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# How receptor diffusion influences gradient sensing

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Chemotaxis, or directed motion in chemical gradients, is critical for various biological processes. Many eukaryotic cells perform spatial sensing, i.e. they detect gradients by comparing spatial differences in binding occupancy of chemosensory receptors across their membrane. In many theoretical models of spatial sensing, it is assumed, for the sake of simplicity, that the receptors concerned do not move. However, in reality, receptors undergo diverse modes of diffusion, and can traverse considerable distances in the time it takes such cells to turn in an external gradient. This sets a physical limit on the accuracy of spatial sensing, which we explore using a model in which receptors diffuse freely over the membrane. We find that the Fisher information carried in binding and unbinding events decreases monotonically with the diffusion constant of the receptors.

## 1. Introduction

Chemotaxis, involving movements that are oriented relative to chemical gradients, is an important and widespread phenomenon among eukaryotic cells. This mechanism is critical to neuronal growth cones navigating to their targets in the developing nervous system [1,2], neutrophils migrating to the site of inflammation [3] and sperm cells swimming towards an egg [4]. In the first steps of chemotaxis, ligand molecules in the environment bind to membrane chemoreceptors, activating them and triggering downstream signalling events [5]. In spatial sensing, cells estimate the external concentration difference across their spatial extent, a comparison whose corruption by noise from the stochastic nature of ligand binding and downstream signalling has been well studied [6–11]. In order to interpret information about binding, cells need to have information about the positions of the receptors concerned. These are generally in constant motion in the membrane, which is itself a highly complex structure that is compartmentalized on multiple scales [12,13]. Receptors undergo diverse modes of diffusion, including fast and slow diffusion, confinement and drift [14–17]; further, differential fluidity of membrane lipids can affect the lateral movement of proteins embedded in the membrane [12], and the diffusive properties of receptors can also be influenced by oligomerization or association with the membrane skeleton [14,18]. Because movement of receptors owing to diffusion represents a smearing out of the spatial information, they can provide about local concentration, diffusion will reduce the accuracy of gradient sensing. However, the importance of this depends on exactly how much information is lost; a quantity that has not previously been calculated. Receptor diffusion poses a challenge that cannot be addressed by previous models of gradient sensing which assume immobile receptors and thus a fixed binding probability for each receptor. 'Snapshot' measurements no longer suffice for the cell to infer the gradient, as information is lost about how long each receptor has been unbound and where it has been. Instead, cells must integrate over time to estimate the gradient efficiently.

Here, we model the effects of receptor diffusion on a one-dimensional 'cell', under the assumption that it is only bound receptors that signal and thus reveal their locations, leaving the cell uncertain about the locations of unbound receptors. In particular, we extend a previous model [19] which

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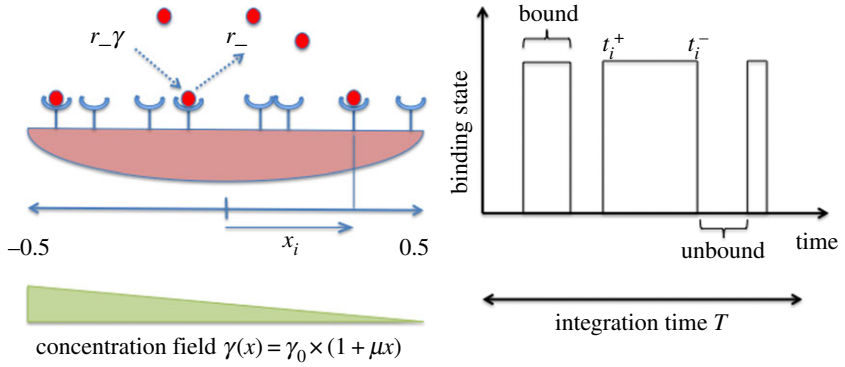


**Figure 1.** Schematic of sensing model. Ligand molecules bind to, and unbind from, receptors with transition rates $r_+$ and $r_-$, where $r_+ = r_-\gamma$ and $\gamma$ is proportional to the ligand concentration. The cell collects information about bound receptors over an integration time $T$. Here, we consider the degradation of gradient estimation owing to receptor diffusion. (Online version in colour.)

assumed that the cell has knowledge of the amount of time the receptors are bound and where the bindings happen, and we compare the accuracy of gradient sensing for receptors that are mobile versus immobile. We show analytically how receptor diffusion reduces the accuracy of gradient sensing, and demonstrate that the reduction increases monotonically with the diffusion constant.

## 2. Model

### 2.1. Immobile receptors

In common with many earlier models, here we take a normative or 'ideal observer' approach to gradient sensing. In particular, we consider the limits to the information available to a cell for decision-making, without addressing the mechanisms by which a cell could access that information via downstream signalling mechanisms. Many such previous models of gradient sensing have assumed, for the sake of simplicity, that receptors are immobile [6,9,10,20,21]. In these models, each receptor has a fixed probability of binding with ligand molecules which depends on the local ligand concentration at the receptor's position. This gives a probability distribution over possible binding patterns, and allows the cell to estimate the gradient from a 'snapshot' measurement of the binding pattern of all the receptors at a single moment. However, if the assumption of immobility is not imposed, each receptor will have a probability of binding that depends on its motion across the cell and thus through the concentration field.

An important alternative to the snapshot approach is to assume that the cell infers the gradient by integrating sequences of binding and unbinding events over time [19,22]. This leads to an upper limit on the information the cell can obtain assuming it knows both the unbound time and the number of bound/unbound transitions. However, these studies also assumed receptors were immobile. Here, we therefore extend the model of Mortimer *et al*. [19] to examine the effects of receptor mobility.

