

A Comparison of Network Characteristics in Metabolic and Manufacturing Systems

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Abstract Both metabolic and manufacturing systems face fluctuating environmental influences and thus share the common challenge to maintain a high level of efficiency for a variety of different conditions. Therefore, transferring methods used for analyzing one of the systems can lead to gaining new insights in the other. Following-up on previous findings on analogies in metabolic and manufacturing systems, our approach now is to analyze and compare complex network measures such as centrality or flow activity in both systems to identify quantified relations. The results show that both systems also display distinct statistical differences in addition to their various structural similarities.

Introduction

The metabolism of a cell and the material flow network of a manufacturing system are both faced with highly variable environmental influences, such as fluctuating input factors or disturbances within the system. Thus, they share comparable challenges: they have to efficiently and sustainably cope with uncertain and varying system conditions while also displaying a high performance under normal circumstances. Therefore, exploring parallels between metabolic and manufacturing systems seems promising, as analysis or control methods that are applicable in one of the two systems can be suitable for the other one as well.

Some analogies of metabolic and manufacturing systems have already been described in the past, such as parallels between certain objects in the systems (e.g.,

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enzymes in metabolism and machines in manufacturing) (Tharumarajah et al. 1998) or the process of evolutionary optimization in both systems (Armbruster et al. 2005). In a previous approach, we have enhanced those ideas by pointing out further similarities, such as in network topology, system dynamics and flow control (Becker et al. 2011). Although the analogies between the two systems seem obvious, approaches so far have stayed on a rather descriptive level, and no quantifiable relation in system behavior of metabolic and manufacturing systems has been revealed yet.

Therefore, in this paper we seek to give a quantitative statement on parallels between metabolic and manufacturing systems by applying and comparing complex network measures to a dataset of a metabolic and a manufacturing network. This allows us, on the one hand, to verify the validity of the existing qualitative analogies between the two system types. On the other hand, this analysis can help finding improved methods for the analysis of networks in manufacturing systems.

The paper is structured as follows. The second section will thus give a description of the analogies between metabolic and manufacturing systems as yet proposed. In the third section, different complex network measures and their application in metabolic and manufacturing systems will be presented. The fourth section illustrates and investigates the results of our comparison of complex network measures in metabolic and manufacturing systems. A discussion and conclusion is then given in the fifth section.

Analogies in Metabolic and Manufacturing Systems

Metabolic and manufacturing systems share obvious commonalities regarding their structure and their functions. Metabolism can be seen as a system dealing with transportation, decomposition, and production of compounds. Helbing et al. (2009) claim that logistics as the organization, coordination, and optimization of material flows is an omnipresent characteristic of biological systems. This similarity has often been the trigger for the development of bio-inspired approaches in logistics and manufacturing. In logistics, methods for transport network design using fungal networks (Bebber et al. 2007; Tero et al. 2010) or optimization methods for logistics processes such as vehicle routing based on ant algorithms (Bell and McMullen 2004) have been proposed. In spite of the high number of bio-inspired approaches in logistics, there have been few investigations so far which attempt to unravel the fundamental mechanisms that enable manufacturing systems to benefit from biological structures. First works point out the structural similarities between biological and manufacturing systems and their components (e.g., cells and production units) (Tharumarajah et al. 1998) as well as similarities in control between the two systems (Ueda et al. 1997).

Our previous work includes a qualitative synopsis of matching elements between metabolic and manufacturing systems on the levels of network topology, network elements, flow organization, and system dynamics (Becker et al. 2011).

The *network topology* of material flow networks in manufacturing systems can be modeled by a directed graph, which consists of *network elements*, in particular of nodes representing machines or assembly stations and (weighted) links representing the corresponding material flow between the machines. Similarly, metabolism as a complete set of biochemical reactions within an organism (e.g., a cell) can be seen as a sequence of transformations of substrates into products. The interactions between substrates, reactions, and products can then be represented as a network. The substrates and products correspond to the raw material and finished products in a manufacturing system. Most reactions in a metabolism are enabled through the catalytic activity of enzymes, which correspond to machines in manufacturing.

