Logist. Res. (2012) 5:79–87
DOI 10.1007/s12159-012-0090-0

ORIGINAL ARTICLE

How do production systems in biological cells maintain their function in changing environments?

Moritz Emanuel Beber · Marc-Thorsten Hütt

Received: 27 August 2012 / Accepted: 17 September 2012 / Published online: 29 September 2012

Abstract Metabolism is a fascinating natural production and distribution process. Metabolic systems can be represented as a layered network, where the input layer consists of all the nutrients in the environment (raw materials entering the production process in the cell), subsequently to be processed by a complex network of biochemical reactions (middle layer) and leading to a well-defined output pattern, optimizing, for example, cell growth. Mathematical frameworks exploiting this layered-network representation of metabolism allow the prediction of metabolic fluxes (the cell's 'material flow') under diverse conditions. In combination with suitable minimal models, it is possible to identify fundamental design principles and understand the efficiency and robustness of metabolic systems. Here, we summarize some design principles of metabolic systems from the perspective of production logistics and explore, how these principles can serve as templates for the design of robust manufacturing systems.

Keywords Systems biology · Metabolic networks · Enzymes · Design principles · Simulated evolution

1 Introduction

There is a deep intrinsic parallel between the metabolism of biological cells and industrial production. Cells function efficiently under typical environmental conditions. At the same time, they are viable (thus maintaining a certain level of function) across a vast range of atypical environments. It is precisely this robustness with respect to large changes (and significant fluctuations) in the composition of the environment (the 'input pattern') that makes metabolic networks a potentially very interesting role model for technical production and distribution systems (see, e.g., [1]).

The network of metabolic reactions in a cell is responsible for providing a wide range of substances at the right time in the right proportions for a specific purpose of consumption. At the same time, metabolic systems construct complicated chemical substances out of nutrients taken up from the environment. With several thousands of interacting machines (enzymes, catalyzing biochemical reactions), the underlying production network is about as complex as the most involved processes of industrial production. The key challenges are comparable: How do systems in both domains ensure robustness with respect to perturbations? How can these systems react rapidly to important changes in their environment by ensuring the achievement of the logistics targets? For metabolism, the young scientific discipline addressing these questions in a strong interplay between mathematical approaches and experimental efforts is called Systems Biology. It is a 'melting pot' of many scientific fields, contributing to the understanding of the larger-scale organization of living cells and their dynamic behavior in response to external and internal stimuli, including disease development (see, e.g., [2, 3, 4]). Systems Biology is situated at the intersection between the Biological Sciences, Mathematics, Statistical Physics, Biophysics, and Computer Science. For the part of Systems Biology discussed here, the principal aim is not the representation of a cell in a computer, but rather it is about understanding function beyond the level

M. E. Beber (✉) · M.-T. Hütt
School of Engineering and Science, Jacobs University, Campus Ring 1, 28759 Bremen, Germany
e-mail: m.beber@jacobs-university.de

M.-T. Hütt
e-mail: m.huett@jacobs-university.de
URL: http://sysbio.jacobs-university.de/

of a few elements: How is robustness achieved? How can a system react rapidly to changes in the environment?

The parallel between metabolism and manufacturing has been emphasized by others before (e.g., [5, 6]; see also [7]). Systems Biology has over the last 6–8 years provided a remarkable basis for a more refined, detailed and quantitative comparison of these two realms. In the present paper, we repeat some of the arguments from Beber et al. [8] and briefly review two articles exploring abstract model representations of metabolic systems [1, 9].

Our focus here is on metabolism as a potential 'template' for manufacturing systems. Other biological principles, like adaptation, self-organization and aspects of biological evolution have been explored to allow manufacturing systems to deal with environmental variability and internal fluctuations. Two important examples are the framework of Biological Manufacturing Systems (see, e.g., [10, 11]) and the idea of Emergent Synthesis [12], which suggests that regulation on all scales requires integration in a self-organized fashion.

The aim of this paper is to review some material from Systems Biology on the functioning of metabolism and then show, how abstract model representations of metabolic systems can serve as a starting point for transferring metabolic design principles to industrial production. We first describe the general features of metabolic systems that form the basis of a comparison with industrial production (Sect. 2) Next, we discuss a broad range of recently identified metabolic design principles of interest to manufacturing (Sect. 3) In Sect. 4, we then explore the possibility of constructing abstract model representations of metabolic systems that are suitable interfaces between Systems Biology and industrial production, helping us to transfer such knowledge into manufacturing contexts. Lastly, in Sect. 5, we discuss, how such biological understanding, in particular of design principles of metabolic systems, can serve as templates for robust technical and industrial systems.