We first describe the original model in Mortimer *et al*. [19] (figure 1). The cell is represented as a one-dimensional array of uniformly distributed receptors whose binding and unbinding provide information about the concentration field that the cell experiences. The receptor state is modelled as a continuous time, two-state Markov process. The transition rate from bound to unbound is $r_-$ and the transition rate from unbound to bound is $r_+ = Ck_+$, where $C$ is the local concentration of ligand at the location of the receptor. The dissociation constant is $K_\mathrm{d} = r_-/k_+$. Writing $\gamma = C/K_\mathrm{d}$ for the dimensionless concentration, we have the relationship between the on- and off-rates: $r_+ = \gamma r_-$. The cell has $N$ receptors at positions normalized by the cell diameter $\boldsymbol{x} = (x_1, x_2, \ldots, x_N) \in [-0.5, 0.5]$, and the linear concentration field is $\gamma(x) = \gamma_0 \times (1 + \mu x)$ with $\mu$ being the gradient, or the fractional change of the concentration, that the cell has to estimate.

It was assumed in Mortimer *et al*. [19] that all receptors start out unbound. The times of binding and unbinding events were written as $t^+_{ji}$ and $t^-_{ji}$, where $j$ is the $j$th receptor and $i$ is the $i$th transition. Similarly, the positions of the receptors at those times were denoted $x^+_{ji}$ and $x^-_{ji}$. The cell was assumed to know about the timings and positions of the binding/unbinding events of the receptors via downstream signalling mechanisms that were not specified.

This implies that binding and unbinding are Poisson processes with rates $r_-$ and $r_-\gamma(x)$. For a Poisson process with rate $r$, the probability density of an event happening at a particular time $t$ after another event at time 0 is $r\exp(-rt)$. Therefore, the probability density for the $j$th receptor to remain bound from $t^+_{ji}$ to $t^-_{ji}$ is

$$P_b(t^+_{ji}, t^-_{ji}) = r_- \exp\left(-r_-(t^-_{ji} - t^+_{ji})\right),$$

and denoting $\gamma_j = \gamma(x_j)$, the probability density of it being unbound from $t^-_{ji}$ to $t^+_{j,i+1}$ is

$$P_u(t^-_{ji}, t^+_{j,i+1}) = r_-\gamma_j \exp\left(-r_-(t^+_{j,i+1} - t^-_{ji})\gamma_j\right).$$

Therefore, the likelihood of observing a time series $\{t^+_{ji}, t^-_{ji}\}$ given concentration $\gamma(x_j)$ at the location of receptor $j$ is

$$\mathcal{L}(T^\mathrm{B}_j, T^\mathrm{U}_j, \gamma_j) \propto r_-^{M^*_j}(r_-\gamma_j)^{M_j} \exp\left(-r_-T^\mathrm{B}_j - r_-T^\mathrm{U}_j\gamma_j\right), \qquad (2.1)$$

where $M_j$ is the number of unbound–bound transitions, and $M^*_j$ is the number of bound–unbound transitions (this equals $M_j$ or $M_j - 1$, because each binding event, with the exception of the last, must be followed by an unbinding event). $T^\mathrm{U}_j$, $T^\mathrm{B}_j$ are the total time unbound and bound, respectively, for receptor $j$. A maximum-likelihood approach suggests finding the value of the parameter of interest that makes the likelihood of observing the data as high as possible; this typically leads to an optimal unbiased estimate. Recalling that $\gamma_j = \gamma_0(1 + \mu x_j)$,

where $\mu$ is the gradient, and making the approximation $\log \gamma_j = \log \gamma_0 + \log(1 + \mu x_j) \approx \log \gamma_0 + \mu x_j - \mu^2 x_j^2/2$, we set the derivative of the log-likelihood to zero,

$$\frac{d\mathcal{L}}{d\mu} = \sum_j (M_j(x_j - \mu x_j^2) - r_- T_j^U \gamma_0 x_j) = 0.$$

Thus, the maximum-likelihood estimate of the gradient is given by

$$\mu_{MLE} = \frac{\sum_j (M_j x_j - r_- \gamma_0 x_j T_j^U)}{\sum_j M_j x_j^2}. \tag{2.2}$$

Equation (2.2) implies that the association between the receptor position and its unbound time (but not its bound time) carries gradient information, similar to a previous result that found unbound intervals carry concentration information [22]. A useful metric to measure the amount of information that an observation carries about an unknown parameter is the Fisher information, defined as the expected value of the second derivative of the log-likelihood function

$$\mathcal{I} = \left\langle -\frac{\partial^2 \log \mathcal{L}}{\partial \mu^2} \right\rangle.$$

As time increases, the variance of the maximum-likelihood estimate approaches the limit set by the inverse of the Fisher information

$$\mathrm{var}(\mu_{MLE}) \geq \mathcal{I}^{-1} = \left\langle \sum_j M_j x_j^2 \right\rangle^{-1}. \tag{2.3}$$

As the average time, it takes the receptor to become bound is $1/\gamma r_-$ and the average time the receptor remains bound is $1/r_-$, during the integration time $T$, the average number of unbound–bound transitions will be approximately

$$\langle M_j \rangle \approx \frac{T}{(1/r_- + 1/\gamma_0 r_-)} = \frac{T r_- \gamma_0}{\gamma_0 + 1}.$$

Hence, the Fisher information can be approximated as

$$\mathcal{I} = \left\langle -\frac{\partial^2 log \mathcal{L}}{\partial \mu^2} \right\rangle \approx \left( \sum_j \frac{T r_- \gamma_0}{\gamma_0 + 1} x_j^2 \right)^{-1}. \tag{2.4}$$

## 2.2. Mobile receptors

We now consider the more realistic case in which receptors are free to diffuse on the cell surface, starting from uniform randomly distributed initial positions. For the sake of simplicity, we consider the case that receptors continuously diffuse and ignore periods of confinement or drift. As unbinding events are independent of the receptor's position, their probability remains unchanged from above.

