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Models of Biological Regulation

by

Moritz Emanuel Beber

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Approved Dissertation Committee:

Prof. Dr. Marc-Thorsten Hütt (chair),
Jacobs University Bremen

Prof. Dr. Georgi Muskhelishvili,
Jacobs University Bremen

Prof. Dr.-Ing. Katja Windt,
Jacobs University Bremen

Prof. Dr. Stefan Bornholdt (external),
Universität Bremen

Date of Defense: April 17, 2015

Department of Life Sciences & Chemistry

Statutory Declaration

I, Moritz Emanuel Beber, hereby declare, under penalty of perjury, that I am aware of the consequences of a deliberately or negligently wrongly submitted affidavit, in particular the punitive provisions of § 156 and § 161 of the Criminal Code (up to 1 year imprisonment or a fine at delivering a negligent or 3 years or a fine at a knowingly false affidavit).

Furthermore I declare that I have written this PhD thesis independently, unless where clearly stated otherwise. I have used only the sources, the data and the support that I have clearly mentioned.

This PhD thesis has not been submitted for the conferral of a degree elsewhere.

Bremen, July 11, 2017

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Moritz Beber

Preface

The following people deserve my sincerest thanks, more so than I can express in words. There are others whom I do not mention here but also deserve my thanks, please know that you are appreciated nonetheless.

First and foremost, I thank my family for showing me, time and again, their unconditional love. Without you I simply would not be here! In particular, I thank my mother Katinka and father Thomas for being calm and analytical when I needed them to but otherwise placing their complete trust in me to go my own way.

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I also thank Prof. Dr. Dirk Helbing for inviting me to Zurich, Switzerland, and Goldrain. It was a marvelous experience. Last but not least, I thank Prof. Dr. Dieter Armbruster for extending an invitation to me to visit him in Phoenix, Arizona. I very much enjoyed our work, the discussions under palm trees in January and being part of a real US campus.

Abstract

In recent years, the structural analysis of networks representing a wide range of real world systems has become common place. Today, the real challenges lie in the functional analysis of those systems and ultimately the control of the dynamic processes that occur on the networks.

Here, the abstract network representation is used to draw analogies between production in cellular metabolism and in logistics companies. The goal is the transfer of beneficial topological, as well as regulatory principles from biology to logistics. Metabolism is thought to be robust against multiple types of perturbations since organisms have survived millions of years of selective evolution. Some of the challenges handled by metabolic systems are the transport, transformation and storage of compounds. All biochemical processes in a cell have to occur at physiological conditions, maintain energy levels and tolerate fluctuating environmental conditions. The organization and regulation of these processes is thus of great interest to the field of logistics where solutions to the dynamic control of complex systems are desperately needed.

However, the functional dynamics of cellular regulation are far from fully understood, hence structural properties and regulatory dynamics are investigated here. As a basis, the metabolism and transcriptional regulatory network (TRN) of *Escherichia coli*, a thoroughly studied experimental model organism, are compared with company networks gleaned from actual production data.

A number of results are established: (i) A direct relation between the unit components of the metabolic and logistics systems. This involves the biochemical reactions and manufacturing steps involved with the material flow on the networks, as well as a concept for the regulatory elements. The results are solidified by a simulation study of adaptive flow control. (ii) Potentially beneficial structural elements of metabolic networks are discussed and the composition of few-node subgraphs as one such indicator is explored in *E. coli*'s metabolic network. (iii) The structure of networks tasked with specific patterns of flow distribution and robust to particular types of local damages are investigated. A clear relation between shared sub-patterns and the occurrence of modular structures is observed. (iv) The large-scale organization of regulation in wild type *E. coli* and two mutants is confirmed to be dominated by the two counterbalancing aspects of digital (transcriptional) and analog (physico-chemical) control over the course of *E. coli*'s growth cycle. (v) A case is made for the recording of results as a function of the increasing amount of knowledge available about objects of study. Accumulation of facts and re-evaluation of existing knowledge can lead to serious drifts of results over time. It is crucial for the conception of future research to know which results stand the test of time.

