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Information transfer through a signaling module with feedback: A perturbative approach

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ABSTRACT

Signal transduction in biological cells is effected by signaling pathways that typically include multiple feedback loops. Here we analyze information transfer through a prototypical signaling module with biochemical feedback. The module switches stochastically between an inactive and active state; the input to the module governs the activation rate while the output (i.e., the product concentration) perturbs the inactivation rate. Using a novel perturbative approach, we compute the rate with which information about the input is gained from observation of the output. We obtain an explicit analytical result valid to first order in feedback strength and to second order in the strength of input. The total information gained during an extended time interval is found to depend on the feedback strength only through the total number of activation/inactivation events.

1. Introduction

Accurate sensing of the environment is crucial for the survival of biological organisms. Bacteria, as well as animal chemoreceptor cells, can sense certain chemicals in their chemical environment with high precision, in some cases near the single-molecule detection limit (Berg and Purcell, 1977; Mao et al., 2003). The effect of the extracellular stimulus on the cell is mediated by the signal transduction pathway – a complex biochemical reaction network. The pathway is based on a sequence of transduction steps, with each subsequent step being effected by the chemical product of the previous step. The first step typically consists in the activation of a receptor protein in the cell membrane by the external stimulus, which results in an ion influx or in the production of a second messenger chemical. This leads to the activation of subsequent steps within the cell. Through molecular feedback loops, the product of a given transduction step may regulate its own production, or influence earlier (upstream) steps of the pathway. As signal transduction pathways are inherently noisy (Ladbury and Arold, 2012), faithful transmission of information through the pathways requires amplification and/or adaptation. This is often accomplished through positive (amplification) and negative (adaptation) feedback built into the reaction network.

Recent years have brought the use of information-based measures to characterize the reliability of biological signal transduction (Tostevin and ten Wolde, 2009; Cheong et al., 2011; Tkačik et al., 2008; Tkačik et al., 2012; de Ronde et al., 2010). Such measures explicitly evaluate the amount of information about the stimulus that it is trasmitted through the signaling pathway. Mutual information between the stimulus and the pathway output (i.e., the product of the final transduction step) was evaluated in, e.g. (Cheong et al., 2011; Tkačik et al., 2008), to assess the precision with which stationary stimuli of different strengths can be distinguished. In many signaling scenarios, however, it is important to faithfully transduce the temporal variations of the input stimulus, which encode biologically important information. Some recent studies have evaluated the transduction reliability for time-varying signals by computing the information transmission rate. In (de Ronde et al., 2010), prototypical signaling pathways with feedback were represented by coupled Langevin equations with additive Gaussian noise, and the frequency-dependent gain-to-noise ratio was computed. In the Gaussian noise approximation, this gain (together with the input power spectrum) determines the mutual information between the time courses of the stimulus and of the output. Some of the stochasticity within a signaling pathway, however, arises directly from the inherent stochastic dynamics of the transduction components, and cannot always betreated as additive

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noise; in such a case, the information calculation cannot be reduced to the evaluation of the gain-to-noise ratio.

In this work, we carry out a perurbative computation of information transfer through a simple prototypical signaling module with biochemical feedback. The module switches stochastically between two states, with switching rates governed by the stimulus (i.e., input) and by the product (i.e., output). No additive external noise is assumed. Such autoregulated stochastic modules arise within various signal transduction and gene regulation pathways (see Section 2). In a previous investigation (Gopalakrishan et al., 2007) negative feedback, in this module, was shown to decrease the signal-to-noise ratio (SNR) at the output, but at the same time to increase the spectral range of the response – thus yielding no obvious expectation on how feedback overall affects information transmission through the module. Here, we address this question by directly quantifying the information that is gained about the external stimulus from following the module output. In order to achieve this we introduce a novel perturbative approach on a conveniently defined relative entropy for stochastic point processes (Goychuk and Hanggi, 2000). This information gain is well-defined for a single stimulus trajectory (i.e., it requires no averaging over stimuli as in mutual-information-based measures) (Goychuk and Hanggi, 2000). We obtain an explicit analytical result valid to first order in feedback strength and to second order in the strength of input. Surprisingly, the total information gained during a long time interval is found to be proportional to the total number of state-switching events, with no further dependence on the feedback strength or on the spectral distribution of the input. We compare this result to previous investigations of information transfer through some related information channels.

