Lower Bounds on the Shannon Capacity of a Biochemical Signal-Transduction Relay

Sierra K. Hampton[1], Christopher C. Ko[1], Peter Park[1], Donald Spencer[1,2] and Peter J. Thomas[2]

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1: Department of Electrical and Computer Engineering, Jacobs School of Engineering, University of California, San Diego.
2: Computational Neurobiology Laboratory, Salk Institute for Biological Studies.

Abstract

Biochemical signal-transduction networks are the biological information-processing systems by which individual cells, from neurons to amoebae, perceive and respond to their chemical environments. We introduce a simplified model of a single biochemical relay and analyse its capacity as a communications channel. A diffusible ligand is released by a sending cell and received by binding to a transmembrane receptor protein on a receiving cell. This receptor-ligand interaction creates a nonlinear communications channel with non-Gaussian noise. We explore the dependence of its channel capacity on parameters such as the diffusion constant, rate of ligand decay, maximum rate of ligand emission, and binding- and unbinding-reaction rates. We conjecture that parameter values maximizing the channel capacity should be observed in diffusion-and-binding mediated signal transduction systems from *Dictyostelium* signaling to synaptic transmission.

1 Background

Biochemical signal-transduction networks are the biological information-processing systems by which individual cells, from neurons to amoebae, perceive and respond to their chemical environments. To begin analyzing biochemical networks as information-processing systems, we study a simple model of a receptor-ligand interaction as a communications channel. A "sending" cell, S, releases a time-varying chemical signal $s(t)$ into a volume containing a "receiving" cell R. The channel "output" takes the values 1 or 0 as the receptor protein of R is bound or unbound to a ligand molecule. The capacity of this communications channel depends on the rate of diffusion and rate of decay of the ligand, on the maximum signal emission rate allowed and on the distance separating S and R, and on the forward and reverse reaction constants of the receptor-ligand interaction. By studying specific encoding schemes for the source S we can determine lower bounds on the channel capacity and their dependence on these parameters. We speculate that parameter values maximizing the capacity should be observed in diffusion-mediated communications such as signaling between *Dictyostelium* amoebae, quorum sensing in bacterial colonies, immune-signal signaling, axonal growth, embryonic development or synaptic transmission.

2 Method

We simulate a biochemical relay system as follows: in a two-dimensional rectangular volume V measuring 5 micrometers by 10 micrometers, we locate two cells spaced 5 micrometers apart. Cell R emits ligand molecules at $x_s = [2.5\mu, 2.5\mu]$ with rate $0 \leq s(t) \leq s_{\max}$; they diffuse with a given diffusion constant D and decay at a rate α. The mean concentration $c(x,t)$ obeys the diffusion equation with reflecting boundary conditions:

$$\begin{aligned} \frac{\partial c}{\partial t} &= D\nabla^2 c - \alpha c \\ \mathbf{n} \cdot (\nabla c)|_{\text{bdy}} &= 0. \end{aligned} \tag{1}$$

We track the positions of each of N particles $\{x_i, i = 1, \cdots, N\}$ at one msec intervals as they undergo Brownian motion. The local concentration in a neighborhood of size σ around x is given by the convolution

$$\hat{c}(x,t) = \int_V \sum_{i=1}^{N} \delta(x' - x_i) g(x - x', \sigma)\, dx' \tag{2}$$

where $g(\cdot, \sigma)$ is a normalized Gaussian distribution with mean 0 and variance σ^2. The motions of the individual particles cause $\hat{c}(x,t)$ to fluctuate about the mean concentration given by solving equations (1), causing the concentration at the receiver cell $\hat{c}(x_r, t)$ to be a noisy, low-pass filtered version of the original signal $s(t)$.

The receptor located at $x_r = [7.5\mu, 2.5\mu]$ registers the presence of ligand through binding and unbinding transitions, which form a Markov process with time-varying transition rates. Given an unbound receptor, the binding transition happens at a rate that depends on the ligand concentration around the receptor: $k_+ \hat{c}(x_r, t)$. The size of the neighborhood σ reflects the "reach" of the receptor, with binding most likely in a small range close to the location of the receptor. Once the receptor is bound to a ligand molecule, no more binding events occur until the receptor releases the ligand. The unbinding transition occurs with a fixed rate k_-.

For concreteness, we initially consider typical values of $D, \alpha, k_-, K_D, \sigma$ and s_max that are plausible for cyclic-AMP signaling between *Dictyostelium* amoebae: $D = 0.25\mu^2$/sec, $1/\text{sec} \leq \alpha \leq 10/\text{sec}$, $k_- = 1/\text{sec}$, $30\text{nMol} \leq K_d \leq 300\text{nMol}$, $\sigma = 0.1\mu$, $s_{\max} = 2000/\text{sec}$ [Ueda2001].

For a constant, uniform distribution of ligand particles, $c(x,t) = c_0 = N/V$, the fraction of time f the receptor is bound approaches

$$f_\infty = \frac{k_+ c_0}{k_+ c_0 + k_-} \tag{3}$$

for arbitrarily long observation times. For observation times of finite length T the binding fraction f will deviate from f_∞ due to the stochastic nature of the Markov transitions. The concentration c_0 at which $f_\infty = 0.5$ corresponds to the equilibrium constant $K_d = \frac{k_-}{k_+}$.

The output of the receiver $r(t)$ is the state of the Markov process at each point in time: 0 when unbound and 1 when bound. For a time varying input signal $s(t)$ we thus have noisy transformations of the original signal in two stages:

$$s(t) \longrightarrow \hat{c}(x_r, t) \longrightarrow r(t).$$

The resulting input-output channel is neither Gaussian nor linear, posing novel challenges for the analysis of its information capacity.

3 Estimating the Shannon Channel Capacity

Let X represent a collection of input signals $r(t)$ occurring with some probability measure P_X. A given input signal leads to a family of output signals $s(t)$; for each input collection X there

is an output collection Y with conditional probabilities $P_{Y|X}$. For a given choice of inputs the mutual information is

$$\begin{aligned} I(X,Y) &= H(X) - H(X|Y) \quad (4) \\ &= H(Y) - H(Y|X) \quad (5) \end{aligned}$$

The channel capacity C is the maximum over all choices of input ensemble (X, P_X) of the mutual information $I(X,Y)$ [CT1991].

By choosing a particular set of input stimuli X we can test the simulated channel and estimate the mutual information of X and Y, thereby obtaining a lower bound on C. For example, we may draw uniformly from a discrete set of constant inputs $\{s_1, \cdots, s_m\}$ and evaluate how well the output $r(t)$ allows us to estimate the input values given a finite observation time T. Alternatively, we may draw $s(t)$ from an ensemble of sinewaves of different frequencies, or from band-pass–filtered white noise. For any given ensemble the mutual information $I_0(X,Y)$ for a single observation increases to an upper limit with increasing observation time T. The information *rate* $I_0(X,Y)/T$ has a maximum for an optimal value of T.

For a given set of stimuli X we can determine how $I(X,Y)$ varies with the parameters D (diffusion constant), α (decay rate of ligand molecules), reaction rates k_+ and k_-. The capacity grows without bound as the maximum power or $s_{\max}$ is increased, and also as the distance between R and S decreases. I increases monotonically but saturates as D increases and as the reaction rates k_+, k_- increase. It has a maximum for intermediate values of α.

4 Discussion

Genotypic variation can change the parameters k_+ and k_- as well as D, α within limits and may act to maximize the potential transmission of information through chemical signal-transduction networks. It will be interesting to investigate whether optimal values observed here correspond to actual values in biological signal-transduction systems.

5 References

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