Overall, there are many yet to explore research avenues that this work has opened up. Especially considerations of the dynamics of the studied systems promise profound insights and this work forms a solid basis to build upon.

Contents

List of Acronyms

ATP adenosine triphosphate
CDS coding sequence
ChIP chromatin immunoprecipitation
CTC control type confidence
DFG Deutsche Forschungsgemeinschaft
DNA deoxyribonucleic acid
ER Erdős-Rényi (random graph model)
FBA flux-balance analysis
FC functional connectivity
GO gene ontology
GPN gene proximity network
GRN gene-gene regulatory network
GU gensor unit
MOMA minimization of metabolic adjustment
NAP nucleoid associated protein
NCBI National Center for Biotechnology Information
ODE ordinary differential equation
ORF open reading frame
OriC origin of chromosomal replication
PDE partial differential equation
PhD Doctor of Philosophy (philosophiae doctor)
PMF probability mass function
PPIN protein-protein interaction network
PTM post-translational modification
RBN random Boolean network
RNA ribonucleic acid
SC structural connectivity
sRNA small ribonucleic acid
Ter terminus of chromosomal replication
TF transcription factor
TRN transcriptional regulatory network
TSP triad significance profile
TU transcription unit
US United States (of America)
wt wildtype

"The important thing is not to stop questioning. Curiosity has its own reason for existence. One cannot help but be in awe when he contemplates the mysteries of eternity, of life, of the marvelous structure of reality. It is enough if one tries merely to comprehend a little of this mystery each day. Never lose a holy curiosity. Try not to become a man of success but rather try to become a man of value. He is considered successful in our day who gets more out of life than he puts in. But a man of value will give more than he receives. [...] Don't stop to marvel."
— *Albert Einstein, Old Man's Advice to Youth: "Never Lose a Holy Curiosity"*

Although curiosity is a strong motivator, there are many tangible reasons that make biological regulation a hot topic[1]. Being able to understand how an organism regulates itself also implies the power to interfere with that regulation to one's own benefit. It is the promise of that power and its applications that has spurred the creation of such a large body of scientific literature and has facilitated the funding of the corresponding research. To mention a few of the actively researched applications: (i) Specific and effective medication to fend off bacterial and viral infections (Alifano et al., 2014). (ii) Treatment or correction of genetic diseases (Peng et al., 2015). (iii) Curbing of cancerous cells and eliciting a targeted immune response (Bachegowda and Barta, 2014). (iv) Genetic and metabolic engineering in order to increase biomass yields (Qin et al., 2012).

In a very broad sense, models are simply a representation of our understanding of our environment. They allow us to formulate our experience about the functioning of the world. Importantly, a model description can be exchanged and verifiable predictions can be postulated. The latter part is, of course, at the very core of the scientific method. Notably, each model also restricts the language in terms of which

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[1]There are more than 675,000 abstracts on PubMed that have been published since 1995 and fit a fuzzy search for biological regulation. The query used to find those abstracts was: `((transcriptional OR metabolic OR regulatory) AND network*) OR ((gene OR genetic OR transcriptional OR metabolic OR biological) AND regulation)`.

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we can describe reality. This restriction means that most models are constrained to describing only a small subset of reality. It is important to acknowledge a model's constraints and specify under what circumstances it applies.

Current models of biological regulation range in scope from describing systems as small as the dynamics of a single biochemical reaction to whole ecosystems. There are some crucial intermediate levels: (i) The dynamics of transcriptional regulation of a handful of genes (Kaplan et al., 2008; Shen-Orr et al., 2002). (ii) The dynamics of pathways. Pathways are collections of a few to dozens of molecular components thought to act as a unit to produce a fixed set of outcomes in a metabolic (Antoniewicz, 2013; Quo et al., 2011), gene regulatory (Moriya et al., 2011) or signal transduction (Ray et al., 2013; Schoeberl et al., 2002) context. (iii) The consideration of a complete regulatory subsystem of a single cell, for example, the TRN (Huerta et al., 1998). (iv) The hormonal and feedback regulation of the metabolism of a whole multicellular organism (Vinciguerra et al., 2014).

