Supplementary Materials for:
An Information Theoretic Framework for Eukaryotic Gradient Sensing

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In this supplement we detail the derivations of analytical formulae given in the main text, we exhibit an additional figure excluded from the main text due to space limitations, and we provide pseudocode detailing the direction and entropy estimation algorithms.

1 Methods: supplemental

1.1 Analysis

1.1.1 Mutual information of the receptors

Let the random variables \{B_j\}_{j=1}^N represent the states of the \(N\) cAMP receptors on the cell surface; \(B_j = 1\) if the receptor is bound to a molecule of cAMP, otherwise \(B_j = 0\). Each receptor is taken to lie on the surface of a sphere of radius \(R = 7.5\mu m\), with displacement from the center of the cell in a direction given by a unit vector \(\vec{x} \in S^2\). We set the center of the sphere to be the origin of our coordinate system. Invoking the assumption of gradient linearity, we take the equilibrium concentration of cAMP at \(\vec{x}\) to be \(c(\vec{x}|g) = a + b(\vec{x} \cdot \vec{g})\) where \(\vec{g} \in S^2\) is a unit vector in the direction of the gradient. The parameter \(a\) is the mean concentration over the cell surface, and \(b = R|\nabla c|\) is half the drop in concentration from one extreme on the cell surface to the other. Before the stimulus occurs, the gradient direction is undefined.

At equilibrium, given a particular gradient direction \(\vec{g}\), the probability of finding the receptor at \(\vec{x}_j\) in the bound state is

\[
P(B_j = 1|\vec{g}) = h(c(\vec{x}|\vec{g})) = \frac{c(\vec{x}|\vec{g})}{c(\vec{x}|\vec{g}) + K_{eq}},
\]

where \(K_{eq} = k_{off}/k_{on}\) is the equilibrium constant for the ligand-receptor binding interaction, and \(h(c) = c/(c + K_{eq})\) is a first-order Hill function with half-saturation at \(c = K_{eq}\).

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where \( d \) bound is gradient indeterminate (\( \vec{g} \) with the ensemble approached equilibrium. Instead we must compare the receptor activity under an imposed gradient all receptors may be in the unbound state) compared with the entropy after the applied gradient has exceeded 16 bits when \( \Phi \) is convex for \( \{ \vec{g} \} \). Whenever the \( \Phi \) is uniformly distributed over \( \mathbb{S}^2 \) the probability of a given receptor being bound is

\[
P(\{B_j\}) = \int_{\vec{g} \in \mathbb{S}^2} P(\{B_j|\vec{g}\}) d\Omega = \int_{\vec{g} \in \mathbb{S}^2} h(c(\vec{x}|\vec{g})) \frac{1}{4\pi} d\Omega,
\]

where \( d\Omega \) represents the surface area element on the sphere, \( d\Omega = \sin(\theta) d\theta d\phi \). By rotational symmetry, when the gradient direction is indeterminate all receptors have the same \( a \) \( p \) \( \theta \) probability of being bound or not. Hence with respect to the ensemble of possible gradient directions, the uncertainty in the state of the receptors is:

\[
H[\{B_j\}] \sim N\Phi[P(\{B_j\})] \text{ (as } N \to \infty) \nonumber
\]

\[
\sim N\Phi \left[ \int_{\theta=0}^{\pi} \int_{\phi=0}^{2\pi} \left( \frac{a + b \cos(\theta)}{a + b \cos(\theta) + K_{eq}} \right) \sin(\theta) \frac{4\pi}{\pi} d\phi d\theta \right].
\]

In both equation (1) and (2), the argument of \( \Phi \) is a probability taking values \( 0 \leq p \leq 1 \). In (1) the values of \( \Phi \) are averaged over the sphere; in (2) \( \Phi \) is evaluated after averaging probabilities. Because \( \Phi[p] \) is convex for \( 0 \leq p \leq 1 \), the integral in equation 1 cannot exceed that in equation 2. Therefore the mutual information

\[
MI[\{B_j\}; \vec{g}] \triangleq H[\{B_j\}] - H[\{B_j\}|\vec{g}] \geq 0,
\]

as expected upon receiving the signal. The analytic solution for equation (1) involves the polylogarithm function. For the parameters shown in the simulation \( a = 1.078 \) nMol, \( b = .512 \) nMol, \( K_{eq} = 25 \) nMol), the mutual information with 980 receptors is 2.16 bits. As one would expect, the mutual information peaks when the mean concentration is close to the \( K_{eq} \) of the receptor, exceeding 16 bits when \( a = 25 \), \( b = 12.5 \) and \( K_{eq} = 25 \) nMol).