2. A two-state signaling module with feedback

We consider a simple signaling module based on a single protein that switches between two conformational states. These may correspond to the open and closed state of an ion channel, or to the active/inactive states of an enzyme within a larger signaling network. We introduce the module by referring to the example of a calcium ion channel that is autoregulated by calcium-mediated feedback. When the channel is open, calcium ions flow from the extracellular space into the cell. This leads to a fast increase of the free calcium concentration in the immediate vicinity of the channel (the increase is localized as calcium buffering in the cytoplasm leads to the formation of a calcium microdomain (Parekh, 2008)). For certain types of calcium channels (such as the voltage-activated L-type channels Peterson et al., 1999 or the cyclic-nucleotide-gated (CNG) channels Bradley et al., 2005; Reidl et al., 2006), the cytoplasmic calcium can inactivate the channel when it binds to the channel/calmodulin complex. This implements an autoregulatory feedback loop that shortens the response to the external gating signal, and thus helps to faithfully transduce fast signal variations. Similar autoregulatory loops, in which the product of a particular step in the pathway downregulates its own production, arise in numerous signal transduction and gene regulation networks (Rosenfeld et al., 2002; Matthews et al., 2003).

The stochastic switching of the channel state is governed by the opening rate (assumed to depend on the extracellular stimulus gating the channel) and the closing rate. The negative autoregulation may be effected through a calcium-dependent increase of the closing rate or decrease of the opening rate. For the CNG channels that motivated us in this study, electrophysiological data indicates that the binding of calcium to the channel/calmodulin complex increases the closing rate. We consequently make only the closing rate depend on the calcium concentration.

The signaling module is shown schematically in Fig. 1. When the channel is in the open state, ions flow into the microdomain at a fixed rate J. Once inside the microdomain, the ions are cleared out through ion pumps or exchangers in the membrane, as well as by diffusion within the cytoplasm; we assume a first-order clearance kinetics with rate constant λ (see Fig. 1). The dynamics of the concentration c of ions in the cell compartment is given by the following equation:

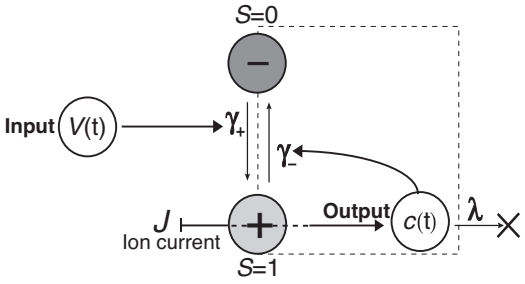

Fig. 1. The ion-channel (gray) opens with rate γ_+ governed by the input $V(t)$ and closes with rate γ_- that depends on the ion concentration $c(t)$ (which is considered to be the output). Ions inside the micro-domain (dashed box) are cleared out at rate λ.

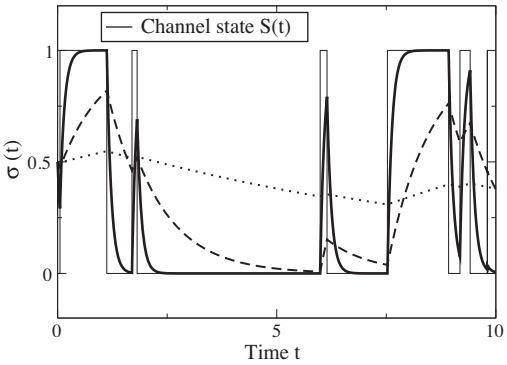

Fig. 2. Examples of time courses for the dimensionless calcium concentration $\sigma(t)$ following from Eq. (2) for a given sequence $\vec{t}_n$ of channel state switches. Thick, dashed and dotted lines correspond to $\lambda = 10.0$, 1.0 and 0.1 respectively.

$$\frac{dc(t)}{dt} = \frac{J}{\Delta} S(t) - \lambda c(t), \tag{1}$$

where J is the flow of ions entering the cell through the open channel, Δ the volume of the cell micro-domain and the two-valued function $S(t) = 1$ or 0 indicates the open or closed state of the channel.

Adopting the dimensionless variable $\sigma(t) = c(t)\lambda\Delta/J$, Eq. (1) becomes

$$\frac{d\sigma}{dt} = \lambda(S(t) - \sigma(t)) \tag{2}$$

and $\sigma(t)$ is restricted to the range [0, 1]. Examples of trajectories of $\sigma(t)$ are shown in Fig. 2. The switching events of the channel between time 0 and t:

$$0 < t_1 < t_2 < \cdots < t_n < t \tag{3}$$

are the realization of a stochastic point process driving the dynamics of $\sigma(t)$. In fact, fixed a sequence $\vec{t}_n = (0, t_1, \cdots, t_n)$ of such events and the initial condition $S(0) = i$ and $\sigma(0) = \sigma_0$, an exact solution for $\sigma(t)$ follows directly from Eq. (2):

$$\begin{aligned} \sigma(t|\vec{t}_{2n}) &= i + \left[\sigma_0 - i + (-1)^i \sum_{j=0}^{n-1} \left(e^{\lambda t_{2j}} - e^{\lambda t_{2j+1}}\right)\right] e^{-\lambda t} \\ \sigma(t|\vec{t}_{2n+1}) &= 1 - i + \left[\sigma(t = t_{2n+1}|\vec{t}_{2n}) - 1 + i\right] e^{-\lambda(t - t_{2n+1})}. \end{aligned} \tag{4}$$

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