2 Metabolism from a production logistics perspective

Metabolism is at the same time a transportation network, an assembly line, and a storage depot. Substances are taken up from the environment (by exchange reactions) and distributed in the cellular compartments (by transport reactions). Large parts of metabolism are responsible for degrading complex substances into more elementary building blocks (catabolism). These chemical building blocks are used in the formation of more complex compounds (anabolism) that are needed for cellular maintenance, growth or storage. The elementary organizational unit of metabolism is the individual biochemical reaction, often represented by the enzyme (or enzyme complex) serving as catalyst for a reaction. Qualitatively speaking, the exchange reactions can be regarded as an input layer, followed by a complex intracellular processing layer. In many modeling approaches, the overall goal of metabolic function is abstracted as a (fictitious) biomass reaction, where each component entering this reaction is known to contribute to cell growth. Figure 1 (left) summarizes this situation.

The flow of substances through the metabolic network is the cell's equivalent of the complex material flows encountered in industrial production. The enzymes represent machines responsible of constructing well-defined products out of a specific set of incoming materials.

The appropriate mathematical tools for analyzing successful configurations of metabolic systems on the scale of

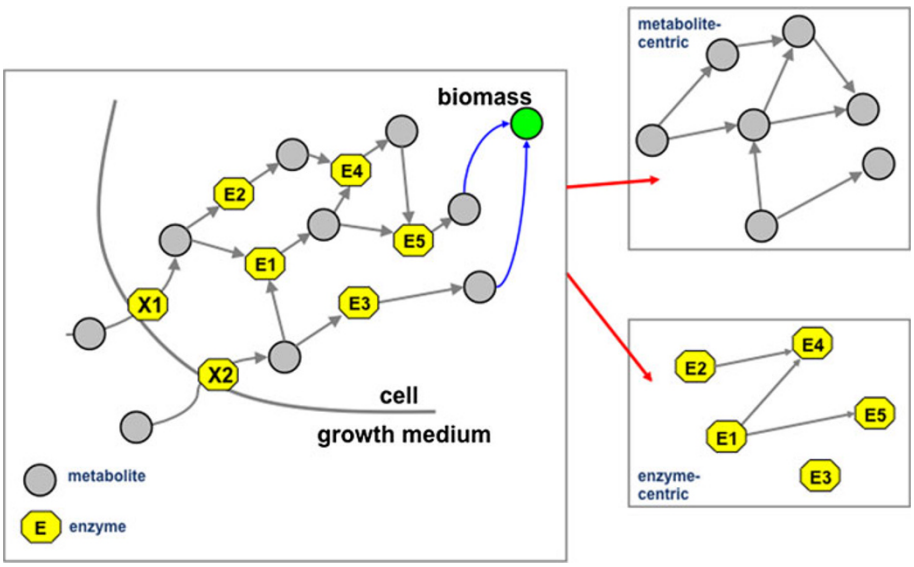

Fig. 1 Network representations of cellular metabolism (*schematic view*), together with the projection of the bipartite representation of metabolism (*left*) to a metabolite-centric graph (*right*; *top*) and to an enzyme-centric graph (*right*; *bottom*). Figure adapted from Smith and Hütt [13]

a whole cell (rather than an individual metabolic pathway) are constraint-based modeling and, more specifically, flux-balance analysis (FBA), reviewed, for example, in [14, 15]. FBA can be used to predict metabolic flux distributions (the biological equivalent of material flow) under various nutrient input patterns and for diverse cellular objective functions (serving as the output pattern of the system maximized during flux-balance analysis).

Within the elegant framework of flux-balance analysis, the optimal steady-state distribution of metabolic fluxes can be predicted, given the structure of the environment (the availability of nutrients) and the cellular objective function (e.g., biomass production or ATP maximization). The objective function, serving as the output pattern of the system, is maximized during flux-balance analysis. FBA has a similar methodological core to many optimization problems in logistics, namely linear programming. It is capable of serving as an interface between the biological and biochemical foundations of metabolic systems and the representation (and conceptual understanding) of metabolism as a complex network.