### 1.1.2 Dimension reduction

As an alternative to the approximations necessary when treating the mutual information of the 980-dimensional set of receptor states and the 3-dimensional gradient direction \( \vec{g} \in \mathbb{R}^3 \), we construct a directional estimator \( \hat{g} \) from the spatiotemporal pattern of receptor binding events. Let \( \{ \vec{x}_j \}_{j=1}^N \) be the spatial locations of the \( N \) receptors on the cell’s surface. With each vector we associate a weight \( w_j \). Whenever the \( j \) receptor binds a cAMP molecule, \( w_j \) is incremented by one; otherwise \( w_j \) decays with time constant \( \tau \). We construct an instantaneous estimate of the gradient direction from the linear combination of receptor positions

\[
\hat{g}_\tau(t) = \sum_{j=1}^{N} w_j(t) \vec{x}_j.
\]
where \( \gamma \) is the Euler-Mascheroni constant. As shown in Figure 2, this approximation agrees with the analytic result for the uniform distribution, \( H_{\text{unif}} = \log_2(4\pi) \approx 3.651 \).
2 Results: supplemental

See Supplemental Figure 1.

3 Direction and entropy estimation algorithms

3.1 Direction estimation

The algorithm we use for creating an estimated direction vector at each timestep is to first calculate for each receptor a Weight vector that is 0 before the receptor binds, 1 at the timestep when the receptor binds, and decays exponentially after a binding. The weight is cumulative, so that a receptor can have a weight above 1. After assembling the weights we then assemble a Directions vector for the run which is created by taking a weighted average across all receptor locations. Note that we do not normalize our weighted average, leaving it simply as a weighted sum. The weights decay at a rate given by rate = 1/τ.

foreach Receptor R
    create a zero vector, W, of length timesteps
    foreach binding event B
        W[B.time] += 1
    foreach timestep t, from B.time+1 to timesteps
        W[t] *= (1-rate * dt)

create a zero vector of Points in \( \mathbb{R}^3 \), D, of length timesteps
foreach timestep t
    foreach Receptor R
        D[t].x += R.W[t] * R.location.x-component
        D[t].y += R.W[t] * R.location.y-component
        D[t].z += R.W[t] * R.location.z-component

3.2 Entropy estimation

To compute the entropy, first, for each run, we construct the Direction vector as outlined above, then construct from that an Angles vector giving the angle between the estimate at each time \( t \) from the correct direction. Then, for each timestep, take the collection of angles from all runs, and apply our adaptation of the method presented by Victor, Kozachenko, and Leonenko (see main text; “KLV method”).

create a matrix M with height num_runs and width num_timeSteps
foreach simulation run
    create the direction vector, d, as described in §3.1
    fill in the corresponding row in M with \( \text{acos}(\cos(d, [-1, 0, 0])) \)

To Estimate Entropy for each timestep
    take from M the corresponding column, C
    initialize a count of the entropy, \( \text{Ent} = 0 \)
    sort C so that each entry will be next to its nearest neighbor
    foreach entry in C, \( \theta \), at index \( i \)
        Dist = \( \min(\text{abs}(\theta - C[i+1]), \text{abs}(\theta - C[i-1])) \)
        \( \text{Ent} += \log_2(Dist) \)
        \( \text{Ent} += \log_2(\sin \theta) \)
        \( \text{Ent} = \text{Ent} \times \text{length}(C) + \log_2(2\pi) + \log_2(2 \times (\text{length}(C)-1)) + \frac{\gamma}{\log_2(2)} \)

As in the main text, \( \gamma \) is the Euler-Mascheroni constant. Algorithm implemented in C++ using the GNU STL.

References


Figure 1: Population timecourse of the directional estimate vector.

**Top:** Average of $M = 600$ directional estimate vectors $\hat{g}_\tau$, $\tau = 500$ msec. The average length is close to zero when the cAMP signal is uniformly distributed; after the stimulus is applied the average estimate grows in the $-x$ direction (descending trace) but not in the $y$ or $z$ directions, indicating that $\hat{g}_\tau$ provides an unbiased estimate of the gradient direction. Similar results obtain for each value of $\tau$ tested.

**Bottom:** Mean resultant length [4] versus time. The mean resultant length is the average of the unit vectors $\hat{g}_\tau / |\hat{g}_\tau|$ obtained by normalizing the directional estimates $\hat{g}_\tau$, and has length bounded between zero (when $\hat{g}$ are uniformly distributed) and one (when $\hat{g}$ are highly clustered in direction). The timecourse of the mean resultant length mirrors that of the mutual information.