Adaptation by State-dependent Inactivation

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Short Abstract — **Many membrane channels and receptors exhibit adaptive, or desensitized, response to a strong sustained input stimulus. One important mechanism that underlies this response is the slow, activity-dependent removal of responding molecules to a pool which is unavailable to respond immediately to the input. Here we study theoretically a class of models which describes this general mechanism and allows to distinguish its universal from system-specific features, giving rise to a variety of system-specific forms of adaptive response: precise or input-dependent, exponential or power-law, as special cases of the same model.**

Keywords — **Adaptation, feedback, biochemical networks.**

I. Introduction

MANY sensing molecules, such as membrane channels and receptors, have mechanisms of activity attenuation following exposure to strong persistent stimulation. Such responses are termed "adaptation" or "desensitization" and have been studied extensively in the context of sensory and neural systems [1] as well as cellular signaling systems [2].

A widely encountered mechanism underlying adaptive response is the slow activity-dependent modulation in the total number of molecules available to respond [3]. This phenomenon characterizes a large class of biological systems and can be implemented physically in many ways. While clearly sharing a common principle, these various systems differ in kinetics and time-scales of response.

Here we formulate and analyze a general mathematical model for activity-dependent inactivation, which generalizes some previously studied models [4,5]. While admittedly oversimplified, it captures faithfully the essence of the phenomenon, allows a solution in the appropriate approximation and a precise mapping of the dynamic behavior onto a control circuit diagram. This enables us to identify the universal aspects of seemingly different biological systems and dynamic behaviors.

II. Results

We consider an ensemble of non-interacting molecules that can switch between active or inactive states with input-dependent transition rate. Adaptive response arises when the molecules can also become temporarily unavailable to respond to the input by a process which is sensitive to the input-dependent state occupancy (active/inactive). This process is slow, approximately input-independent but strongly state-dependent. We analyze the extreme case in which transitions occur exclusively from the active state:

$$\underbrace{\text{inactive} \underset{\beta(u)}{\overset{\alpha(u)}{\rightleftarrows}} \text{active}}_{\text{available}} \underset{\Delta}{\overset{\gamma}{\rightleftarrows}} \text{unavailable}$$

Where Δ symbolizes a general recovery kinetics. We show that, regardless of the form of Δ, this class of systems can be mapped onto a control circuit implementing multiplicative integral control, with a slow degree of freedom that obeys a bilinear control equation. The recovery term Δ determines the kernel of feedback and thus the type of adaptation in the system. We analyze 3 cases of interest: first order kinetics, leading to exponential input-dependent adaptation; zero order kinetics, leading to exact adaptation; and multiple-time-scale kinetics described by a nonexponential residence time distribution in the unavailable state, leading to power-law adaptation. This unified description draws analogies with seemingly different biological systems, highlights their quantitative common features and allows a clear identification of the ingredients underlying each type of adaptive response.

III. Conclusions

The level of availability of responding molecules is a slow degree of freedom which averages over past activity, obeys a bilinear control equation, and implements a multiplicative feedback circuit regardless of the details of its kinetics. On the other hand, the recovery kinetics determines the functional form of the averaging kernel within the feedback branch and is a crucial ingredient in determining the adaptive dynamics and timescales. We find as special cases of the same general model exponential and power-law, exact and input-dependent adaptive responses.

References

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