In virtually all Systems Biology studies, statistical methods play an important role in identifying the intrinsic mechanisms behind the performance of a system. More precisely, the analysis of system-wide information with any statistical methods requires a clear concept of a null hypothesis, a random background, against which the observations can be compared. Expressing levels of cellular organization in terms of networks has turned out to be particularly helpful for the task of formulating the appropriate null models. The strength of graph theory is that it can represent a complex system in a unified formal language of nodes and links.

A suitable network representation of metabolic systems is a bipartite graph, that is, a graph with two types of nodes (here: metabolites and enzymes) interacting in an alternating fashion. Typically, projections of this bipartite graph are discussed: a metabolite-centric projection, where two metabolites are linked, if an enzyme catalyzes the conversion from one to the other; a enzyme-centric projection, where two enzymes are linked, if they share a common metabolite. Figure 1 illustrates the three network representations of metabolism.

At this point, we wish to emphasize that in spite of the apparent simplicity and autonomy of metabolism as a network converting an input vector (nutrients) into an output vector (biomass), metabolism is also embedded in an intricate system of regulation, the gene-regulatory network and the regulatory action of genome structure (see, e.g., [16]).

How are complex networks characterized? The degree of a node is the number of links entering or leaving this node. It is thus the number of direct neighbors of a node. A network with a degree distribution given by a power law is called 'scalefree', because such networks do not contain a particular scale of reference: There is no typical (e.g., average) degree of a node. The degree is a node property spread over several orders of magnitude. In a scalefree network, the vast majority of nodes only have very few links. At the same time, the network contains nodes, which have several orders of magnitude more links. These hubs are topologically the most important system components. It is surprising that many natural and technical systems seem to follow this scheme (see, e.g., [17]).

Remarkably, the degree distribution of the metabolite-centric graph approximates a power law. Thus, the most appropriate random network representation of this graph is a scalefree graph [18]. Early studies on metabolic network topologies mostly focused on this broad degree distribution of the metabolite-centric graph [19, 20, 21]. In contrast, the degree distribution of the enzyme-centric projection has a rather narrow peak with no heavy tail and thus more resembles an Erdős-Rényi (ER) random graph [22].

All these observations are interesting starting points for a quantitative comparison of metabolic systems and industrial manufacturing systems. While many characteristics of network architecture are similar between the two types of production systems (metabolic and industrial), in [23] striking differences on the level of dynamical quantities (in particular, material flows) are observed. More details on all of the topics listed in this Section can be found in [8].

3 Metabolic design principles

Metabolic networks are at the same time scalefree [19], modular [24], layered (one can for example distinguish between the input layer given by the set of uptake reaction, the collection of all reactions directly contributing to biomass as an output layer, and a 'processing layer' consisting of all reactions in between) and bipartite (with metabolites and reactions/enzymes forming the two sets of nodes). Their projections contain two categories of bidirectional links (a bidirectional link can be truly bidirectional or the co-occurence of two opposite unidirectional links), as well as substantial degree correlations (see, e.g., [25]). These complications all make it a formidable challenge to explore the interrelations between network topology and dynamical function for metabolic systems [26, 27].

Many attempts have been formulated over the last 7 years to understand the structure of metabolic networks from first principles using evolutionary or biochemical arguments [28, 29, 30, 31, 32]. Robustness of metabolic networks beyond the single-knockout level (i.e., with more severe perturbations than the loss of a single enzyme) has been explored using flux-balance analysis [33] and

elementary flux modes [34]. Several works have argued that the network topology of metabolic systems is markedly optimized for robustness. The study by Marr et al. [35] uses binary probes to measure, whether fluctuations are on average dampened out or enhanced on metabolic network architectures.

There seems to be a selection for minimal metabolic pathways, given the environmental conditions (i.e., the set of available nutrients). The accessible nutrients for a species may thus be inferred by analyzing the network topologies [36].

Temperature differences of typical habitats correlate with structural differences in metabolic networks [37], a phenomenon that can be qualitatively reproduced in a simple model involving gene duplications [38]. On a more theoretical side, suitable definitions of a metabolic 'null model' have been formulated recently [39].

For the bacterium, *Escherichia coli*, the remarkable success of flux-balance analysis in predicting growth rates for mutants has been demonstrated by Fong and Palsson [40]: Even though FBA over-estimates the initial growth rate for most single-gene mutants, in many cases, an adaptive evolution over several generations will allow the cells to converge to the computationally predicted growth rates.