Flow control in both network types depends on the structure and plasticity of the network. Although the control mechanisms themselves are rather different, there are similar layers of control: on the one hand, there are global ‘strategies’, represented by a production plan in manufacturing systems and by external signals that control metabolic functions. On the other hand, there are local feedback mechanisms, e.g., dispatching rules in manufacturing and concentration-triggered suppression or stimulation of reactions.

The *system dynamics* layer depicts the actual routing functions within a material flow or metabolic network. This routing happens at each node in the system and determines the subsequent path of the flow elements through the network. In manufacturing systems, the system dynamics are influenced by lot sizes, setup times, and technological restrictions. Metabolic structures are more complex, as metabolic regulation is controlled by gene regulation, covalent enzyme modifications, and regulation of the enzyme through non-covalent binding with other molecules.

Complex Network Theory and Measures

Research on complex systems using approaches from graph theory or statistical mechanics (Albert and Barabási 2002) is a well-established scientific field. Different types of networks, such as random graphs (Erdős and Renyi 1959), small-world (Watts and Strogatz 1998), or scale-free networks (Barabási and Albert 1999) have been identified and analyzed. Therefore, a large variety of network measures regarding topology and structure of networks (Costa et al. 2007; Ziv et al. 2005) has been defined.

As a considerable number of real world networks, such as social or biological networks, implicate the characteristics of complex systems, a wide range of scientific disciplines focus on the application of findings from complex network theory to real networks in order to understand and predict system behavior. So far, many different system types, such as communication (Albert et al. 1999), biological (Barabási and Oltvai 2004), or social networks (Newman and Park 2003), have been analyzed using complex network measures.

The study of metabolic networks from a graph-theoretical point of view has been a search for specific characteristics that can be attributed to principles of evolution. In this context, degree distribution (Jeong et al. 2000), modularity (Hartwell et al. 1999), hierarchy (Ravasz et al. 2002), and architectural robustness (Giaever et al. 2002; Papin and Palsson 2004) have been investigated and a very characteristic non-randomness of metabolic systems has been established. Despite the success of topological analyses the *true* features of metabolic networks are a matter of ongoing debate (Montañez et al. 2010), and a connection to evolutionary design principles is difficult (Papp et al. 2009).

In manufacturing, complexity poses an increasing challenge: manufacturing systems tend to become larger (i.e., increase the amount of elements) and highly connected. Therefore research in manufacturing focuses on finding ways to describe, measure, and manage complexity, in order to competitively deal with it (Papakostas et al. 2009; Vrabič and Butala 2011). First applications of complexity measures, such as degree distributions or clustering coefficients, exist for material flow networks in logistics (Hammel et al. 2008; Peters et al. 2008). Thus, complex networks measures seem as an ideal common analysis method for the comparison of metabolic and manufacturing systems on a structural level.

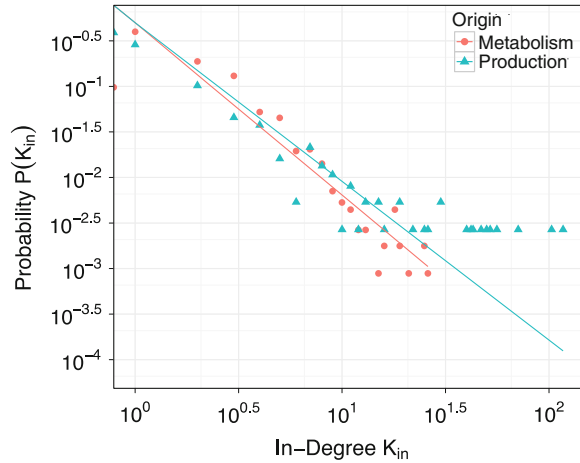
Comparison of Network Measures in Metabolic and Manufacturing Systems

In this section, we analyze and compare a metabolic and a manufacturing network using different complex network measures. Here, we use a network representation of all reactions occurring in *Escherichia coli* K-12 metabolism. Currency metabolites (energy carrier molecules) were manually removed to reveal the underlying disparate structure (Ma and Zeng 2003). The resulting bipartite network (bipartite, as it contains both metabolite and reaction nodes) was then projected onto the reactions nodes. The resulting network contains only reactions nodes and they are linked if they share a common metabolite. The metabolic fluxes were computed using a flux balance approach (Varma and Palsson 1994) on the latest model *E. coli* metabolism (Feist et al. 2007).