Binding events are treated as a Cox process, i.e. an inhomogeneous Poisson process whose intensity is also stochastic. Consider a single receptor (thus temporarily ignoring subscript $j$) that starts from initial position $x(0) = x_0$ and diffuses freely by Brownian motion independently of the binding (although the binding is not independent of the motion). In this case, the binding rate $\lambda(t)$ is a function of the random position $x(t)$ of the receptor at time $t$: $\lambda(t) = r_- \gamma_0(1 + \mu x(t))$. We use the concept of the Brownian bridge, i.e. Brownian motion fixed at two ends $x(t_{i-1}^-) = x_{i-1}^-$ and $x(t_i^+) = x_i^+$. According to the Cox process, the conditional density of a binding event at $t_i^+$ given the unbinding time $t_{i-1}^-$ and the path $\omega_i = (x_{i-1}^- \ldots x_i^+)$ of the receptor is

$$p(t_i^+ | t_{i-1}^-, \omega_i) = \lambda(x_i^+) \exp\left(-\int_{\omega_i} \lambda(x(t))\, dt\right), \tag{2.5}$$

where the first term accounts for the binding at $t_i^+$ and the second for the absence of binding over the time period $(t_{i-1}^-, t_i^+)$. Marginalizing over the unknown trajectory $\omega_i$, the conditional likelihood given only the positions $(x_{i-1}^-, x_i^+)$ at the unbinding and binding times is

$$P(t_i^+ | t_{i-1}^-, x_{i-1}^-, x_i^+) = \lambda(x_i^+) \mathbb{E}\left[\exp\left(-\int_{\omega_i} \lambda(x(t)) dt\right)\right], \tag{2.6}$$

where $\lambda(x) = r_- \gamma_0(1 + \mu x)$ is the binding rate, and the expectation is taken with respect to the diffusion bridge, but subjected to the boundary condition $-0.5 < x < 0.5$, as the receptors can diffuse only on the cell. We now proceed to find the expectation terms in the expression above

$$\begin{aligned} \mathbb{E}\left[\exp\left(-\int_{\omega_i} \lambda(x(t)) dt\right)\right] &= \mathbb{E}\left[\exp\left(-\int_{\omega_i} r_- \gamma_0(1 + \mu x(t)) dt\right)\right] \\ &= \exp\left(-r_- \gamma_0 (t_i^+ - t_{i-1}^-)\right) \\ &\quad \times \mathbb{E}\left[\exp\left(-r_- \gamma_0 \mu \int_{\omega_i} x(t) dt\right)\right]. \end{aligned} \tag{2.7}$$

The receptors undergo Brownian motion: $x(t) = x_0 + \sqrt{D} W(t)$, where $W(t)$ is a standard Brownian motion and $D$ is the diffusion constant. Only paths that satisfy the condition $-0.5 < x(t) < 0.5$ contribute to the expectation. We assume that the concentration is sufficiently high such that the probability of paths beyond this boundary is very small (i.e. $\langle t_{i+1}^+ - t_i^- \rangle D = D/\gamma r_- \ll R^2$ and $R$ is the radius of the cell). This assumption implies that including such paths does not affect the calculation. We discretize $t$ into $n$ intervals of $\delta t = (t_i^+ - t_{i-1}^-)/n$:

$$\int_\omega x_s ds = \lim_{n \to \infty} \sum_{k=1}^n x_k \delta t.$$

For brevity, we write $a = x_{i-1}^-, b = x_i^+, t_1 = t_{i-1}^-, t_2 = t_i^+$. The distribution of $x(t)$ at time $t \in (t_1, t_2)$ is normal with mean

$$a + \frac{t - t_1}{t_2 - t_1}(b - a),$$

and the covariance between $x(s)$ and $x(t)$ with $s < t$ is

$$D \frac{(t_2 - t)(s - t_1)}{t_2 - t_1}.$$

Therefore, $x_k$'s are the components of a multivariate normal vector with mean

$$\boldsymbol{X} = \left[a + \frac{\delta t}{t_2 - t_1}(b - a), \ \ldots a + \frac{(n-1)\delta t}{t_2 - t_1}(b - a), b\right].$$

and $n \times n$ covariance matrix

$$\Gamma_{kl} = D \frac{1}{t_2 - t_1} k(n - l)(\delta t)^2 \quad k < l.$$

We know that the sum of the components of a multivariate normal vector has a univariate normal distribution with mean

$$\alpha = \sum_k X_k = na + \frac{n(n+1)/2}{t_2 - t_1}(b - a) \approx n(a + b)/2$$

and covariance

$$\beta^2 = \sum_{k,l} \Gamma_{k,l} = \delta t^2 n^2 (n+1)^2/12(t_2 - t_1) \approx Dn^2(t_2 - t_1)/12.$$

Therefore, $\int_\omega x_s ds$ is also a normal random variable with mean $(x_i^+ + x_{i-1}^-)(t_i^+ - t_{i-1}^-)/2$ and variance $D(t_i^+ - t_{i-1}^-)^3/12$. Thus, $\exp(-r_-\gamma_0\mu\int_\omega x_s ds)$ follows a lognormal distribution with mean $m$ and variance $v$

$$m = \exp\left(\frac{\beta^2}{2+\alpha}\right)$$
$$= \exp\left(\frac{r_-^2\gamma_0^2\mu^2 D(t_i^+ - t_{i-1}^-)^3}{24} - \frac{r_-\gamma_0\mu(x_i^+ + x_{i-1}^-)(t_i^+ - t_{i-1}^-)}{2}\right)$$
$$v = (\exp(\beta^2) - 1)\exp(\beta^2 + 2\alpha).$$

The likelihood of a full observation $\{t_i^+, t_i^-, x_i^+, x_i^-\}$

$$\mathcal{L}(t_i^-, x_i^-, t_i^+, x_i^+ \ldots x_0) \propto$$
$$\prod_{i=1}^{M} r_- \exp(r_-(t_i^- - t_i^+))\lambda(x_i^+)\mathbb{E}\left[\exp\left(-\int_{\omega_i}\lambda(x(t))ds\right)\right]$$
$$\propto \exp\left(\sum_{i=1}^{M} r_-^2\gamma_0^2\mu^2\frac{D(t_i^+ - t_{i-1}^-)^3}{24} - \frac{r_-\gamma_0\mu(x_i^+ + x_{i-1}^-)(t_i^+ - t_{i-1}^-)}{2}\right)$$
$$\times \prod_{i=1}^{M}(1 + \mu x_i^+).$$

The maximum-likelihood estimate of the gradient is

$$\mu_{\mathrm{MLE}} = \frac{\sum_{i,j}^{M_j,N}(-r_-\gamma_0(x_{ji}^+ + x_{j,i-1}^-)(t_{ji}^+ - t_{j,i-1}^-)/2 + x_{ji}^+)}{\sum_{i,j}^{M_j,N}(-r_-^2\gamma_0^2 D(t_{ji}^+ - t_{j,i-1}^-)^3/12 + x_{j,i}^{+2})}.$$

A caveat of this calculation is that it assumes the cell knows the time series and locations of each receptor individually. That is, a pair of unbinding and binding events can be associated with each other, even though the receptor may have mingled with other receptors in the meantime. This is a reasonable assumption when diffusion is not too rapid or receptor density is low, such that the receptors are far enough apart and move sufficiently small distances for the cell to be able to distinguish between them after their unbinding period.