A refined method [41], called 'minimization of metabolic adjustment' (MOMA), selects the mutant flux composition relative to the flux composition of the unperturbed system (the 'wildtype'). The view that MOMA rather predicts the initial growth rates of mutants, while FBA predicts the maximally achievable growth rates has been used to establish the concept of 'synthetic rescues' [42] (see also [43]): On the basis of these growth-rate differences between MOMA and standard FBA predictions, *compensatory mutations* can be applied selectively to the differences between the underlying flux distributions predicted by MOMA and standard FBA, respectively. These compensatory mutations transform the lower MOMA growth rate into the higher FBA growth rate.

Among the approaches mentioned so far, three seem of particular interest for application to manufacturing systems: (1) elementary flux modes, which is the counting of the number of paths compliant with certain subsidiary conditions; in this way, the importance of a system component is represented by the number of paths it is involved in; this general principle may well be applicable to manufacturing (see [44] for a first attempt in this direction); (2) evaluating network robustness with simple dynamic probes; often, it is unfeasible to perform realistic dynamical simulations due to limited knowledge of the large number of parameters; the organization of binary dynamics on a network may provide a rapid orientation, which sites are prone to large fluctuations; (3) restoring a function lost due to component failure by compensatory perturbations, as in the case of synthetic rescues; the low-performance states a system settles into under component failure may be local optima, and additional targeted perturbations may be necessary to guide the system into a (more) global optimum; for metabolism, the various forms of flux-balance analysis are capable of providing clear practical guidelines for the compensatory perturbations.

4 Abstract models of metabolic systems

On the technical level, in spite of the deep functional parallels between these two systems—material flow in processes of industrial production and metabolic flow in biochemical networks in cells—and the strong similarities in challenges and unsolved problems, methodological exchanges and attempts of quantitative comparison are difficult. They are in particular impeded by the lack of a common terminology and common formal representation of these systems. Identifying design principles in abstract model representations can provide guidelines, what signatures of, for example, robustness to expect, how to search for them in data and how to transfer the 'structural essence' of an enhanced function (like robustness) into the other realm. Here we will briefly summarize our work on two such abstract model representations at the interface of metabolism and industrial production: generic flow networks and networks of cyclic machines.

4.1 Generic flow networks

Recently [9], we analyzed the successful networks in the Kaluza–Mikhailov model of evolved flow networks, exploring their topological properties in more detail than in the previous work [45, 46, 47]. The networks consist of three distinct layers: an input layer that may only connect to the intermediate layer of nodes; the middle layer that may interconnect and are also linked to the input and output nodes; output nodes that have only incoming links from the middle layer. The process invoked on these networks is one of the flow distributions. A unit flux is applied to each input node. At each node, the incoming flux is distributed equally over all outgoing links, before it is finally gathered again at the output nodes. For each network, a prescribed *output matrix* (the 'target structure' during the simulated evolution) is determined in a random process, prescribing the proportions, in which each input should reach the outputs. The matrix is thus a set of output vectors, one per unit flux inserted in each input node.

Given a network with random initial links and a prescribed output pattern, two distinct goals are required of the evolutionary algorithm, yet both goals depend on the

output pattern. The first goal, and thus the first phase of the evolution, is to adjust the topology of the network in such a way that its output matches the prescribed pattern. This is achieved with a simulated annealing that minimizes a quantity termed 'flow error', a sum of squares over the difference between elements of the actual output and the prescribed pattern. We call the first phase of the evolution 'pattern recognition'.

In a second phase of the evolution, the topology of the network is further altered to maintain an output with a flow error below a threshold in the presence of certain types of damage. The damage applied to these networks is either removal of links, removal of nodes, or small fluctuations of the connectivity of the network, leading to 'link-robust', 'node-robust' and 'noise-robust' networks. We will refer to this second phase as 'robust pattern recognition'.

Examples of evolved node-robust networks at three different 'complexities' of the output pattern (given by the orthogonality of the individual output vectors and thus measuring, how distinct the individual goals are that each output vector provides) are shown in Fig. 2.

