Adaptive Response and Background Signal Compensation

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Short Abstract — **Many signaling proteins exhibit adaptive response, or desensitization, following exposure to a sustained input stimulus. Adaptive response is thought to be related to crucial cellular functions such as homeostasis and enlargement of dynamic range by background compensation. Here we study the quantitative relation between adaptive response and background compensation theoretically. We show that any particular type of adaptive response is neither sufficient nor necessary for effective background compensation. We analyze a mechanism relying on multiple modifications originally proposed for bacterial chemotaxis. Without the constraint for a particular type of adaptive response, this mechanism is general and can be implemented by different biological processes analogous to methylation and phosphorylation.**

Keywords **— Adaptive response, biochemical feedback, dynamic range, signal transduction.**

I. Background

Organisms in general and cells in particular face the continuous challenge of sensing their environment and responding accordingly. The related sensing and signaling proteins often exhibit adaptive response, or desensitization, following a strong persistent stimulus. Its qualitative hallmark is observed when exposing the system to a step input signal: an abrupt change in response is followed by a slow relaxation on a longer timescale.

Adaptive responses have been described and studied for many years in different areas of biology. Recently they have been the topic of much theoretical work [1-4]. It is often stated that adaptive response is functionally important for maintaining sensitivity over a broad dynamic range, the intuition being that homeostasis of an output set-point enables re-sensitization to further incoming signals. In this work we examined the relation between adaptive response and enlargement of dynamic range, or background signal compensation, in the framework of mathematical models.

II. Main Results

We quantified the response to transient signals on top of constant backgrounds for various models exhibiting different forms of adaptive response. First, we examined the response of a family of 3-state models which implement integral feedback control [5]. We found that regardless of the form of adaptive response, the system does not exhibit an effective enlargement of dynamic range by background compensation. This is because the 3-state models, relying on activity-dependent inactivation of two-state proteins, all implement a multiplicative feedback which is unable to expand the dynamic range for effective response.

Next we analyzed a more complex model with a cascade of modifications for two-state proteins [8]. We showed that the system exhibits an enlargement of dynamic range regardless of the form of adaptive response and without sensitivity to kinetic details. This effect is caused by a redistribution of proteins between states with graded responsiveness.

III. Conclusions

Our results show that any particular form of adaptive response is neither sufficient nor necessary for background signal compensation. In particular, exact adaptation does not imply this property, whereas it can be achieved by systems displaying non-exact and even non-exponential adaptation.

We showed that a generalized version of the Asakura-Honda model, originally proposed to describe multiple methylations in bacterial chemoreceptors, exhibits enlargement of dynamic range regardless of kinetic details. Relaxing the requirement for exact adaptation in this model makes it much more general, and therefore possibly relevant also for other biological systems such as photoreceptors. These results suggest that the role of multiple modifications, such as methylation and phosphorylation, can affect directly the signal-processing function of proteins.

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