j=1}^{m} v_{ji}\langle a_j(x(t))\rangle$$

For example, for receptor binding, there are three species $C$, $R$ and $L$. Suppose that there are $n_R$, $n_C$, and $n_L$ molecules of free receptor, bound receptor and free ligand respectively. Let the random variable $x := (n_C, n_R, n_L)$ represent the state of the system, and denote by $P(x, t)$ the probability distribution that the system is at this state at time $t$.

There are two reactions,

$$1: \quad R + L \to C, \quad \text{and} \quad 2: \quad C \to R + L$$

with propensity functions $a_1(x) = k_1' n_R n_L = k_1' x_2 x_3$, and $a_2(x) = k_2' n_C = k_2' x_1$. Moreover, the stochiometric vectors, which state how many molecules of $x$ are produced/destroyed by each of the reactions, are

$$v_1 = \begin{bmatrix}1 & -1 & -1\end{bmatrix}, \quad \text{and} \quad v_2 = \begin{bmatrix}-1 & 1 & 1\end{bmatrix}$$

The resultant chemical master equation is therefore

$$\begin{aligned}\frac{\partial P(x,t)}{\partial t} &= a_1(x - v_1)P(x - v_1, t) + a_2(x - v_2)P(x - v_2, t) \\ &\quad - (a_1(x) + a_2(x))P(x,t) \\ &= k_1'(x - v_1)P(x - v_1, t) + k_2'(x - v_2)P(x - v_2, t) \\ &\quad - (k_1' + k_2')xP(x,t)\end{aligned}$$

By multiplying by $x_i$, and averaging, one can obtain a

differential equation for the mean of $x_i$. For example, this leads to the following equation for the mean value of $x_1 = n_C$:

$$\begin{aligned}\frac{d\langle x_1\rangle}{dt} &= -k_2'\langle x_1\rangle + k_1'\langle x_2 x_3\rangle \\ &\approx -k_2'\langle x_1\rangle + k_1'\langle x_2\rangle\langle x_3\rangle \end{aligned} \quad (3)$$

Dividing this equation by the cellular volume $\Omega$ (and possibly converting units from number/volume to M) one finds that the deterministic equation (1) is equivalent to that for the mean (3) with $k_f = k_1'/\Omega$ and $k_r = k_2'/\Omega$.

To obtain distributions of the random variable $x$ requires the solution of the master equation. Except for the simplest of systems, however, direct computation of the master equation is intractable. Instead, it is customary to obtain distributions by repeated Monte Carlo simulation of the system. A popular method for accurate simulation is known as the Gillespie algorithm [11].

An alternative approach is by simulation and analysis through a stochastic differential equation (known in the field as the chemical Langevin equation [9], [12]). This equation consists of the deterministic equation for the mean (3) with an additive, state-dependent, noise term. In general it is given by

$$\frac{dx_i}{dt} = \sum_{j=1}^{m} v_{ji} a_j(x(t)) + \sum_{j=1}^{m} v_{ji}\sqrt{a_j(x(t))}w_j(t)$$

where $w_j(t)$ are two independent Gaussian white noise processes. In the case of receptor binding, the Langevin equation is given by

$$\frac{dC}{dt} = -k_r C + k_f R L + \sqrt{k_r C}w_1(t) - \sqrt{k_f R L}w_2(t)$$

Note that the last two terms can be combined by introducing a new Gaussian white noise process $v(t)$:

$$\frac{dC}{dt} = -k_r C + k_f R L + \sqrt{k_r C + k_f R L}v(t)$$

### B. Guidance mechanism

Once the external chemoattractant field has been sampled, the cell must interpret this information and make a decision as to the direction of migration. Chemotaxing organisms can be separated into two broad groups, depending on the mechanism by which they detect external chemoattractant gradients: temporal vs. spatial sensing.

*1) Temporal sensing:* Cells that employ a temporal sensing mechanism continuously move and sample their environment (a technique properly referred to as klinotaxis). They detect temporal changes in the concentration of the sensed chemical to determine the nature of the external chemoattractant field and guide their locomotion. The best-studied chemotactic organism, the bacterium *E. coli* relies on such a mechanism [13]. Other multicellular organisms, including the nematode *C. elegans* also rely on temporal sensing [14].