The evolved flow networks show strikingly clear topological signatures that we can attribute to function (like modularity) and robustness (like the subgraph composition and degree correlations, depending on the specific type of robustness enhanced during the simulated evolution). In Fig. 2, the strong modularity, as well as the increase in modularity with output pattern complexity, is clearly visible.

From our perspective, the results of [9, 45, 46, 47] on the subgraph composition and the modularity of robust evolved flow networks suggest that a specific imprint of robustness and function in the network topology can also be expected for metabolic networks and manufacturing networks. On the basis of these studies, we now come to a set of hypotheses relevant to general flow systems and potentially testable in empirical observations: (1) Output pattern complexity regulates the modularity of the successful networks. (2) If the network is robust against link removal, we should see a specific motif signature; if on the other hand the network is robust against node removal, we may expect negative degree correlations (even though we assume that other not yet identified topological features may also help characterizing node and noise-robust networks and may even discriminate between node and noise robustness).

As already mentioned in the Introduction, one can think of metabolism as a layered flow system, much like the flow networks in the Kaluza–Mikhailov model. The input layer is given by the available nutrients (or, more specifically, by the list of uptake reactions capable of metabolizing those nutrients), while all reactions directly contributing to the cellular objective function (the required 'output pattern'; e.g., biomass production) can be summarized as output nodes. The robustness of metabolic systems against various forms of perturbations, as well as the modularity of metabolic systems, has been under intense investigation in systems biology (see, e.g., [48, 15, 34]). Across species, the size of the input layer and the diversity of the environments vary substantially. The impact of environmental diversity and other habitat properties on network architecture have been discussed from a variety of perspectives (see, e.g., [49]). The relevant 'pattern recognition' task for metabolic networks is to convert the diverse, given set of input patterns all into optimal outputs. We thus expect the modularity of the metabolic networks to positively correlate with the environmental diversity. Some evidence for this relationship can be seen in [36]. Additionally, we expect that biological evolution has enhanced the robustness of metabolic networks against the loss of enzymes, rather than the loss of metabolites. On the basis of the results from [9, 45, 46, 47], we therefore expect a very specific subgraph composition of metabolite-centric metabolic networks. Some evidence for a non-random subgraph signature of metabolic network is found in [50, 25]. Due to the proper selection of a metabolic null model (see also [25, 39]), the computation of a reliable motif signature of metabolic networks is non-trivial and has yet to be done.

4.2 Networks of cyclic machines

In [1], first steps toward a framework suitable for modeling scenarios from traffic, metabolism, and production logistics have been presented. In particular, cyclic machines (periodic devices) are taken as the basic constituents of the system and explore how they shape system behavior. Figure 3 summarizes the representation of machines and enzymes as periodic devices. A commonly used production logistics model, the throughput element, describes the different phases of processing that are repeated in a specific operation [51]. The phases are divided into inter-operation time (consisting of transport time and waiting time of the material) and operation time (consisting of setup time and actual processing time of the machine). Therefore, a machine cycles through the two states of setup and operation for each production lot (Fig. 3a). The observation that enzymes can be represented as interacting cyclic machines capable of synchronization and collective behaviors goes back to Stange et al. [52].Similarly, in order to depict the cyclic performance of allosteric enzymes that bind substrate and regulatory molecule, release product, and resume their initial state, Casagrande et al. [53] used a stochastic phase oscillator model (Fig. 3c). In fact, all catalytic enzymes that are returned to their initial state inherently have a cyclic nature (see Fig. 3b) that can be used for such an abstraction (and the vast majority of enzymes belong to this category). Generally, enzymes (or enzyme complexes)