The manufacturing network is based on a job shop production system of a tool manufacturer. The product range comprises around 5,000 different variants and the system consists of around 300 workstations. To depict this system as a graph, the nodes represent the workstations, whereas the links represent the material flow between the work stations. The amount of material flow was derived from a data set of feedback data from one year of production in the job shop.

Firstly, we compare the in-degree distributions in both networks. The degree of a node indicates its connectivity within the network. The out-degree and the total degree of the nodes are similarly distributed for both networks, so we only show the in-degree, which is most relevant for the dynamic data. Figure 1 illustrates the

Fig. 1 In-degree distribution of the metabolic and the manufacturing network. The data was fit with a power-law using maximum likelihood estimation. The power-law coefficient α was determined to be 1.742 with a 95 % confidence interval of 1.644–1.848 for the production network and 1.891 with an interval of 1.835–1.951 for the metabolic network



in-degree distribution for the metabolic and the manufacturing network. The distributions clearly show that both networks are characterized by a small number of nodes with high degrees, whereas the majority of nodes have only a few links connected to them. This points to the existence of “hub” nodes in the network having a central task or a gateway function.

The second measure regarding network topology is the betweenness centrality distribution. The betweenness centrality B_k , of a node k , is defined as the sum over the number of shortest paths between all pairs of nodes i and j that pass through node k divided by the total number of shortest paths between i and j (Freeman 1977). It similarly quantifies the importance of the respective node in the system. Usually, there is a significant correlation between node degree and betweenness centrality in a network, which is the case for the networks considered here. As one would expect, the betweenness centrality values of the metabolic and the manufacturing networks indicate that there is a limited number of central nodes, while the majority of nodes is of moderate centrality (see Fig. 2). Therefore, we conclude that, although both networks originate from two particular different domains, their topology in terms of a connectivity pattern is to a high extent alike. In order to question this likeness, we produced random ensembles for both networks with an edge-switch algorithm (Milo et al. 2002). The deviation from randomness is apparent but cannot be adequately systematized.

Thirdly, we compare the distribution of active nodes, in order to determine how the activity of flows is distributed among the nodes in the networks in contrast to the topological key figures presented above. The metabolic system has been simulated in a variety of environments. For each node we have counted the number of environments in which this particular node has been active. As the manufacturing system does not operate in different environments, we have alternatively separated the manufacturing data in periods of time of equal length. These periods can serve as surrogates for environments, because each period comprises distinct demand represented by an individual set of production orders. After analyzing

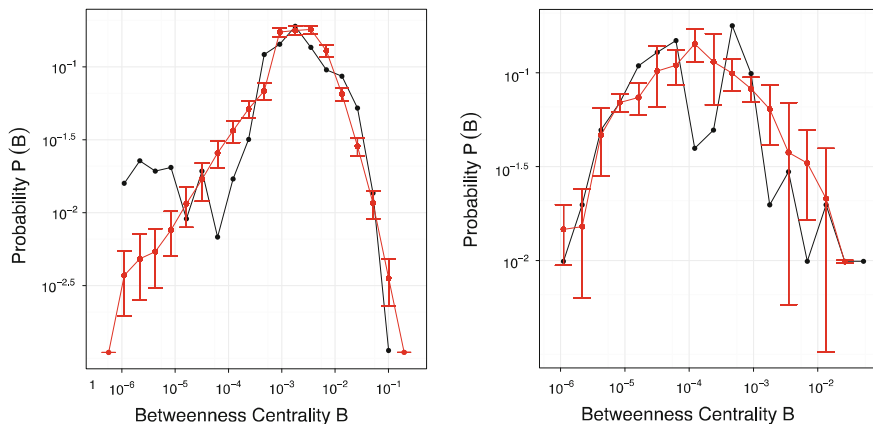
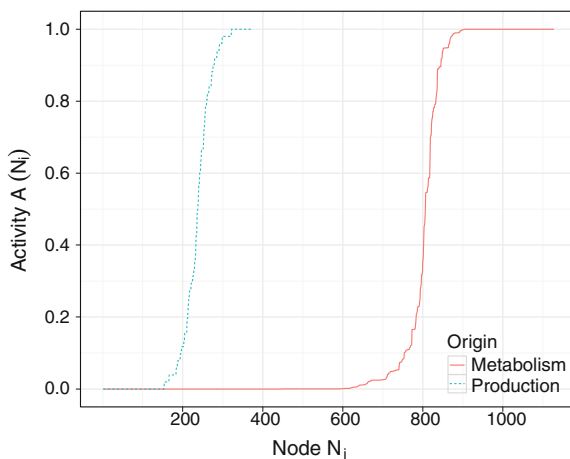