A cell can obtain an estimate of the concentration gradient by simple differentiating over time the sensed signal. Suppose that the location of the cell in the environment is $\mathbf{x} \in \mathbf{R}^3$ and that $L(\mathbf{x})$, denotes the concentration field of chemoattractant. Assuming that receptor binding is fast, so that (1) can be assumed to be in equilibrium, the sensed signal equals

$$C(t) = \frac{k_f L(t)}{k_f L(t) + k_r} R_T$$

Differentiation this with respect to time leads to

$$\frac{dC}{dt} = \frac{k_r}{(k_r + k_f L)^2} R_T \frac{dL}{dt}$$

Moreover, the time derivative of the ligand concentration to which the cell is exposed is given by the Lie derivative along the cell's trajectory:

$$\frac{dL}{dt} = \frac{\partial L}{\partial x}\frac{dx}{dt} + \frac{\partial L}{\partial y}\frac{dy}{dt} + \frac{\partial L}{\partial z}\frac{dz}{dt} = \underbrace{\nabla L}_{gradient} \cdot \underbrace{\frac{d\mathbf{x}}{dt}}_{velocity} \quad (4)$$

It follows that the change in receptor occupancy over time is proportional to the gradient and cellular velocity and to their respective spatial alignments.

Of course, simple differentiation is not advisable in a noisy environment. Noise can enter the system in two ways.

First, as argued above, receptor-ligand binding can give rise to considerable stochastic fluctuations in the perceived signal. This prevents the cell from having an exact picture of the external chemoattractant field. This can be a serious problems for *E. coli*. Because of their size, the number of chemotactic receptors on the surface of *E. coli* is relatively small; approximately 10,000. (For comparison, larger eukaryotic cells like *D. discoideum* have approximately 80-100 thousand chemoattractant receptors.) Moreover, these receptors tend to be found in several different conformations. For example, a possible model of receptor activation could separate receptor dimers (where two receptors are interacting) into 256 states depending on which methylation sites are occupied [15]. When distributed evenly amongst all 256 states, the average number of receptor dimers per state is no more than about 20. For this number of molecules, the stochastic deviations can be large.

Second, changes in the cellular velocity will also be amplified by temporal differentiation. Thus, abrupt changes in the direction of the cell can give rise to significant changes in the perceived field. This is also of importance in the motion of *E. coli*. The small size of a bacterium, a rod approximately 1 $\mu$m in diameter and 2 $\mu$m in length, leads to considerably noisy movement [13]. When swimming it is subject to rotational diffusion; when not swimming, it is affected by translational diffusion. Both of these imply that a stochastic fluctuation in the velocity relative to the gradient (in the last term of (4).

It follows that straight differentiation of the measured signal $C(t)$ is not possible. Instead, the bacteria relies on a low-passed filtered derivative to guide its motion.

A model of the signaling mechanism is given in Appendix A. In transfer function terms, the signaling pathway can be represented by

$$G(s) = \underbrace{\frac{k_1}{s+a_1}}_{\substack{\text{Receptor} \\ \text{binding}}} \times \underbrace{\frac{k_2 s}{s+a_2}}_{\substack{\text{Low pass filtered} \\ \text{differentiation}}}$$

Evidence of this form of the transfer function can be found in experiments in which the ligand concentration is changed in step-like fashion. The observed response (described below) first experiences a transient, but recovers to its prestimulus level — a process known to biologists as perfect adaptation.

In both biology and control engineering, there has been considerable interest in this adaptation mechanism. It has been demonstrated experimentally as well as theoretically that the adaptation mechanism is robust [16]–[18]. Specifically, changes in the concentration of the key enzymes regulating chemotactic signaling do not affect the perfect adaption property. Moreover, it has been demonstrated that this robustness is a consequence of an integral control mechanism [18], [19].

Less attention has been placed on the effect of varying the enzyme concentrations on the noise filtering properties of the cell, and the effect that they have on chemotaxis. Using models of the signaling pathway, it is possible to show that the filter bandwidth greatly influences the chemotactic behavior of the cell. Mutant cells that have too low a bandwidth respond sluggishly to changes in the sensed concentration, and therefore does not allow them to chemotax as well. On the other hand, cells in which the bandwidth is too high tend to respond too much to noise leading them astray. Again, these cells do not move as far along the chemoattractant field as a cell with the optimal bandwidth. Using a model of the the noise that is present in the system of wild-type cells it is also possible to show that the filtering bandwidth present in *E. coli* is near optimal [20].

*2) Static spatial sensing:* A second technique by which cells interpret directions is by simultaneously comparing the chemoattractant concentrations at different parts of the organism (referred to as tropotaxis).

One way of testing whether the system is able to detect gradients spatially is to observe the response of an immobilized cell to an external chemoattractant gradient. For several cell types, including the amoeba *D. discoideum* and neutrophils, this is possible by tagging intracellular proteins with fluorescent markers [21]. These markers go to the anterior or posterior of a migrating cell. For immobilized cells in a static chemoattractant gradient, however, these markers also polarize. This is evidence that the cell can compare chemical concentrations across the length of the cell.

