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The influence of receptor positioning on chemotactic information

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ABSTRACT

Chemotaxis, or gradient following, is important in many biological systems, but suffers from noise. How receptors are positioned on the cell or sensing device influences the quality of the inferences they can support about the gradient, suggesting that their configuration might be optimised. We show that for an elliptical sensing device, inhomogeneous receptor placement could be a potential approach for cells to eliminate bias in the posterior distribution of the gradient direction. We use information theory to calculate the mutual information between the gradient and the binding pattern, thus finding the optimal receptor arrangement for gradient sensing.

1. Introduction

Many biological systems rely on chemotaxis. These include neutrophils migrating to sites of inflammation (Downey, 1994), the slime mold *Dictyostelium discoideum* hunting for food (Swaney et al., 2010), and neuronal growth cones navigating to find their targets in the developing nervous system (Mortimer et al., 2008; Lowery and Van Vactor, 2009). The ability of such sensing devices to detect chemical gradients depends sensitively on unavoidable stochastic fluctuations due to the limited numbers of receptors, intracellular signalling molecules, and ligand molecules available in the gradient itself (Berg and Purcell, 1977; Bialek and Setayeshgar, 2005). Detecting a gradient can thus be seen as a paradigmatic problem of reasoning in the face of uncertainty (Mortimer et al., 2009). Here we focus on noise due to receptor binding fluctuations.

A powerful approach for analysing such problems is to consider the *optimal* statistical inference that an ideal observer would perform (Andrews and Iglesias, 2007; Mortimer et al., 2009; Fuller et al., 2010; Hu et al., 2010, 2011a; Mortimer et al., 2011). This involves combining available information with prior assumptions. However a critical unanswered question is the extent to which some spatial distributions of receptors admit better gradient detection than others. Starting from the familiar model of the sensing device (hereafter 'cell') as a two-dimensional ellipse with receptors distributed on the surface, we derive the mutual information between the gradient and binding pattern as a target quantity to maximise in order to achieve optimal inference.

A recent theoretical analysis shows that with a uniformly distributed set of receptors, an elliptical cell can make incorrect inferences about the gradient when the concentration and the gradient steepness are low (Baba et al., 2012). Surprisingly, the cell has a strong bias to infer that the gradient is parallel to the minor axis, regardless of the actual gradient direction. This is because equal spacing of receptors on a non-circular surface leads to highly unequal variances in the estimates of the x and y components of the gradient. Here we show that this can be overcome by a nonuniform placement of receptors so that the inference is free of biases due to the shape of the cell.

2. Model

We consider the cell as estimating the gradient $\vec{\mu}$ of a spatial function $C(\vec{r}) = C_0 \exp(\vec{\mu}\,\vec{r})$. Receptor positions $\vec{r}$ are relative to the 'standard' length scale 10 μm and the gradient $\vec{\mu}$ is dimensionless. We assume that the information available about C consists of independent binary random variables b_i representing the bound and unbound states of a set of n receptors located at positions $\vec{r}_i \in \mathcal{R}^2, i = 1 \ldots n$. Standard Michaelis–Menten kinetics implies that the binding probability of each receptor is

$$P(b_i = 1) = \frac{C(\vec{r}_i)}{(K_d + C(\vec{r}_i))}$$

with K_d being the dissociation constant. The likelihood function of the complete binding state is

$$\mathcal{L}_{\mathbf{b}}(\vec{\mu}, C_0) = \prod_{i=1}^{n} \left(\frac{C(\vec{r}_i)}{K_d + C(\vec{r}_i)} \right)^{b_i} \left(\frac{K_d}{K_d + C(\vec{r}_i)} \right)^{1-b_i}$$

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whose logarithm is

$$\ln\mathcal{L}_{\mathbf{b}}(\vec{\mu}, C_0) = \sum_{i=1}^{n} b_i \ln\left(\frac{C(\vec{r}_i)}{K_d}\right) - \sum_{i=1}^{n} \ln\left(\frac{K_d + C(\vec{r}_i)}{K_d}\right)$$