The Fisher information for this case is

$$\mathcal{I} = \left\langle -\frac{\partial^2 \log \mathcal{L}}{\partial \mu^2}\right\rangle = \left\langle \sum_{i,j}^{M_j,N}\left(-r_-^2\gamma_0^2 D\frac{(t_{ji}^+ - t_{j,i-1}^-)^3}{12} + x_{j,i}^{+2}\right)\right\rangle. \quad (2.8)$$

As expected, we can see that as $D$ increases, the Fisher information decreases and when $D = 0$, this expression reduces to equation (2.3). This expression cannot be evaluated analytically, but needs to be approximated. In order to approximate the first term, we recall that $\langle M_j\rangle \approx Tr_-\gamma_0/(\gamma_0 + 1)$ and $t^+ - t^-$ is an exponentially distributed variable with mean $1/(r_-\gamma_0)$, thus $\langle(t^+ - t^-)^3\rangle = 6/(r_-\gamma_0)^3$. Thus,

$$\left\langle -\sum_{i,j}^{M_j,N} r_-^2\gamma_0^2\frac{D(t_i^+ - t_{i-1}^-)^3}{12}\right\rangle \approx -\frac{\mathrm{TND}}{2(\gamma_0+1)}. \quad (2.9)$$

We adopt the approach of Mora & Wingreen [23] to approximate the second term as follows

$$\left\langle \sum_{i,j=1}^{M_j,N} x_{ji}^{+2}\right\rangle \approx \sum_j^N \int_0^T r_-\langle b_j(t)\rangle x_j^2(t)dt \quad (2.10)$$

with

$$\langle b_j(t)\rangle = \frac{r_-\gamma(x_j(t))}{r_- + r_-\gamma(x_j(t))} \approx \frac{r_-\gamma_0}{r_- + r_-\gamma_0}.$$

This approximation leads to

$$\mathcal{I} = \left\langle -\frac{\partial^2 log\mathcal{L}}{\partial\mu^2}\right\rangle$$
$$\approx -\frac{\mathrm{TND}}{2(\gamma_0+1)} + \left\langle \sum_j^N \int_0^T \frac{r_-\gamma_0}{1+\gamma_0} x_j(t)^2 dt\right\rangle. \quad (2.11)$$

We now need to calculate $\langle x(t)^2\rangle$ subjected to the boundary condition $-0.5 < x(t) < 0.5$. We employ the reflection principle to calculate this term. For a freely diffusing receptor without any boundary condition, the probability density function of $x(t)$ given the initial position $x_0$ is

$$p(x_0, 0; x, t) = \frac{1}{\sqrt{2\pi Dt}}\exp\left(-\frac{(x - x_0)^2}{2Dt}\right).$$

If the receptor is reflected back when it reaches the boundary $\pm 0.5$, then the probability density function of $x(t)$ is equal to that of a Brownian motion starting at $x_0$ plus those of its reflections across the boundary.

$$p(x_0, 0; x, t) = \frac{1}{\sqrt{2\pi Dt}}\left[\exp\left(-\frac{(x - x_0)^2}{2Dt}\right) + \sum_{n=-\infty}^{\infty}\exp\left(\frac{(n - x_0 - x)^2}{2Dt}\right)\right].$$

We assume that receptors cannot diffuse too much while being unbound, and thus include only two reflection terms. The mean square displacement is then

$$\int_0^T \langle x(t)^2\rangle dt = \sqrt{DT/2\pi}\left[\exp\left(-\frac{(1.5 - x_0)^2}{2DT}\right)(0.5 - x_0)\right.$$
$$+\exp\left(-\frac{(0.5-x_0)^2}{2DT}\right)(-1.5+x_0) + \exp\left(-\frac{(0.5+x_0)^2}{2DT}\right)(-0.5+x_0)$$
$$-\exp\left(-\frac{(0.5-x_0)^2}{2DT}\right)(0.5+x_0) + \exp\left(-\frac{(1.5+x_0)^2}{2DT}\right)(0.5+x_0)$$
$$\left.-\exp\left(-\frac{(0.5+x_0)^2}{2DT}\right)(1.5+x_0)\right] + \frac{1}{2}\left[-(DT + (-1+x_0)^2)\right.$$
$$\mathrm{erf}\left(\frac{-1.5+x_0}{\sqrt{2DT}}\right) + (DT + (1+x_0)^2)\mathrm{erf}\left(\frac{1.5+x_0}{\sqrt{2DT}}\right)$$
$$\left.-\left(\mathrm{erf}\left(\frac{0.5+x_0}{\sqrt{2DT}}\right) + \mathrm{erf}\left(\frac{0.5-x_0}{\sqrt{2DT}}\right)\right)(2x_0+1)\right].$$

These approximations are good as long as $D/\gamma r_- \ll R^2$. Diffusion constants of relevant receptors such as epidermal growth factor receptor (EGFR) and platelet-derived factor receptors are of order $10^{-2}\,\mu\mathrm{m}^2$, whereas the dissociation constants are of order $10^{-1}$ s, suggesting that this approximation is valid at $K_\mathrm{d}$ and higher concentrations [24–28].