At the cellular level, this technique is typically favored by larger eukaryotic cells. There are several reasons why these cells may favor this approach. They are significantly larger and so the difference in concentration between two sides of the cell is greater than for a smaller cell. On the other hand, they are also considerably slower cells. Neutrophils, which are some of the fastest mammalian cells, move at approximately one body length per minute. Fibroblasts, which are another chemotactic cell of the immune system move only about a body length per hour. In contrast, bacteria can swim at ten body lengths per second. Thus, in a given time interval, slow moving cells are not able to sample enough of their environment to be able to employ a temporal sensing mechanism.

It has been argued that even for small bacteria, spatial sensing may be advantageous for chemotaxis, particularly if the chemoattractant gradients are small [22]. This is true if, in contrast to *E. coli*, the bacteria swim along their short axis. Recently, experimental evidence has shown that at least one type of bacteria, the bipolar flagellated vibrioid bacteria, does rely on spatial sensing [23]. These cells ellipsoids in shape, approximately $2 \times 6\,\mu$m. They swim in the direction of their short axis but can sense gradients perpendicular to their axis of motion. Their ability to sense gradients spatially can be explained by a system in which there are sensors at either end of the long axis.

Static spatial sensing is sometimes found in cells that also have the ability to sense gradients temporally. Both neutrophils and *D. discoideum* can detect spatially homogeneous, temporal changes in the external chemoattractant concentration. The response to this stimulus is reminiscent of that of *E. coli*. In particular, a transient response is followed by perfect adaptation to the cell's prestimulus state. However, this response is not used to guide the cells. Instead, its role is to filter out the mean level of chemoattractant. Thus cells sense gradients equally well in gradients where the number of occupied receptors varies from 100–200 or 1100–1200 [24].

However, not all of the eukaryotic cells that are able to perform chemotaxis have this ability to adapt perfectly. For example, when fibroblasts, which are connective tissue cells that are used during wound healing, are stimulated by a uniform stimulus, their responses are not adaptive [25].

To perform spatial sensing requires that information from receptors at different locations be integrated, and a preferred directional decision be made. In fact, neutrophils and *D. discoideum* have receptors evenly spaced along the cell membrane. Moreover, these cells can chemotax accurately even in shallow gradients where the concentration differences between front and back differ by no more than 1–2%. The development and analysis of models of static sensing mechanisms is a particularly active field; a model that has been used to explain the combination of perfect adaptation and static spatial sensing is found in Appendix B. For other models and further study see [25]–[30] and the references therein.

### C. Amplification Mechanism

The chemotaxis systems of both *E. coli* and *D. discoideum* are exquisitely sensitive. That is, cells can respond accurately to very small gradients. This requires that the cells amplify the signals obtained by receptor occupancy.

In bacterial chemotaxis the amplification seems to occur at two steps along the sensing pathway. Receptors are clustered tightly. Moreover, these receptors work in a highly cooperative manner [31]. Thus, ligand binding to one receptor can not only change the activity of that receptor, but that of neighboring receptors [32]. At the level of the output the flagellar motor is also highly cooperative so that the input-output characteristic is switch-like [33].

The nature of the amplification step found in the chemotaxis pathway of neutrophils and *D. discoideum* is still not well understood. There is evidence that cells amplify the spatial heterogeneity in receptor occupancy by regulating complementarily the spatial distribution of several molecules [29], [34]. Excitatory enzymes are segregated from inhibitory enzymes, creating a biological push-pull amplifier. Relative to receptor occupancy, this complementary regulation leads to amplified localization.

## III. Connected problems

So far we have focused on the motion response of cells to chemoattractant stimuli. However, cells are typically mobile even when not sensing chemoattractant. Several of the interesting open problems in understanding the signaling pathways regulating chemotaxis lie in understanding how this guided locomotion is coupled to the undirected motility mechanism.

Over time, cells that are moving in a chemoattractant gradient acquire a polarized morphology. That is, over time, differences are formed between the parts of the cell closest to and farthest away from the chemoattractant source. These differences, however, remain even if the chemoattractant gradient is removed. How is this polarization established and maintained? In particular, cells seem to polarize even when no gradient is present. It has been conjectured that this polarization may be the product of a change of equilibria [26]. However, the precise mechanism is not understood. More importantly, how this mechanism is coupled to the directional sensing system is not understood.

## IV. Conclusions

In this paper we have introduced chemotaxis or directed cell migration. As we have argued, this is an extremely important cellular process. Moreover, it is a process in which knowledge of control system can be used to understand the system.

## Appendix

### A. Temporal sensing via receptor modification

Here we illustrate a simple model, originally from [19] that can explain how temporal sensing is mediated in *E. coli*. The model is a modified form of that used in [5], [35], [36]. Both free and bound receptors are found in two states: $R_1$ and $R_2$, and $C_1$ and $C_2$ respectively. Two enzymes mediate reversible transitions between states. The inhibitory enzyme $I$ catalyzes the modification from $R_1$ ($RL_1$) to $R_2$ ($C_2$), whereas the reverse process is catalyzed by the excitation enzyme $E$.