Fig. 2 Betweenness centrality distribution in the metabolic (*left*) and the manufacturing network (*right*). Comparison of the network in *black* with an ensemble of randomized networks in *red*

different period lengths, we decided to use a length of seven days, resulting in 51 complete periods. All alternative period lengths (except extreme values like one day or 365 days) basically show a similar pattern of distribution. We picked one week as an appropriate period, because it is able to represent a common, yet individual set of processing orders in this specific manufacturing company.

Figure 3 illustrates the activity distribution of the metabolic and the manufacturing network. The general shapes of the two curves are fairly similar and of sigmoidal shape. The curve of the metabolic system shows a long plateau of highly active nodes and a rather long tail of seldom-active nodes, which means that there are a high number of standard reactions as well as extremely specialized reactions, whereas only few reactions show intermediate activity. Compared to the metabolic

Fig. 3 Distribution of active nodes in the metabolic network (for different media) and in the manufacturing network (for different time intervals)



system, the manufacturing system seems slightly less specialized. The tail indicates that a considerable amount of machines is not active most of the time, meaning that a higher amount of nodes is active for the majority of environments (i.e., for most of the production orders carried out). However, as mentioned above, the shape of the curve depends to a certain extent on the sampling of environmental conditions and, in the case of the industrial network, on the time discretization.

The fourth measure to be compared is the mean throughput per node in relation to its standard deviation, normalized by the mean throughput. We chose a logarithmic scale for analyzing the flows in the networks as we are focusing on smaller flows and activity (see Fig. 4). For the metabolic system, there is a tendency that flows have a higher relative variation in general, whereas the variations of the production system seem to follow a more distinct pattern: the majority of nodes have a small flux yet a high variation. We assume that there is a focus on the stability of high fluxes while smaller fluxes show stronger fluctuations.

Finally, we want to analyze the interaction of flow with network topology. Therefore, Fig. 5 depicts the betweenness centrality of a node depending on the mean flux. This enables us to check whether there is a relation between the importance of a node in terms of throughput and its topological position in the network. Although we saw in the beginning that on a topological level, hub nodes exist, it now looks as if these hubs are not that clearly visible in terms of flow intensity. Seemingly, there is no correlation between flux and centrality in the metabolic network. However, the manufacturing network shows a slight relation between centrality and flux for higher centrality values.

Fig. 4 Mean throughput per node in relation to the standard deviation normalized by the mean throughput in the metabolic and the manufacturing network. The distribution of the fluxes in the production network follows a tight power-law (not shown)

