Design Principles of Perfect Adaptation in Biochemical networks

Wenzhe Ma[1,2,3], Ala Trusina[2,3], Hana El-Samad[2,4], Wendell Lim[2,5], and Chao Tang[1,2,3,4*]

1 Centre for Theoretical Biology, Peking University, Beijing, China, **2** California Institute for Quantitative Biosciences, University of California, San Francisco, California, United States of America, **3** Department of Biopharmaceutical Sciences, University of California, San Francisco, California, United States of America, **4** Department of Biochemistry and Biophysics, University of California, San Francisco, California, United States of America, **5** Department of Cellular and Molecular Pharmacology, University of California, San Francisco, California, United States of America

Cells are able to sense and respond to a variety of inter- and intra-cellular signals. Often the cell's response returns to the pre-stimulus level even when the stimulus persists, a phenomenon called perfect adaptation. Perfect adaptation is widely utilized in biological systems to increase the dynamical range of sensing, to detect gradients, or to maintain a homeostasis. Here we investigate the design principles underlying the perfect adaptation for given sets of biochemical interactions (enzymatic or transcriptional). By enumerating all possible 3-node networks, we ask which of the network topologies are robust to perform the function of the perfect adaptation—that is the network can respond to changes in the input and can adapt to a persistent input with a range of the network parameters. We found that the robust topologies can be classified into a few classes, the structures of which depend on the biochemical interactions used. Remarkably, the chemotaxis network in *E. coli*—a prototypical example of the perfect adaptation—can be mapped to the simplest

* To whom correspondence should be addressed. E-mail: chao.tang@ucsf.edu

robust topology of enzymatic regulation. Analysis of the distribution of the functional parameters reveals mechanisms for perfect adaptation, origins of robustness, and potential trade-off in functional performance between achieving high sensitivity and minimizing the adaptation error. Our results suggest that there is a function-topology relationship which can be exploited in understanding natural systems as well as in synthesizing artificial. The approach may also provide a framework for categorizing other functional modules.