For example, in *E. coli* receptors can be methylated ($R_1$, $C_1$) or not ($R_2$, $C_2$). Demethylation is catalyzed by the methylesterase CheB whereas methylation is catalyzed by the methyltransferase CheR.

A scheme for robust adaptation for *E. coli* was suggested in [16]. It makes use of several key "structural" assumptions about the system. The first is that only fractions of the unmodified receptors, $\alpha_1 R_1$ and $\alpha_2 R_2$, are "active." Moreover, the inhibitor enzyme $I$ acts only on these active states. The kinetic constants for both these states are otherwise the same. The second assumption concerns the regimes in which the two enzymatic reactions are operating: The forward reaction (mediated by $I$) is occurring in the linear regime, whereas the reverse reaction (regulated by $E$), occurs at saturation. Using these assumptions we can write the following equations to describe the system replaced by

$$\frac{d}{dt}\begin{bmatrix} R_1 \\ C_1 \\ R_2 \\ C_2 \end{bmatrix} = \begin{bmatrix} k_{-1}E - k_1 I\alpha_1 R_1 - k_r R_1 L + k_{-r} C_1 \\ k_{-2}E - k_1 I\alpha_2 C_1 + k_r R_1 L - k_{-r} C_1 \\ -k_{-1}E + k_1 I\alpha_1 R_1 - k_d R_2 L + k_{-d} C_2 \\ -k_{-2}E + k_2 I\alpha_2 C_1 + k_d R_2 L - k_{-d} C_2 \end{bmatrix}$$

Note that the first two equations are decoupled from the second two; this is a consequence of the assumption that $E$ acts at saturation. We now perform a state-variable transformation. Define states $x_1 = \alpha_1 R_1 + \alpha_2 C_1$, (which corresponds to the activity) and $x_2 = (R_1 + C_1)/k_1 I$. This leads to

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{bmatrix} x_1 \\ x_2 \end{bmatrix} = \begin{bmatrix} -a_1(L,I) & a_0(L,I) \\ -1 & 0 \end{bmatrix} x + \begin{bmatrix} b_1(I) \\ 1 \end{bmatrix} r \qquad (5)$$

where

$$\begin{aligned} a_0(L,I) &= (\alpha_1 k_{-r} + \alpha_2 k_r L + \alpha_1\alpha_2 k_1 I)k_1 I \\ a_1(L,I) &= k_r L + k_{-r} + (\alpha_1 + \alpha_2)k_1 I \\ b_1(I) &= \frac{(\alpha_1 k_{-1} + \alpha_2 k_{-2})k_1 I}{k_{-1} + k_{-2}} \end{aligned}$$

with $r = \kappa(E/I)$ and $\kappa = (k_{-1} + k_{-2})/k_1$.

The differential equation for $x_2$:

$$\frac{dx_2}{dt} = -x_1 + r \qquad (6)$$

demonstrates the integral control. Specifically, at steady-state the activity $x_1$ is independent of ligand concentration. Moreover, this property does not depend on any of the parameter values.

### B. Spatial sensing: Local excitation-Global Inhibition

Our model is based on the general principle that the cellular response is regulated by the balance between a local excitation and a global inhibition. Both these processes are

regulated by receptor occupancy. Details are found in [19], [28], [30].

We assume that a molecule whose presence is related to the response of the system is found in one of two states: active, $R$, or inactive ($R_T - R$). As with the previous general model, excitation and inhibition processes regulate the change:

$$\frac{dR}{dt} = -k_{-r} I R + k'_r E[R_T - R] \quad (7)$$

$$\approx -k_{-r} I R + k_r E \quad (8)$$

Note that, as in the bacterial chemotaxis model, the response is proportional to the ratio $E/I$. Activation of these processes is assumed to be regulated by the occupied receptor.

$$\frac{dE}{dt} = -k_{-i} I + k_i C \quad (9)$$

$$\frac{\partial I}{\partial t} = -k_{-i} I + k_i C + D\nabla^2 I \quad (10)$$

Note that the latter equation is a reaction-diffusion equation.

When the input is spatially homogeneous the diffusion term is zero. At steady-state, $E$ and $I$ are both proportional to $C$ and so cancel out in the steady-state equation for $R$.

In contrast, a spatially heterogeneous distribution of ligand give also gives rise to a spatial distribution of $C$. At steady-state, this will be mirrored by the distribution of $E$. Diffusion, however, blurs the distribution of $I$. In the limit of infinite diffusion, the concentration of $I$ will be spatially homogeneous, at a level proportional to the mean level of receptor occupancy.

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