As a general rule, the less components are part of a model, the greater the feasible level of detail. When talking about the dynamics of a system, we usually consider the model as a system of coupled ordinary (ODEs) or partial differential equations (PDEs). Yet, despite an exponential growth of computational power, the size of such systems is often limited by the availability of experimental data required for the fitting of parameters[2]. An alternative approach has thus been the recording of interactions between cellular molecules and the accumulation of those interactions to networks. The topology of such a network represents a static map of all possible (experimentally measured) interactions. A network is an abstract representation of the relationships (links) between components (nodes) of a system and has been used to study systems as large as the Internet which has billions of nodes[3]. This work deals with networks of less than 10,000 nodes.

1.1   Network Topology

Networks have become a successful approach to modeling large complex systems in many different disciplines, for example, spin systems (Aleksiejuk et al., 2002), traffic (Lammer and Helbing, 2008), production (Wiendahl and Lutz, 2002), disease propagation (Lindquist et al., 2011), transcriptional regulation (Shen-Orr et al., 2002), metabolism (Jeong et al., 2000), financial transactions (Schweitzer et al., 2009) or social interactions (Ellison et al., 2007). It is the power of abstraction, of reducing a system to simple nodes and links, that has led to the success of network representations. The same graph theoretical methods are suddenly available to the investigation of systems that at first glance appear to be radically different.

Despite all the success, it is often difficult to establish a link between the topology of a system and its function or dynamic behavior. It is intuitively obvious to most scientists that the architecture of a system of interest must contain an imprint of its function. Otherwise interactions would occur between different components of the system leading to another topology. It is challenging, however, to determine

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[2]The Human Brain Project (https://www.humanbrainproject.eu/) is a notable exception to this rule.

[3]http://googleblog.blogspot.de/2008/07/we-knew-web-was-big.html

exactly what makes a certain architecture particular and how that peculiarity is linked to its function. Null models allow a statistical assurance whether a topology is different from randomness but tying a certain topological aspect to the function of the system often remains speculative at best. Devising appropriate random null models requires a lot of insight into the system at hand and it is a problem that will reappear in chapters 2, 4, 5, 6 and 7.

This work is mainly concerned with four types of networks: (i) The intrinsically bipartite, metabolic network. It consists of compound and reaction nodes. A directed link is then drawn from a compound node to a reaction node that consumes it. Alternatively, a link is drawn from a reaction to a compound that is produced by that reaction. A larger structure exists since compounds are shared between reactions. The topology is thoroughly discussed in chapter 4. (ii) Conceptually similar to the metabolic network, the production logistics network consists of processing nodes that produce parts. The network is fully introduced in chapters 2 and 3 which also elaborate on the parallels between the two systems. (iii) The TRN is the most important network when talking about biological regulation. It consists of gene nodes whose expression can be enhanced or inhibited by the products of (other) genes. Those products are proteins or more specifically transcription factors (TFs). This type of network is heavily used in chapters 6 and 7. (iv) A completely different type of network is the undirected gene proximity network (GPN). Unlike the others, links encode spatial proximity of genes on a chromosome. It can thus serve as an indicator of expression patterns that are similar in certain neighborhoods of genes. The GPN is mostly employed in chapter 6 but also appears in chapter 7.

1.2 Network Function

Since understanding a system and characterizing its function are often the main goals of an investigation, how can the aforementioned challenges be overcome? Full functional dynamics would require systems of ordinary differential equations (ODEs) or PDEs. Just what we wanted to avoid in the first place. Two approaches are followed in this work: (i) Devising a simplified model of the real dynamics and simulating results on top of a given topology. In chapter 2, an extremely simple stochastic model of traffic is applied to different architectures and an adaptive control method regulates the traffic flow. Flow distribution through a network with local perturbations is the theme of chapter 5. The networks undergo a simulated evolution in order to achieve a prescribed output pattern and increase their robustness towards certain types of damages. The study in chapter 6, partly makes use of a random Boolean network model where ON/OFF states are propagated via activating or inhibitory links. (ii) Mapping of experimental or other data reflecting reality onto a network representation. The distribution of that data is then evaluated in the context of the architecture. This is done for metabolic fluxes in chapter 4, time-resolved gene expression data in chapter 6 and differentially expressed genes in chapter 7.