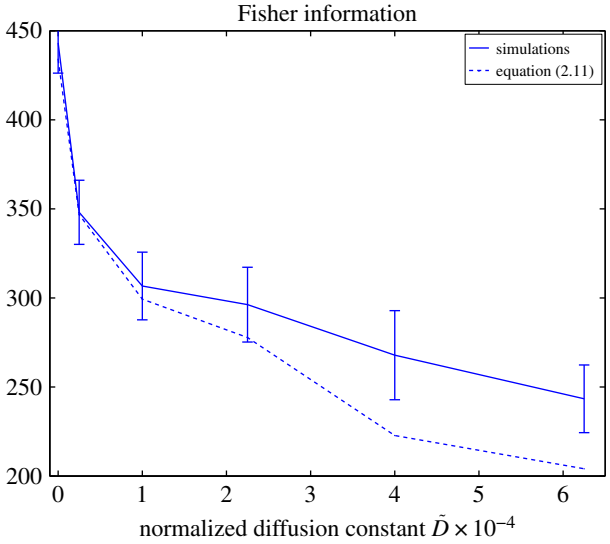


**Figure 2.** Diffusion reduces information. Comparison of Fisher information as a function of the dimensionless diffusion constant $\tilde{D}$ between simulations and the approximation in equation (2.11) ($r_- = 0.002$, $\gamma_0 = 10$). The faster the receptors diffuse, the less information the measurement contains. A normalized diffusion constant of $10^{-4}$ corresponds to an actual diffusion constant of 0.125 $\mu m^2\, s^{-1}$. (Online version in colour.)

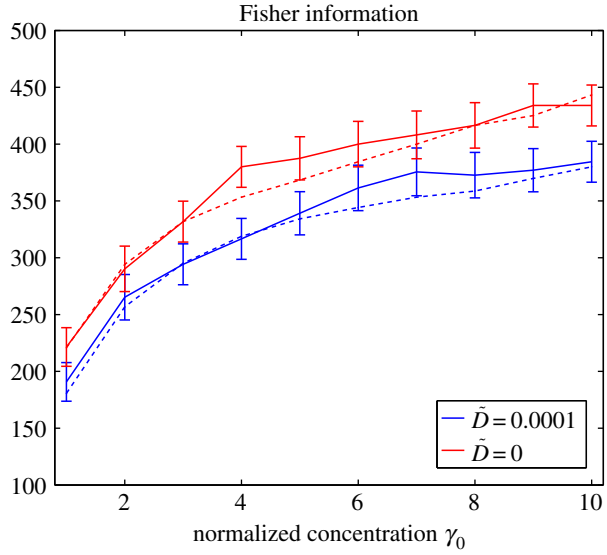


**Figure 3.** Information increases with concentration. The Fisher information as a function of the normalized concentration $\gamma_0$ with $r_- = 0.005$. The solid lines represent simulations, and the dashed lines represent approximations in equation (2.11). As $\gamma_0$ increases, more binding and unbinding events happen, resulting in greater Fisher information. (Online version in colour.)

We plot the quality of the approximations as a function of what is a convenient quantity, the normalized diffusion constant $\tilde{D}$ in figure 2. The unit of this normalized diffusion constant is $R^2/t$, where $R$ is the radius of the cell (which we assume for numerical calculations to be 5 μm) and $t$ is the duration of each time step of our simulation (set in our case to 0.02 s). The concentration is 10 $K_d$ (i.e. the normalized concentration is $\gamma_0 = 10$) and the gradient is 10% across the cell surface. Here, we used a discrete approximation to diffusion by initializing the positions of the receptors as uniform random numbers between −0.5 and 0.5 and, at each time step, making each move left or right a fixed amount $\sqrt{\tilde{D}}$, being 'reflected' if it hits −0.5 or 0.5. The probability of being bound at each time step is $r_-\gamma(x(t))$, if currently unbound, and the probability of becoming unbound is $r_-$, if currently bound. We assume off-rates of 0.001–0.01 per time step, equivalent to 0.05–0.5 $s^{-1}$. In our simulation, a normalized diffusion constant of $10^{-4}$ corresponds to an actual diffusion constant of 0.125 $\mu m^2\, s^{-1}$. In 20 000 time steps (400 s of real time) of each simulation, with this diffusion constant, the mean square displacement of each receptor is $2R^2 = 50\ \mu m^2$. Although this is only a one-dimensional model, the parameters are biologically plausible.

The approximate analytical values of the Fisher information come within 20% of their numerically simulated values (quantified via the inverse of the variance of the maximum-likelihood estimates over 2000 trials lasting 20 000 time steps). The quality of the approximation worsens as $\tilde{D}$ increases. One reason for this is that the estimate of $\langle x(t)^2 \rangle$ only included two reflection terms, whereas higher-order terms could become more significant in that regime. A famous theorem in statistics called the Cramer–Rao lower bound implies that the reciprocal of the Fisher information is a lower bound on the variance of the estimates (equation (2.3)). For example, if the Fisher information $\mathcal{I} = 400$ for a gradient of 10%, this means the lower limit to the variance is 0.0025. Gradient estimates will be approximately normally

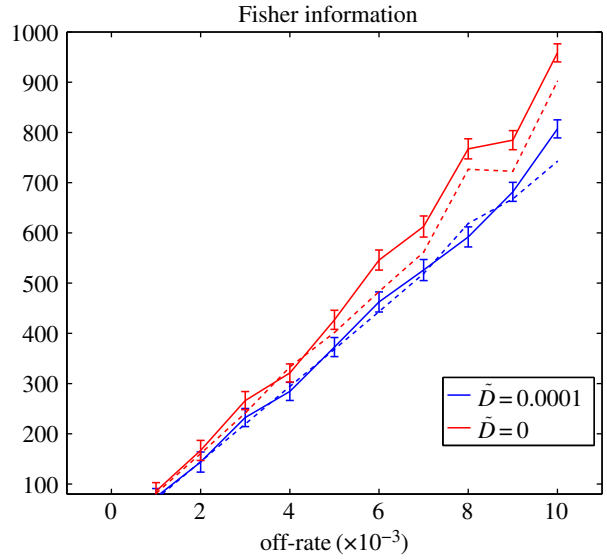


**Figure 4.** Information increases with off-rate. The Fisher information as a function of the off-rate $r_-$ with $\gamma_0 = 10$. (Online version in colour.)

distributed, with an unbiased mean of 10% and a standard deviation of 5%. Figure 1 implies that to achieve the same accuracy as in the case that the receptors are static, diffusing receptors force the cell to integrate over a longer time. Figures 3 and 4 show that as the concentration or the off-rate increases, more binding and unbinding events will happen, so that the measurement contains more information.