The cell should combine likelihood information with its *a priori* estimate of the gradient. The prior has two components: the first is the direction $\phi = \angle\vec{\mu}$, which is conventionally represented as a von Mises distribution as in Hu et al. (2011a):

$$P(\phi) = \frac{\exp(\kappa\cos(\phi-\delta))}{I_0(\kappa)},$$

where δ is the prior bias of the cell regarding the gradient direction, κ is the strength of bias, and $I_0(\kappa)$ is the modified Bessel function of the first kind. This prior could be determined by previous measurements, as in a filtering scheme, or by an intrinsic bias. The second component is the strength $s = |\vec{\mu}|$ of the gradient. For convenience, we considered a simple, half-Gaussian form for this $P(s) = 2\sqrt{\beta/\pi}H(s)\exp(-\beta s^2)$, where β parameterizes the uncertainty. This favors small gradients, a conclusion invited by the exquisite sensitivity of many sensing systems (Mortimer et al., 2009; Mao et al., 2003). However, its precise form is not expected to influence the results very strongly, provided it is smooth and covers the range of relevant values. We consider these two components to be independent, making the overall prior $P(s,\phi) = P(s) \times P(\phi)$.

Expanding the likelihood function to second order around 0 in $\vec{\mu}$:

$$\ln\mathcal{L}_{\mathbf{b}} \simeq \sum_i b_i \ln\frac{C_0}{K} + n\ln\frac{K}{C_0+K} + \vec{\mu}\Delta_{\mathbf{b}}\vec{r} - \frac{1}{2}\vec{\mu}^T S\vec{\mu} \tag{1}$$

where

$$\Delta_{\mathbf{b}}\vec{r} = \sum_{i=1}^{n}\left(\vec{r}_i b_i - \frac{C_0}{C_0+K}\right), \quad S = \sum_i \vec{r}_i\vec{r}_i^{\,T}\frac{C_0K}{(C_0+K)^2} \tag{2}$$

leads to the maximum likelihood estimate (MLE)

$$\vec{\mu}^{\mathrm{ML}} = S^{-1}\Delta_{\mathbf{b}}\vec{r}$$

This formula is more general than that derived in Hu et al. (2010) since it does not assume a circular cell or a uniform distribution of receptors on the cell's surface. The average binding probability $\mathbb{E}[b_i]$ at each receptor is

$$\mathbb{E}[b_i] = \frac{C_0\exp(\vec{\mu}\cdot\vec{r})}{K + C_0\exp(\vec{\mu}\cdot\vec{r})} \approx \frac{C_0}{C_0+K} + \frac{C_0K}{(C_0+K)^2}\vec{\mu}\cdot\vec{r},$$

and therefore

$$\mathbb{E}[\vec{\mu}_{\mathbf{b}}^{ML}] = \frac{C_0K}{(C_0+K)^2}(\vec{r}^{\,T}\vec{r})S^{-1}\vec{\mu} = \vec{\mu},$$

confirming that the expectation of $\vec{\mu}^{ML}$ over all possible binding patterns is the actual gradient.

In the large n limit, the properties of the MLE ensures that $\vec{\mu}^{ML} \to \mathcal{N}(\vec{\mu}, S^{-1})$. S^{-1} is the covariance matrix of the maximum likelihood estimate and only depends on the positions of the receptors, not the shape of the cell. We call S the 'receptor matrix' as it ultimately encodes information about the receptor arrangement. As S is a symmetric matrix it can be diagonalised, implying that there exists a coordinate system defined by the two eigenvectors of S (shown in Fig. 1) such that the two orthogonal components of $\vec{\mu}^{ML}$ are uncorrelated, and their variances are the eigenvalues of the matrix S^{-1}. Henceforth, we will define all angles relative to this coordinate system, with x,y axes identified with the first and second eigenvectors of S^{-1}. Note that these axes will in general be different from the axes of the elliptical cell.