1.3 Reserach Goals

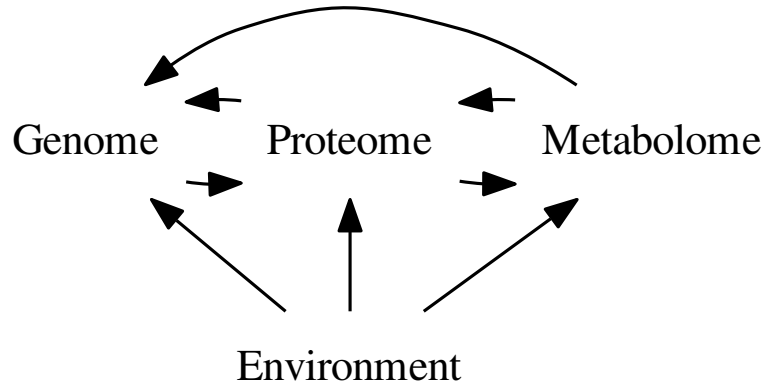There are two overarching goals that have driven this work:

FIGURE 1.1: Coupling between organizational components of the holistic unit. Adapted from (Sobetzko, 2012).

1. Identify principles of robustness found in metabolic production and transfer them to the design of man-made manufacturing systems.

2. Understand the functioning of the organizational unit, i.e., the interaction of the various components of system-scale cellular regulation.

The first goal spells out a need in the discipline of logistics. Logistics is struggling with the increased complexity of production, transport, and storage systems. Problems arise with the increase in their size and the number of complicated interactions between their components. These problems are further exacerbated due to global production processes, outsourcing of suppliers, and more product variants as a consequence of an increased demand for individualized products. Shorter development cycles and time-to-market lead to larger fluctuations in contract volumes. The changing processing steps for product variants combined with a goal for saving on storage costs require ever more flexible production. These issues are discussed in much more detail in chapters 2 and 3.

Over the course of millions of years, living cells have evolved to integrate environmental signals in their own regulation and ensure their survival despite fluctuating nutrient levels. Comprehending the mechanics and interconnectedness of all components and levels of organization of cellular biology as a holistic unit is the declared second goal. The idea of a holistic unit was introduced over a number of publications (Blot et al., 2006; Geertz et al., 2011; Muskhelishvili and Travers, 2013; Muskhelishvili et al., 2010), the concept is shown in figure 1.1 and is investigated most obviously in chapter 6.

Note

The opening chapter is intentionally minimal in terms of the data, models and methods presented since each article in the following chapters contains its own introduction explaining those in much more detail. It is rather a frame that specifies where each chapter fits in the overall work.

Even though I am second author on (Becker et al., 2011), I choose to include it here because the research work — in particular the network analyses and simulation studies — that forms the basis of the article was jointly performed by Till Becker and myself during a two month stay with Prof. Dr. Dirk Helbing at the ETH in Zurich. The descriptions of the metabolic system and meditations on regulation are also my authorship. The article contains a thorough description of our considerations and the necessary abstractions that allow for a uniform discussion of metabolic and logistics systems. It is therefore necessary reading for understanding this important aspect of my work towards a PhD.

This is an article published by Becker, Beber, Windt, Hütt, and Helbing in *Journal of Statistical Mechanics: Theory and Experiment*, available online at `http://stacks.iop.org/1742-5468/2011/i=05/a=P05004`.

While chapter 2 introduced the terminology and concepts that make metabolic and logistics systems comparable, (Beber and Hütt, 2012) reviews some of the important results related to the architecture of the metabolic network. It describes existing findings on robustness and discusses the applicability of the flux-balance analysis (FBA) modeling framework in-depth.

This is an article published by Beber and Hütt in *Logistics Research*, available online at `http://dx.doi.org/10.1007/s12159-012-0090-0`.

In (Beber et al., 2012), we explored the difficulties that arise in a few-node subgraph analysis of metabolic networks. We proposed solutions to overcome those issues and evaluated the distribution of metabolic fluxes across the identified few-node subgraphs.