## 3. Delayed signalling

So far, we have assumed that as soon as the receptors become bound, they start signalling immediately. However, in reality, it takes time for the receptor to change its conformational state or for the downstream cytosolic molecules to be recruited to the activated receptor. Therefore, there might

be a delay between ligand binding and the initiation of the signalling cascade. It has been suggested that bound receptors slow down significantly, so that the cell can pinpoint exactly where the extracellular signal is coming from [12]. Whether this has any benefit for gradient sensing is not clear. By calculating the Fisher information in the case that the receptors can still move freely after being bound, we find that the cell gains no extra information about the gradient if the bound receptors are immobilized, because it is only unbound times which carry information.

We now consider the consequence of a time delay between the binding event and the report of the location, implying that the latter does not reflect exactly where the receptor was at the time of binding. We denote the positions at which the transduction pathways for receptor $i$ are activated and inactivated as $y_i^-, y_i^+$. Now, instead of knowing exactly where the binding and unbinding events occur on the surface, the cell only has access to partial information about these locations, represented by Gaussian distributions $x^+ \sim \mathcal{N}(y^+, \sigma_y)$, $x^- \sim \mathcal{N}(y^-, \sigma_y)$. If we assume that the time delay $t_\mathrm{d}$ is constant (a stochastic delay is also possible), then the uncertainty in the location of the binding/unbinding events will be $\sigma_y = \sqrt{Dt_\mathrm{d}}$. We can now examine how this extra noise adds to the uncertainty of the gradient estimate. The conditional probability of binding now has an expectation taken over all possible paths with all possible endpoints

$$\begin{aligned}
&P(t_i^+|t_{i-1}^-, y_{i-1}^-, y_i^+, \sigma_y)\\
&= \mathbb{E}_{P(x_i^+, x_{i-1}^-)}\left[\lambda(x_i^+)\mathbb{E}_{P(\omega)}\left[\exp\left(-\int_{t_i^-}^{t_{i+1}^+}\lambda(x(t))\mathrm{d}t\right)\right]\right]\\
&\propto \exp\left(\frac{r_-^2\gamma_0^2\mu^2 D(t_i^+ - t_{i-1}^-)^3}{24} - r_-\gamma_0\mu\frac{(x_i^+ + x_{i-1}^-)(t_i^+ - t_{i-1}^-)}{2}\right)\\
&\times \gamma_0(1+\mu x_i^+)\exp\left(-\frac{(x_i^+ - y_i^+)^2 + (x_{i-1}^- - y_{i-1}^-)^2}{2Dt_d}\right)\mathrm{d}x_i^+\mathrm{d}x_{i-1}^-\\
&= \exp\left(-C(y_i^+ + y_{i-1}^-) + C^2Dt_d\right)\gamma_0(1 + y_i^+\mu - CDt_d\mu)\\
&\quad\times\exp\left(\frac{r_-^2\gamma_0^2\mu^2 D(t_i^+ - t_{i-1}^-)^3}{24}\right),
\end{aligned}$$

where $C = r_-\gamma_0\mu(t_i^+ - t_{i-1}^-)/2$. The Fisher information is now

$$\begin{aligned}
\mathcal{I}_\mathrm{del} &= \mathcal{I} - \left\langle\sum_{i,j}\left(-\frac{r_-^2\gamma_0^2(t_{j,i}^+ - t_{j,i-1}^-)^2}{2} + r_-\gamma_0(t_{j,i}^+ - t_{j,i-1}^-)\right)Dt_\mathrm{d}\right\rangle\\
&\approx \mathcal{I},
\end{aligned}$$

where $\mathcal{I}$ is the Fisher information given in equation (2.8), because $\langle(t_{j,i}^+ - t_{j,i-1}^-)^2/2\rangle \approx 1/(r_-\gamma_0)^2$ and $\langle t_{j,i}^+ - t_{j,i-1}^-\rangle \approx 1/(r_-\gamma_0)$. This means the delay in signalling does not add any noise to gradient sensing. Thus, surprisingly, in this framework, confining the cytoplasmic signal to the precise place where the extracellular signal was received (i.e. immobilizing the receptor following binding) is not substantially beneficial to the cell.

## 4. Discussion

The lipid bilayer that forms cell membranes has been extensively investigated. Among other key characteristics, it has been found that membrane-bound receptors display complex behaviours, including hop diffusion, drift and confinement [12]. Here, we investigated the role of this receptor diffusion in spatial gradient sensing, exploring for simplicity the scenario in which receptors diffuse freely. Diffusion reduces the positional information that receptors carry about the signal they receive from the environment, and so potentially degrades the quality of gradient measurement. The speed of diffusion of receptors can vary depending on receptor and cell type. However, well-known receptors in chemotaxis such as EGFR in human mammary epithelial cells, TrkA in growth cones and PDGF in fibroblasts have diffusion constants of the order of $10^{-1}$ to $10^{-2}$ $\mu\mathrm{m}^2\,\mathrm{s}^{-1}$ [25,29,16]. In the typical time it takes cells to respond to chemical gradients, i.e. around a few minutes, the mean square displacement of receptors can be comparable to cell size (several micrometres). These parameter ranges suggest that diffusion of receptors can contribute to a significant loss of information during that integration time.

We modelled the cell as a one-dimensional array of independent chemoreceptors whose bindings with ligand molecules depend on their stochastic positions on the cell surface. We considered the regime of fast diffusion of the ligand molecules, and thus neglected rebinding of particles. We assumed that only bound receptors signal their positions to the cell, with the timings of the bindings also being known, either precisely or after a time delay. We derived an approximation to the Fisher information about the concentration gradient, and showed the approximation error to be small given a long integration time. One caveat with the model is that the cell has to associate times and positions with particular receptors. If the receptors are sparse and far apart, then this would be straightforward. However, if in a typical binding time the receptors can intermingle, then this is harder. It may be that the cell carries out a simpler computation that will underperform the maximum-likelihood estimate. Alternatively, receptors may signal constitutively, and so provide a means of being tracked. The gradient measurement is based on a quantity that depends on both the unbound intervals and the receptor positions (equation (2.2)). If the receptors can move and yet only snapshot measurements are used, the cell will have lost the information as to how long each receptor has been unbound or where it has been. Thus, unlike the immobile case, receptor diffusion therefore necessitates integration of information over a time window.