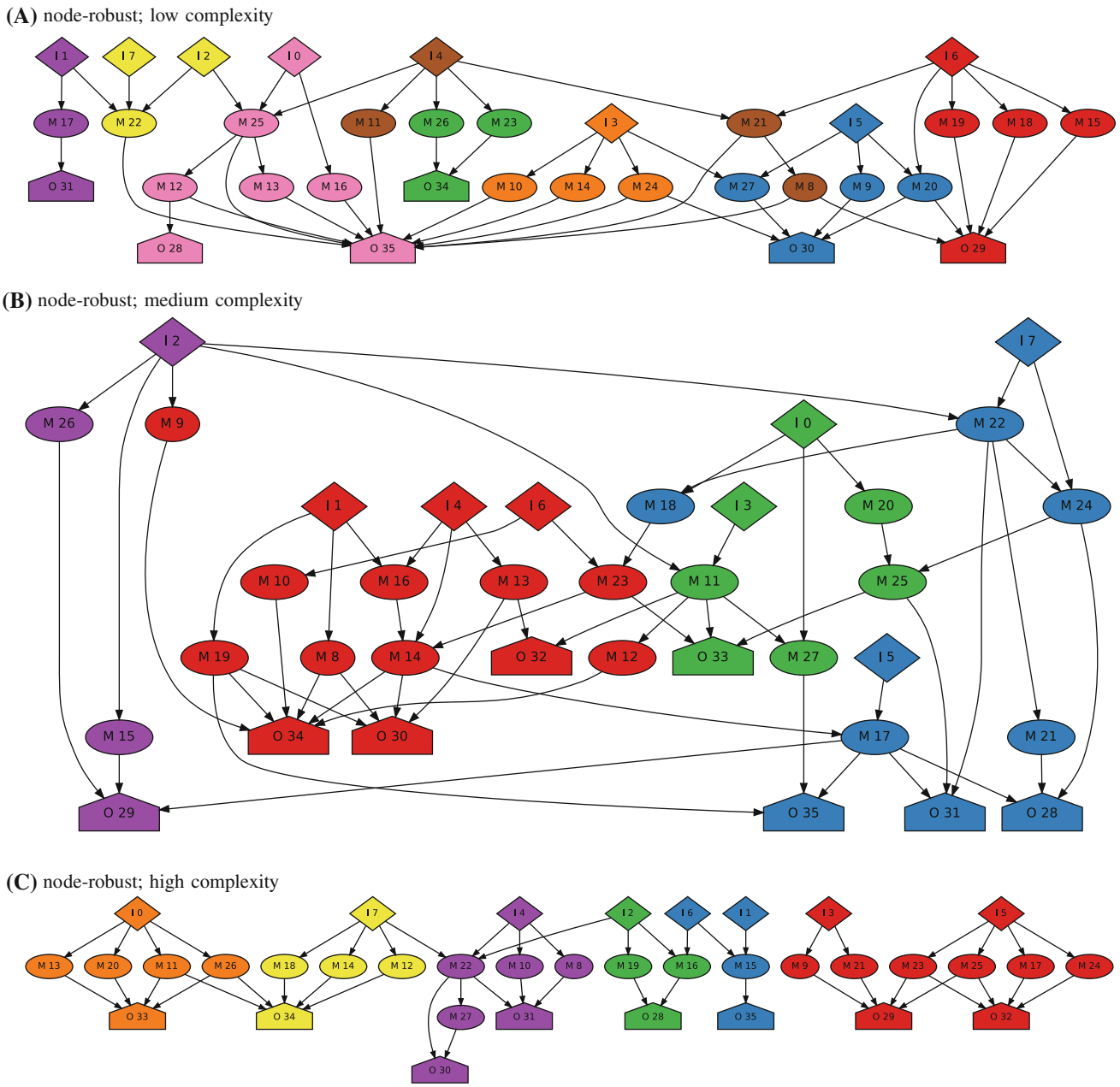

Fig. 2 Example of evolved node-robust flow networks arising in the Kaluza–Mikhailov model with increasing output pattern complexity. Input nodes, middle nodes and output nodes are *diamonds*, *ellipses* and *house-shaped polygons*, respectively. Figure adapted from Beber et al. [9]

catalyze a specific reaction as long as the substrates are present at favorable concentrations, until there is a regulation event that prevents them from processing the compounds involved, or until they are removed from the cell by, for example, degradation.

What can be achieved with such an abstract model representation? Even though some of the organizational features are comparable, transportation, manufacturing and metabolism all are represented by very different network architectures and are controlled by very different regulatory systems. It is therefore not a priori clear that optimization methods from one domain can be applied successfully in another domain. A proof of principle has been given in [1], where a strategy (adaptive control) from one domain (traffic modeling, see [54, 55]) can also be successfully applied to the other domains (industrial production, metabolic systems).