This is an article published by Beber, Fretter, Jain, Sonnenschein, Müller-Hannemann, and Hütt in *Journal of The Royal Society Interface*, available online at http://rsif.royalsocietypublishing.org/content/9/77/3426.

A simple model of flow distribution was investigated in (Beber et al., 2013). The results on how various requirements of that flow distribution affect the network topology should be general and thus can be investigated in metabolic and production logistics networks.

This is an article published by Beber, Armbruster, and Hütt in *The European Physical Journal B*, available online at http://dx.doi.org/10.1140/epjb/e2013-40672-3.

Time-resolved transcriptomes that represent snapshots of the growth cycle of *Escherichia coli* and two mutants were analyzed in (Beber et al., 2016b). There, we investigated the balance between the digital and analog control components of bacterial regulation at specific points in time.

This is an article published by Beber, Sobetzko, Muskhelishvili, and Hütt in *EPJ Nonlinear Biomedical Physics*, available online at http://dx.doi.org/10.1140/epjnbp/s40366-016-0035-7.

In (Beber et al., 2016a), we highlighted an important aspect of bioinformatics and any other scientific work: The accumulation of knowledge may significantly change the way we model systems and subsequently cause a drift of results in time. Predicting the future of such a development is impracticable but monitoring results and pinpointing the effect of changes to the system on results will lead to a more profound understanding, improve credibility and can generally be considered good scientific practice.

This is an article published by Beber, Muskhelishvili, and Hütt in *Database*, available online at `http://dx.doi.org/10.1093/database/baw003`.

Conclusion and Outlook

At the beginning of this work, two main goals were postulated:

1. Identify principles of robustness found in metabolic production and transfer them to the design of man-made manufacturing systems.

2. Understand the functioning of the organizational unit, i.e., the interaction of the various components of system-scale cellular regulation.

So in terms of these goals, what has been achieved and where might future research lead to? Chapter 2 introduced the deep parallels between the individual units of work in metabolic and production logistics systems. This means that any findings in either system can now be directly transferred to the other system. We clearly demonstrated that fact by applying a method for adaptive traffic control to a metabolism-like network topology. The original idea was, of course, the transfer of knowledge in the other direction.

At the level of periodic devices, we are talking about regulating material flow. A desirable property of metabolism is the relatively stable output given fluctuating inputs. Despite the challenges mentioned in section 1.1, design and implementation of a metabolism-inspired regulation of material flow will be a necessary next step. This should probably start at the level of a pathway for which detailed models exist (Chassagnole et al., 2002) and that is well understood. The method of regulation could then be transferred to an ODE or stochastic model of production in logistics. Known methods of metabolic regulation, such as positive or negative feedback, can then be tested in a logistics setting. Such feedback is probably also present in the planning of a logistics processes and by the job shop manager but such rules and the controlling actions taken need to be clarified and cataloged. The possibility of an immediate response via, for example, autonomous control (Scholz-Reiter et al., 2004), could open the door to improved handling of fluctuations.

Homeostasis, the tendency ascribed to living cells to maintain stable physiological conditions, is one of the main concepts that have made biology desirable for logistics. One important aspect of homeostasis is the organization of a cell as a holistic

unit Muskhelishvili and Travers (2013). In terms of production, the large-scale organization of metabolism into catabolism and anabolism is extremely interesting. Catabolic reactions break down molecules into precursor building blocks which are then used by anabolic reactions to produce other essential molecules. The building blocks can be produced from a wide range of compounds found in the environment. A specific investigation of supply chain disruption and risk diversification with metabolic network structures in mind could afford strategies for greater production reliability. A potential starting point could be the model proposed by Schmitt and Singh (2012) but with a stronger focus on company internal network dynamics.

The results from chapters 5 and 4 help illuminate other potential topological measures. The architectures of metabolic systems are clearly particular and the dynamics of some few-node subgraphs are highly favorable (Kaplan et al., 2008). Nonetheless, we have been unable to generate networks with a desired subgraph content[1]. However, a profiling of essentiality on few-node subgraphs, as was done for *E. coli*'s metabolic network in chapter 4, has never been attempted for logistics networks.