Using both simulations and the analytical approximations, we found that receptor diffusion can cause a substantial reduction in the quality of gradient sensing. This quality reduces roughly linearly with the diffusion constant of the receptors. This is intuitive, because the cell knows less about where the receptors have been before they became bound. Consistent with a previous paper [19], the performance increases with ligand concentration and the unbinding rate. This is expected, because the higher these parameters, the more binding/unbinding events occur and the more information the measurement contains. This model also assumes that the cell has infinite precision in measuring the binding delay. A more realistic mechanism for measuring time intervals by the production of second messenger molecules has been discussed in more detail in reference [19]. We have also not considered the issue of noise coming from downstream signalling, for instance from the diffusion of intracellular second messengers, focusing instead on the optimal possible performance only limited to noise owing to ligand binding. Ligands can alter the activation rate of downstream molecules

proximal to receptors, as demonstrated in the cAR1 receptor and its G protein in *Dictyostelium* cells [30].

Finally, we also considered a more realistic model in which the binding events are not registered immediately by the cell, but only after a time delay. By the time the bound receptors start signalling, they will have moved to another position, implying that the cell will have lost precise knowledge as to where the binding events happened. However, this does not substantially affect the information the measurement carries. This implies that immobilization is unlikely to serve the purpose of preserving the signal, and might rather have a different effect, such as facilitating the interactions between the bound receptors and the cytosolic molecules or other membrane-bound proteins.

Recently, Iyengar & Rao [31] found that there is a phase transition in sensing strategies as a function of receptor density and efficiency. At low receptor density, the optimal strategy is freely diffusing receptors. At higher density, the optimal solutions are either static receptors on a regular lattice grid or a mix of freely diffusing receptors and clusters. However, this model assumes that each receptor can sample the environment directly at regular time intervals. By contrast, our model is based on the arguably more realistic proposal that the receptors do not sample the gradient itself, but have to infer it from sequences of binding and unbinding events. We also do not assume measurements at regular intervals or that the locations of the receptors are known at all times.

One key simplifying assumption we made is that diffusion is unfettered. In fact, the traditional view of the membrane as a homogeneous fluid has been challenged and replaced by a more sophisticated model incorporating heterogeneous microdomains [12]. Indeed, in a gradient, receptors can have differential binding rates of ligand, changing diffusion constants among different populations of receptors or undergo redistribution [32–34]. The non-uniformity in motion has been hypothesized to be due to the existence of lipid rafts or the compartmentalization actin-based membrane–skeleton 'fences' and anchored transmembrane protein 'pickets'. These microdomains might serve as signalling platforms where the activated receptor can interact with cytosolic signalling molecules recruited to the cell membrane. Receptors might change their affinity with lipid rafts upon ligand binding and activate different signalling pathways depending on whether they are in a lipid raft or not. In these circumstances, the diffusion might allow the cell more flexibility to regulate receptor signalling; understanding the consequences of the heterogeneity—for instance, whether receptors can be adaptively slowed in the regions of low signal/noise remains to be investigated.

