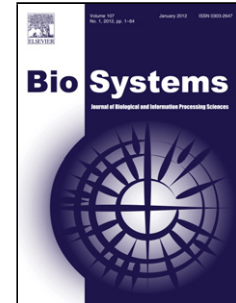


Accepted Manuscript

Title: Analysis of Network Motifs in Cellular Regulation:
Structural Similarities, Input-Output Relations and Signal
Integration

Author: Ronny Straube



PII: S0303-2647(17)30370-2
DOI: <https://doi.org/doi:10.1016/j.biosystems.2017.10.012>
Reference: BIO 3799

To appear in: *BioSystems*

Received date: 21-9-2017
Revised date: 22-10-2017
Accepted date: 23-10-2017

Please cite this article as: Ronny Straube, Analysis of Network Motifs in Cellular Regulation: Structural Similarities, Input-Output Relations and Signal Integration, *BioSystems* (2017), <https://doi.org/10.1016/j.biosystems.2017.10.012>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Analysis of Network Motifs in Cellular Regulation: Structural Similarities, Input-Output Relations and Signal Integration

Ronny Straube

Max Planck Institute for Dynamics of Complex Technical Systems Magdeburg, Sandtorstr. 1, D-39106 Magdeburg

Abstract

Much of the complexity of regulatory networks derives from the necessity to integrate multiple signals and to avoid malfunction due to cross-talk or harmful perturbations. Hence, one may expect that the input-output behavior of larger networks is not necessarily more complex than that of smaller network motifs which suggests that both can, under certain conditions, be described by similar equations. In this review, we illustrate this approach by discussing the similarities that exist in the steady state descriptions of a simple bimolecular reaction, covalent modification cycles and bacterial two-component systems. Interestingly, in all three systems fundamental input-output characteristics such as thresholds, ultrasensitivity or concentration robustness are described by structurally similar equations. Depending on the system the meaning of the parameters can differ ranging from protein concentrations and affinity constants to complex parameter combinations which allows for a quantitative understanding of signal integration in these systems. We argue that this approach may also be extended to larger regulatory networks.

Keywords: ultrasensitivity, substrate competition, cooperativity, covalent modification cycles, two-component systems

1. Introduction

Biological networks are complex – not just by the number of their components, but also by the number and specificity of their interactions. Despite increasing knowledge of the molecular keyplayers involved in specific regulatory systems and signaling pathways simulating larger networks does not necessarily lead to deeper insights. It has thus become a useful strategy to analyze smaller recurring network structures called network motifs. Since the seminal work of Milo et al. (Milo et al., 2002), which originally focused on gene regulatory networks, the systematic analysis of network motifs has led to an increasing list of circuits that may generate specific input-output behavior such as ultrasensitivity and thresholds (Goldbeter and Koshland Jr., 1981; Gunawardena, 2005; Gomez-Urbe et al., 2007), fold-change detection (Geontoro et al., 2009; Adler et al., 2014; Olsman and Geontoro, 2016), concentration robustness (Shinar et al., 2007, 2009; Shinar and Feinberg, 2010) or multistability (Ferrell, Jr., 2002; Markevich et al., 2004; Tiwari et al., 2011; Straube and Conradi, 2013). Using methods from control theory network motifs were also analyzed from an engineering perspective (Sauro and Kholodenko, 2004).

Despite this increasing knowledge it has remained challenging to predict the behavior of larger networks based on the known behavior of its constituent parts (Rosenfeld et al., 2007). Exceptions are multistationarity and certain forms of robustness which can be detected based on algebraic properties of a network (Craciun et al., 2006; Conradi et al., 2007; Shinar and Feinberg, 2010; Dexter et al., 2015; Sontag, 2017), i.e. without detailed knowledge of reaction rates and parameters. However, while these methods can be used to decide whether a given sys-

tem has a certain property they often do not say much about the parameter range or the biological conditions under which a certain behavior occurs. Obtaining this type of information typically requires more detailed analysis of the governing equations which will be the strategy advocated in this review.

To this end, we shall focus on mass-action networks with at most bimolecular interactions. Starting with the most simple of such systems, the receptor-ligand binding motif, we will stepwise extend the analysis to more complex network motifs. First, we show how thresholds and ultrasensitivity can arise through cooperativity in ligand binding and substrate competition. Subsequently, we consider covalent modification cycles which represent the elementary building blocks for many eukaryotic signaling networks such as protein kinase cascades or multisite phosphorylation systems, which are reviewed elsewhere (Heinrich et al., 2002; Salazar and Höfer, 2009; Ferrell Jr. and Ha, 2014). Finally, we discuss regulatory properties of two-component systems which share some similarity with covalent modification cycles, but occur mostly in bacteria (Stock et al., 2000). Again, we focus on the most simple regulatory structures leaving out more complicated architectures such as phosphorelay systems (Tiwari et al., 2011).

A major goal of this review is to highlight structural similarities that exist between the steady state equations characterizing the input-output behavior of different network motifs. Despite the fact that the transient dynamics will, in general, be different for different systems it turns out that in certain limiting regimes the steady state behavior of the network motifs considered in this review can be characterized by one of the following three

Download English Version:

<https://daneshyari.com/en/article/8406688>

Download Persian Version:

<https://daneshyari.com/article/8406688>

[Daneshyari.com](https://daneshyari.com)