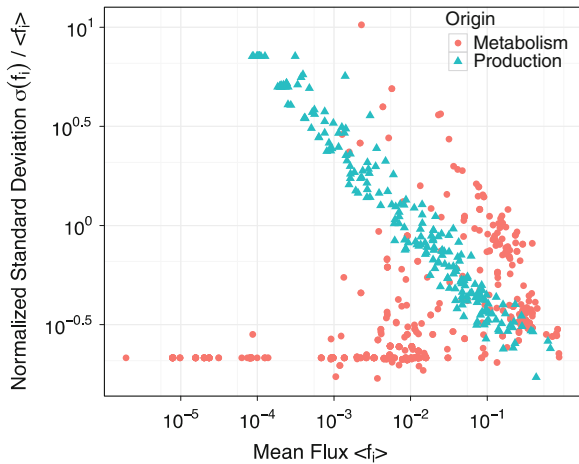
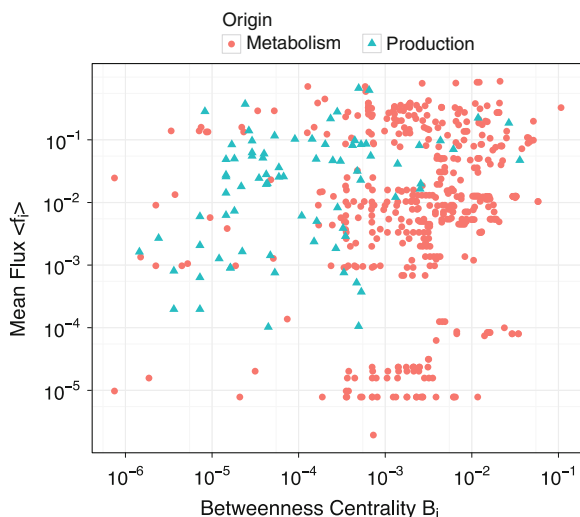


Fig. 5 Mean throughput per node in relation to its betweenness centrality



Conclusion and Outlook

In this paper, we have analyzed and compared different network measures for data from a metabolic and a manufacturing network. Following-up on other approaches that compare biological and engineered systems on a network level (6), we use networks as a common language that allows for the comparison of abstract measures between systems with fundamentally different purpose. We show for the first time that technical and biological ‘production networks’, in addition to their many structural similarities also display distinct statistical differences. Strikingly, the differences identified here concern the dynamics of material flow in these networks. In particular, the variation of intermediate-sized and very large fluxes is systematically suppressed (i.e., evolutionarily controlled) in the metabolic network, compared to the manufacturing network. Also, in the manufacturing network the mean flow through a node is coupled to the node’s betweenness centrality, which is not observed in the metabolic network. We see further potential in the analysis of such dynamic aspects, yet future approaches will also have to focus on a larger-scale analysis based on datasets of several metabolic and manufacturing networks.