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## References

1. Mortimer D, Fothergill T, Pujic Z, Richards LJ, Goodhill GJ. 2008 Growth cone chemotaxis. *Trends Neurosci.* **31**, 90. (doi:10.1016/j.tins.2007.11.008)
2. Lowery LA, Van Vactor D. 2009 The trip of the tip: understanding the growth cone machinery. *Nat. Rev. Mol. Cell Biol.* **10**, 332. (doi:10.1038/nrm2679)
3. Downey GP. 1994 Mechanisms of leukocyte motility and chemotaxis. *Curr. Opin. Immunol.* **6**, 113. (doi:10.1016/0952-7915(94)90042-6)
4. Friedrich BM, Julicher F. 2007 Chemotaxis of sperm cells. *Proc. Natl Acad. Sci. USA* **104**, 13 256–13 261. (doi:10.1073/pnas.0703530104)
5. Bagorda A, Parent CA. 2008 Eukaryotic chemotaxis at a glance. *J. Cell Sci.* **121**, 2621–2624. (doi:10.1242/jcs.018077)
6. Berg H, Purcell E. 1977 Physics of chemoreception. *Biophys. J.* **20**, 193. (doi:10.1016/S0006-3495(77)85544-6)
7. Bialek W, Setayaeshgar S. 2005 Physical limits to biochemical signaling. *Proc. Natl Acad. Sci. USA* **102**, 10 040–10 045. (doi:10.1073/pnas.0504321102)
8. Ueda M, Shibata T. 2007 Stochastic signal processing and transduction in chemotactic response of eukaryotic cells. *Biophys. J.* **93**, 11. (doi:10.1529/biophysj.106.100263)
9. Mortimer D *et al*. 2009 A Bayesian model predicts the response of axons to molecular gradients. *Proc. Natl Acad. Sci. USA* **106**, 10 296–10 301. (doi:10.1073/pnas.0900715106)
10. Hu B, Chen W, Rappel WJ, Levine H. 2010 Physical limits on cellular sensing of spatial gradients. *Phys. Rev. Lett.* **105**, 048104. (doi:10.1103/PhysRevLett.105.048104)
11. Nguyen H, Dayan P, Goodhill GJ. 2014 The influence of receptor positioning on chemotactic information. *J. Theor. Biol.* **360**, 95–101. (doi:10.1016/j.jtbi.2014.06.022)
12. Kusumi A, Nakada C, Ritchie K, Murase K, Suzuki K, Murakoshi H, Kasai RS, Kondo J, Fijiwara T. 2005 Paradigm shift of the plasma membrane concept from the two-dimensional continuum fluid to the partitioned fluid: high-speed single-molecule tracking of membrane molecules. *Annu. Rev. Biophys. Biomol. Struct.* **34**, 351–378. (doi:10.1146/annurev.biophys.34.040204.144637)
13. Suzuki KGN. 2012 Lipid rafts generate digital-like signal transduction in cell plasma membranes. *Biotechnol. J.* **7**, 753–761. (doi:10.1002/biot.201100360)
14. Shibata SC, Hibino K, Mashimo T, Yanagida T, Sako Y. 2006 Formation of signal transduction complexes during immobile phase of NGFR movements. *Biochem. Biophys. Res. Commun.* **342**, 316. (doi:10.1016/j.bbrc.2006.01.126)
15. Callegari A, Luin S, Marchetti L, Duci A, Cattaneo A, Beltram F. 2012 Single particle tracking of acyl carrier protein (ACP)-tagged TrkA receptors in PC12nnr5 cells. *J. Neurosci. Methods* **204**, 82–86. (doi:10.1016/j.jneumeth.2011.10.019)
16. Marchetti L, Callegari A, Luin S, Signore G, Viegi A, Beltram F, Cattaneo A. 2013 Ligand signature in the membrane dynamics of single TrkA receptor molecules. *J. Cell Sci.* **126**, 4445. (doi:10.1242/jcs.129916)
17. Miyanaga Y, Matsuoka S, Ueda M. 2009 Single-molecule imaging techniques to visualize chemotactic signaling events on the membrane of living *Dictyostelium* cells. *Methods Mol. Biol.* **571**, 417–435. (doi:10.1007/978-1-60761-198-1_28)
18. Treanor B, Depoil D, Gonzalez-Granja A, Barral P, Weber M, Dushek O, Bruckbauer A, Batista FD. 2010 The membrane skeleton controls diffusion dynamics and signaling through the B cell receptor. *Immunity* **32**, 187–199. (doi:10.1016/j.immuni.2009.12.005)
19. Mortimer D, Dayan P, Burrage K, Goodhill GJ. 2010 Optimizing chemotaxis by measuring unbound–bound transitions. *Physica D.* **239**, 477. (doi:10.1016/j.physd.2009.09.009)
20. Baba A, Hiraiwa T, Shibata T. 2012 Directional sensing of deformed cells under faint gradients. *Phys. Rev. E* **86**, 060901. (doi:10.1103/PhysRevE.86.060901)
21. Fuller D, Chen W, Adler M, Groisman A, Levine H, Rappel WJ, Loomis WF. 2010 External and internal constraints on eukaryotic chemotaxis. *Proc. Natl Acad. Sci. USA* **107**, 9656–9659. (doi:10.1073/pnas.0911178107)
22. Endres RG, Wingreen NS. 2009 Maximum likelihood and the single receptor. *Phys. Rev. Lett.* **103**, 158101. (doi:10.1103/PhysRevLett.103.158101)
23. Mora T, Wingreen NS. 2010 Limits of sensing temporal concentration changes by single cells. *Phys. Rev. Lett.* **104**, 248101. (doi:10.1103/PhysRevLett.104.248101)

24. Tolmachev V, Varasteh Z, Honarvar H, Hosseinimehr SJ, Eriksson O, Jonasson P, Frejd FY, Abrahmsen L, Orlova A. 2014 Imaging of platelet-derived growth factor receptor beta expression in glioblastoma xenografts using affibody molecule 111In-DOTA-Z09591. *J. Nucl. Med.* **55**, 294–300. (doi:10.2967/jnumed.113.121814)
25. Ljunquist-Hoddelius P, Lirvall M, Wasteson A, Magnusson KE. 1991 Lateral diffusion of PDGF beta-receptors in human fibroblasts. *Biosci. Rep.* **9**, 63–73. (doi:10.1007/BF01117512)
26. Kholodenko BN, Demin OV, Moehren G, Hoek JB. 1999 Quantification of short term signaling by the epidermal growth factor receptor. *J. Biol. Chem.* **274**, 30 169–30 181. (doi:10.1074/jbc.274.42.30169)
27. Hiroshima M, Sako Y. 2011 Single-molecule kinetic analysis of receptor protein tyrosine kinases. In *Cell signaling reactions*, ch. 1 (eds Y Sako, M Ueda), pp. 1–32. Berlin, Germany: Springer.
28. Low-Nam ST, Lidke KA, Cutler PJ, Roovers RC, van Bergen en Henegouwen PMP, Wilson BS, Lidke DS. 2011 ErbB1 dimerization is promoted by domain co-confinement and stabilized by ligand binding. *Nat. Struct. Mol. Biol.* **18**, 1244–1249. (doi:10.1038/nsmb.2135)
29. Orr G, Hu D, Ozcelik S, Opresko LK, Wiley HS, Colson SD. 2005 Cholesterol dictates the freedom of EGF receptors and HER2 in the plane of the membrane. *Biophys. J.* **89**, 1362–1373. (doi:10.1529/biophysj.104.056192)
30. Xu X, Meckel T, Brzostowski JA, Yan J, Meier-Schellersheim M, Jin T. 2010 Coupling mechanism of a GPCR and a heterotrimeric G protein during chemoattractant gradient sensing in *Dictyostelium*. *Sci. Signal*. **3**, ra71. (doi:10.1126/scisignal.2000980)
31. Iyengar G, Rao M. 2014 A cellular solution to an information-processing problem. *Proc. Natl Acad. Sci. USA* **111**, 12 402–12 407. (doi:10.1073/pnas.1406608111)
32. Ueda M, Sako Y, Tanaka T, Devreotes P, Yanagida T. 2001 Single-molecule analysis of chemotactic signaling in *Dictyostelium* cells. *Science* **294**, 864–867. (doi:10.1126/science.1063951)
33. van Hemert F, Lazova MD, Snaar-Jagaska BE, Schmidt T. 2010 Mobility of G proteins is heterogeneous and polarized during chemotaxis. *J. Cell. Sci.* **123**, 2922–2930. (doi:10.1242/jcs.063990)
34. Bouzigues C, Morel M, Triller A, Dahan M. 2007 Asymmetric redistribution of GABA receptors during GABA gradient sensing by nerve growth cones analyzed by single quantum dot imaging. *Proc. Natl Acad. Sci. USA* **104**, 11 251–11 256. (doi:10.1073/pnas.0702536104)