In principle, the results presented in chapter 5 could help in the design of production networks. As was suggested in that chapter, the relation between output pattern complexity and network structure can be studied systematically in metabolism and production alike. Furthermore, given a desired output pattern, the simulated evolution of those types of networks could serve as a guideline for the design of a production network that will contain modules of shared work, where possible, and is robust against, for example, node removal (machine failure).

Continuing the topology-based approach, there have been a number of recent studies investigating cascading failures (Buldyrev et al., 2010; Lorenz et al., 2009) and evaluating topological node essentiality, as well as methods to improve network robustness (Rohden et al., 2012). A further comparative study of these methodologies in metabolic and logistics networks could further illuminate structural differences and beneficial principles.

FBA, introduced in detail in chapter 3, actually has its origins in operations research. However, the ubiquitous representation of metabolism as mass-balanced reactions in FBA is virtually unknown in logistics. Since each manufacturing step has clearly defined parts and products, the same modeling approach can readily be extended to logistics. There are two benefits to following this line of thought: (i) Within the linear programming framework that is FBA, a cost can be defined for the acquisition and maintenance of machines. The balance between increased throughput and thus profit and the costs of introducing multiple machines can be integrated in the model. Additionally, the benefit of increased redundancy in case of failure can be computed. (ii) Waste material of each processing step can be explicitly modeled as "side products". Improvements that decrease the amount of waste have a direct effect on model fluxes and the savings of reduced waste are immediately apparent. Moreover, models of the evolution of metabolism (Tosh and McNally, 2015) also consider an energy cost per protein and still redundant networks appear. Is the lack of redundancy in man-made systems a consequence of underestimating failure costs or is the abundance of redundancy in living organisms a consequence of

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[1]This was the topic of Pencho Yordanov's master's thesis.

life having no other insurance policies?

Regarding the second goal, chapter 6 presents a quantitative confirmation of the counterbalancing of digital and analog control introduced before (Marr et al., 2008). In (Muskhelishvili et al., 2010), it was proposed that any part of the organizational unit is a reflection of the state of the other parts and thus of the whole. The network coherence method used in a number of studies (Marr et al., 2008; Sonnenschein et al., 2011) excels at quantifying such global states but it fails to answer questions such as: What initiated a change in global state? What is the dynamic response to the initiation of change and how is this propagated to the other components of the holistic unit? In other words, what defines the interface between the different components?

In a reductionist approach, the *fis* and *hns* mutants of *E. coli* are not ideal subjects of study as they play an important role in digital control via direct binding in the promoter region of transcription units (TUs), as well as in the analog component via stabilization of larger-scale chromosomal structures. Studying other proteins whose effects are unique to one of the control components could yield further insight.

In all of this work, only the regulation and metabolism of *E. coli* have been considered. This choice is reasonable considering that it is a unicellular prokaryote, i.e., considered to have rather simpler mechanisms of regulation, and is one of the best studied experimental model organisms. Nevertheless, relying only on one dataset, as we have also shown in chapter 7, is problematic. It increases the risk of over-fitting models and over-interpreting results. Fortunately, there are a number of resources that can be exploited: The BioCyc (Karp et al., 2005) database comprises manually curated metabolic pathway information for the following model organisms that have been and could be used in the creation of metabolic models: *E. coli* - EcoCyc, *Homo sapiens* - HumanCyc, *Saccharomyces cerevisiae* - YeastCyc, *Arabidopsis thaliana* - AraCyc, *Leishmania major* - LeishCyc, and MetaCyc which combines pathways from many different organisms. The KEGG (Kanehisa and Goto, 2000; Kanehisa et al., 2012) database is another excellent resource in a similar vein to MetaCyc. Whole genome models can be found in publications, the BiGG (Schellenberger et al., 2010) database and the BioModels (Chelliah et al., 2014; Le Novère et al., 2006; Li et al., 2010) database in addition to manually curated models today contains 2641 automatically generated whole genome models using the Path2Models tool(Buchel et al., 2013).

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