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References

- Albert R, Barabási A-L (2002) Statistical mechanics of complex networks. *Rev Mod Phys* 74:47–97
- Albert R, Jeong H, Barabási A-L (1999) Diameter of the world-wide web. *Nature* 401:130–131
- Armbruster D, Degond P, Ringhofer C (2005) Continuum models for interacting machines. In: Armbruster D, Kaneko K, Mikhailov A (eds) *Networks of interacting machines*. World Scientific Publishing, Singapore
- Barabási A-L, Albert R (1999) Emergence of scaling in random networks. *Science* 286:509–512
- Barabási A-L, Oltvai ZN (2004) Network biology: understanding the cell's functional organization. *Nat Rev Genet* 5:101–113
- Bebber DP, Hynes J, Darrach PR, Boddy L, Fricker M (2007) Biological solutions to transport network design. *Proc R Soc B* 274:2307–2315
- Becker T, Beber ME, Windt K, Hütt M-T, Helbing D (2011) Flow control by periodic devices: a unifying language for the description of traffic, production, and metabolic systems. *J Stat Mech: Theory Exp* 2011:P05004
- Bell JE, McMullen PR (2004) Ant colony optimization techniques for the vehicle routing problem. *Adv Eng Inform* 8:41–48
- Costa LDF, Rodrigues FA, Travieso G, Boas PRV (2007) Characterization of complex networks: a survey of measurements. *Adv Phys* 56:167–242
- Erdős P, Renyi A (1959) On random graphs, *Publicationes Mathematicae (Debrecen)*. 6:290–297
- Feist AM, Henry CS, Reed JL, Krummenacker M, Joyce AR, Karp PD, Broadbelt LJ, Hatzimanikatis V, Palsson BØ (2007) A genome-scale metabolic reconstruction for *Escherichia coli* K-12 MG1655 that accounts for 1260 ORFs and thermodynamic information. *Molecular Systems Biology* 3 (June 2007)
- Freeman LC (1977) A set of measures of centrality based on betweenness. *Sociometry* 40:35–41
- Giaever G, Chu AM, Ni L, Connelly C, Riles L, Veronneau S, Dow S, Lucau-Danila A, Anderson K, Andre B et al (2002) Functional profiling of the *Saccharomyces cerevisiae* genome. *Nature* 418:387–391
- Hammel C, Flemming A, Schulze F, Peters K (2008) Anwendung von Methoden aus der Theorie Komplexer Netzwerke für die Optimierung der Layouts von MFS, Technische Universität Chemnitz (Hrsg.): 4. Fachkolloquium der WGT, pp. 81–91
- Hartwell LH, Hopfield JJ, Leibler S, Murray AW (1999) From molecular to modular cell biology. *Nature* 402:C47–C52
- Helbing D, Deutsch A, Diez S, Peters K, Kalaidzidis Y, Padberg-Gehle K, Lämmer S, Johansson A, Breier G, Schulze F et al (2009) Biologistics and the struggle for efficiency: concepts and perspectives. *Adv Complex Syst* 12:533–548
- Jeong H, Tombor B, Albert R, Oltvai ZN, Barabasi A-L (2000) The large-scale organization of metabolic networks. *Nature* 407(6804):651–654 October 5, 2000
- Ma H, Zeng A-P (2003) Reconstruction of metabolic networks from genome data and analysis of their global structure for various organisms. *Bioinformatics* 19(2):270–277 January 22, 2003
- Milo R, Shen-Orr S, Itzkovitz S, Kashtan N, Chklovskii D, Alon U (2002) Network motifs: simple building blocks of complex networks. *Science* 298(5594):824–827 October 2002
- Montañez R, Medina MA, Solé RV, Rodríguez-Caso C (2010) When metabolism meets topology: reconciling metabolite and reaction networks. *BioEssays: News Rev Mol, Cell Dev Biol* 32(3):246–256 March 2010
- Newman MEJ, Park J (2003) Why social networks are different from other types of networks. *Phys Rev E* 68:036122-1–036122-8
- Papakostas N, Efthymiou K, Mourtzis D, Chryssolouris G (2009) Modelling the complexity of manufacturing systems using nonlinear dynamics approaches. *CIRP Ann Manufact Technol* 58:437–440
- Papin JA, Palsson BO (2004) Topological analysis of mass-balanced signaling networks: a framework to obtain network properties including crosstalk. *J Theor Biol* 227:283–297

- Papp B, Teusink B, Notebaart RA (2009) A critical view of metabolic network adaptations. *HFSP J* 3(1):24
- Peters K, Seidel T, Lämmer S, Helbing D (2008) Logistics networks: coping with nonlinearity and complexity. In: Helbing D (ed.): *Managing complexity: insights, concepts, applications*, Springer
- Ravasz E, Somera AL, Monaru DA, Oltvai ZN, Barabási A-L (2002) Hierarchical organization of modularity in metabolic networks. *Science* 297(5586):1551–1555 August 2002
- Tero A, Takagi S, Saigusa T, Ito K, Bebbber DP, Fricker MD, Yumiki K, Kobayashi R, Nakagaki T (2010) Rules for biologically inspired network design. *Science* 327:439–442
- Tharumarajah A, Wells AJ, Nemes L (1998) Comparison of emerging manufacturing concepts. In: *SMC'98 Conference. Proceedings of 1998 IEEE international conference on systems, man, and cybernetics*, pp. 325–331
- Ueda K, Vaario J, Ohkura K (1997) Modelling of biological manufacturing systems for dynamic reconfiguration. *CIRP Ann Manufact Technol* 46:343–346
- Varma A, Palsson BØ (1994) Metabolic flux balancing: basic concepts, scientific and practical use. *Nat Biotech* 12(10):994–998 October 1994
- Vrabič R, Butala P (2011) Computational mechanics approach to managing complexity in manufacturing systems. *CIRP Ann Manufact Technol* 60:503–506
- Watts DJ, Strogatz SH (1998) Collective dynamics of 'small-world' networks. *Nature* 393:440–442
- Ziv E, Koytcheff R, Middendorf M, Wiggins C (2005) Systematic identification of statistically significant network measures. *Phys Rev* 71:1–8