Author's Accepted Manuscript

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Zhe F. Tang, David R. McMillen

PII: S0022-5193(16)30170-9
DOI: http://dx.doi.org/10.1016/j.jtbi.2016.06.036
Reference: YJTBI8724

To appear in: *Journal of Theoretical Biology*

Received date: 10 December 2015
Revised date: 22 June 2016
Accepted date: 28 June 2016

Cite this article as: Zhe F. Tang and David R. McMillen, Design principles fo the analysis and construction of robustly homeostatic biological network *Journal of Theoretical Biology,* http://dx.doi.org/10.1016/j.jtbi.2016.06.036

Design principles for the analysis and construction of robustly homeostatic biological networks

Zhe F. Tang and David R. McMillen

Dept of Chemical and Physical Sciences and Impact Centre
University of Toronto Mississauga
3359 Mississauga Rd, Mississauga Ontario L5L 1C6
Canada

Abstract

Homeostatic biological systems resist external disturbances, allowing cells and organisms to maintain a constant internal state despite perturbations from their surroundings. Many biological regulatory networks are known to act homeostatically, with examples including thermal adaptation, osmoregulation, and chemotaxis. Understanding the network topologies (sets of regulatory interactions) and biological parameter regimes that can yield homeostasis in a biological system is of interest both for the study of natural biological system, and in the context of designing new biological control schemes for use in synthetic biology. Here, we examine the mathematical properties of a function that maps a biological system's inputs to its outputs, we have formulated a novel criterion (the "cofactor condition") that compactly describes the conditions for homeostasis. We further analyze the problem of robust homeostasis, wherein the system is required to maintain homeostatic behavior when its parameter values are slightly altered. We use this condition to examine previously-reported examples of homeostasis, showing that it is a useful way to unify a number of seemingly-different analyses into a single framework. Based on the observation that all previous robustly homeostatic examples fall into one of three classes, we propose a "strong cofactor condition" and use it to provide an algorithm for designing new robustly homeostatic biological networks, giving both their topologies and constraints on their parameter values. Applying the design algorithm to a three-node biological network, we construct several robustly homeostatic genetic networks, uncovering network topologies not previously identified as candidates for exhibiting homeostasis.

Keywords: biological regulation; perfect adaptation; regulatory networks; synthetic biology; integral control

1. Introduction

Homeostasis is the biological property of maintaining a fixed state despite external perturbations, generally achieved by coupling a biological sensing mechanism to a feedback loop, so when perturbations attempt to change the state of the system, the feedback mechanism acts to resist these changes and restore the system to its default state (Langley, 1973; Drengstig et al., 2012a). Homeostatic

Email address: david.mcmillen@utoronto.ca (Zhe F. Tang and David R. McMillen)