Extending the formal view of periodic devices characterized by a phase variable to (empirical and simulated) data from a large-scale transportation system, in [56], the synchronization of arrival/departure events in the network of long-distance train connections has been analyzed. It has

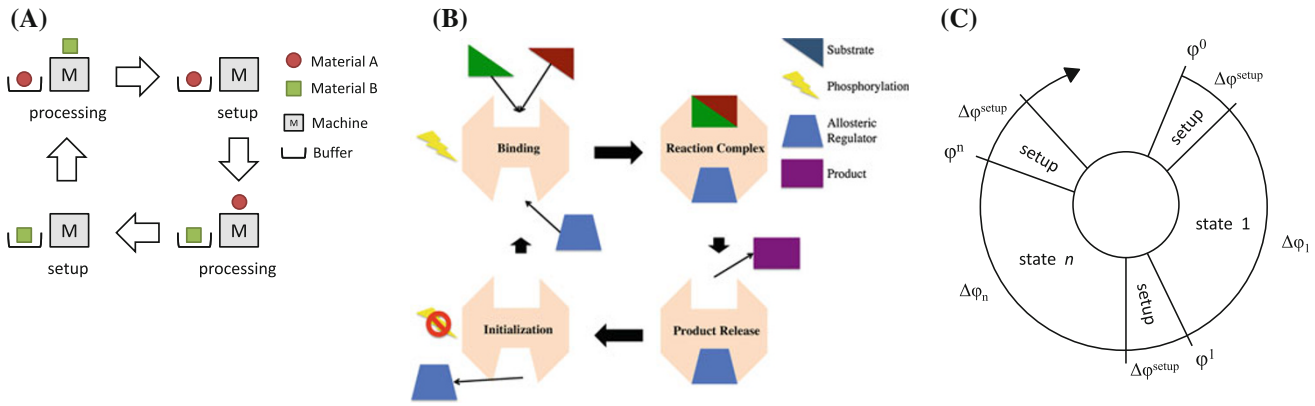

Fig. 3 Representation of production processes (**a**) and metabolic reactions (**b**) as periodic devices (**c**). Figure adapted from Becker et al. [1]

been shown that the performance (in a very general sense) of a given timetable of train connections is essentially determined by its phase pattern and thus the intrinsic levels of synchronization. The results show a clear and surprising negative correlation between the synchronization index of a station and its robustness to delays. This negative correlation between synchronization and robustness that was observed in the data could also be understood in a minimal model of delay propagation [56].

5 Conclusion

The main purpose of the present article is to emphasize the strong parallel between metabolic systems in a biological cell and processes of industrial production. Putting the diverse findings together that have emerged from Systems Biology investigations over the last decade, we start to understand, how production systems in biological cells compute efficient metabolic states under diverse environmental conditions. Specifically, we have made some progress over the last years in understanding some design principles of metabolic systems (e.g., [35, 57]) and making them accessible to industrial production [8, 23]. For addressing such 'transferable' metabolic design principles, we employed abstract model representations of metabolic systems [9, 1] and the analysis of biological data [58] in combination with flux-balance analysis [16, 57] and the exploration of metabolic networks with dynamic probes [35]. The next natural steps are to quantitatively compare material flow in both domains and understand the relationships between fluctuations in supply and demand on the one hand and material flow patterns (or effective network architectures) on the other.

From our perspective, the most important topic to be addressed jointly by the two disciplines, Systems Biology and Production Logistics, is systemic robustness. The balance between the antagonistic pair of requirements, efficiency and robustness, is of broad interest across many disciplines, ranging from industrial production to cell biology and ecology. Lack of robustness due to too high efficiency is related to the notion of systemic risk, which has recently been discussed from a theoretical perspective, for example in the context of complex economical systems (see, e.g., [59]).

For cellular processes, this balance between efficiency and robustness has been explored in a multitude of ways resorting to both analysis of experimental data and the mathematical modeling of cellular processes. Motivated by graph theory and nonlinear dynamics, an influential trend in systems biology at the moment is to relate robustness to small regulatory devices [60, 61], serving, for example, as a noise buffer or providing a suitable amount of redundancy for maintaining systemic function even under perturbations.

With these thoughts, we hope to contribute to the onset of a rich and stimulating dialogue between the two disciplines, Systems Biology and Production Logistics.

Acknowledgments MEB is supported by a Deutsche Forschungsgemeinschaft grant to MTH (grant HU-937/6). We are indebted to Nikolaus Sonnenschein (San Diego, USA) for providing his expertise on flux-balance analysis. We gratefully acknowledge discussions and close collaboration with Katja Windt (Bremen, Germany) on the parallels of metabolism and manufacturing.

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