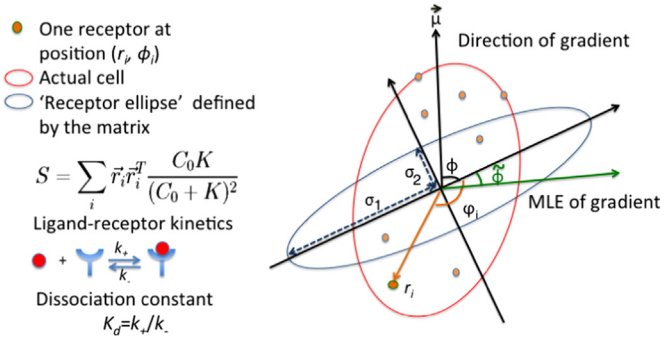

Fig. 1. Schematic problem representation. The orange dots represents receptors. The axes of the coordinate system are the two eigenvectors of the 'receptor ellipse' matrix $S = \sum_i \vec{r}_i\vec{r}_i\, C_0K/(C_0+K)^2$ (blue) which might or might not coincide with the axes of the actual cell (red). The two axes of the 'receptor ellipse' determines the properties of gradient estimation. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

We define $1/\sigma_1^2$ and $1/\sigma_2^2$ to be the corresponding eigenvalues of the matrix S^{-1} and

$$\begin{bmatrix} Z_1 \\ Z_2 \end{bmatrix} = \begin{bmatrix} \mu_x^{ML}\sigma_1^2 \\ \mu_y^{ML}\sigma_2^2 \end{bmatrix} = \begin{bmatrix} \sum\sigma_1^2 b_i(r_i\cos\varphi_i - \frac{C_0}{K+C_0}) \\ \sum\sigma_2^2 b_i(r_i\sin\varphi_i - \frac{C_0}{K+C_0}) \end{bmatrix}$$

where r_i, φ_i are the positions of the receptors in polar coordinates, and thus recover the familiar Gaussian approximation for the likelihood function (Hu et al., 2010):

$$P(\vec{Z}|s,\phi) = \frac{1}{2\pi\sigma_1\sigma_2}\exp\left[-\frac{(Z_1 - s\sigma_1^2\cos\phi)^2}{2\sigma_1^2} - \frac{(Z_2 - s\sigma_2^2\sin\phi)^2}{2\sigma_2^2}\right]$$

3. Eliminating bias

For certain receptor distributions for which $\sigma_1 \neq \sigma_2$, the variances in μ_x^{ML} and μ_y^{ML} can differ, causing the cell consistently to estimate the gradient direction

$$\tilde{\phi} = \tan^{-1}\left(\frac{\mu_x^{ML}}{\mu_y^{ML}}\right)$$

parallel to its minor axis at low concentration or gradient steepness, as seen in Baba et al. (2012). At first glance, this result might be counter-intuitive. However, if $\sigma_1 \gg \sigma_2$, equivalent to a 'receptor ellipse' elongated in the x direction, the cell can much more easily detect the asymmetry in the concentration in the x direction (low variance) than in the y direction (high variance). The inequality in variances leads to bias in the MLE due to the highly nonlinear nature of the function $\tan^{-1}$. Therefore, at shallow gradients the estimated direction of the gradient has a tendency to favor the minor axis (the y direction). The estimated direction also has higher variance if the true gradient is in the x direction than if it is in the y direction as illustrated in Fig. 2.

For simplicity we assume that the cell is only interested in the gradient direction rather than its magnitude. In order to find the maximum *a posteriori* (MAP) estimate for the actual gradient direction ϕ_{true}, we seek to solve $\hat{\phi}_{MAP} = \arg\max_\phi P(\phi|\vec{Z})$ where

$$P(\phi|\vec{Z}) \propto \int P(\vec{Z}|s,\phi)P(s)P(\phi)\,ds$$
$$\propto \frac{1}{\sqrt{A}}\exp\left(\frac{B^2}{4A} - C\right)\left(1 - \mathrm{erf}\left(-\frac{B}{2\sqrt{A}}\right)\right) \tag{3}$$

where

$$A = 1/2(\sigma_1^2\cos^2\phi + \sigma_2^2\sin^2\phi) + \beta$$
$$B = Z_1\cos\phi + Z_2\sin\phi$$