

Theoretical Systems Biology in biotechnology: Promises, success stories and limitations

Stefan Schuster

Jena University, Dept. of Bioinformatics

Ernst-Abbe-Platz 2, 07743 Jena, Germany

phone: +49-3641-946450, FAX +49-3641-946452

e-mail: Stefan.schu@uni-jena.de

<http://pinguin.biologie.uni-jena.de/bioinformatik/en>

The new, emerging field of Systems Biology has gained continuously growing scientific and commercial attention and impact in recent years. In fact, Systems Biology is not really new – its main ideas date back to the work of A. Turing, I. Prigogine, H. Haken, D. Noble and others on self-organization and systems-theoretical modelling in the middle of the 20th century. Monographs such as that by Savageau (Biochemical Systems Analysis, 1976) and Reinhart Heinrich and myself (The Regulation of Cellular Systems, 1996) proposed systemic approaches as well. The new quality in recent years arises from the advent of high-throughput technologies and powerful computational resources. A further “trademark” of modern Systems Biology is the iterative cycle formed by modelling and experiment. This has led to a great potential of applications in biotechnology and medicine and, in numerous cases, to practical applications already.

The impressive advances as well as the present limitations of theoretical Systems Biology can be exemplified by metabolic pathway analysis. This research field, which is part of constraint-based modelling, is based on a decomposition of complex metabolic networks into the smallest functional entities, which can be interpreted as biochemical pathways. A central concept is that of elementary flux modes. This has manifold applications in bioengineering, such as microbial strain improvement and determining the robustness to knockouts. Examples are provided by the engineering of *Saccharomyces cerevisiae* to produce the biopolymer, polyhydroxy-butyrac acid and the (perhaps counter-intuitive) increase in molar yields of several products by knockouts of some enzyme genes based on theoretical calculations. An example of a successful theoretical prediction of a novel pathway is provided by the PEP-glyoxylate cycle in central metabolism in *Escherichia coli*.

Elementary-modes analysis meets with the problem of combinatorial explosion of the number of pathways with increasing system size. Two novel approaches are promising in overcoming this obstacle. The first starts by computing the shortest elementary mode, followed by computing the second-shortest etc., up to a certain length. The second concept is called elementary flux patterns. Within a large metabolic network, elementary flux patterns are defined as sets of reactions that represent the basic routes of any steady-state flux of the network through a particular subsystem that are compatible with admissible fluxes in a (possibly) much larger metabolic network. This allows one to predict novel metabolic pathways in genome-scale networks.

Another methodology describing systemic aspects and emerging properties arises from Evolutionary Game Theory. The engineering of microorganisms to produce a variety of extracellular enzymes, for example, for producing renewable fuels and in biodegradation of xenobiotics, has recently attracted increasing interest. Productivity is often reduced by "cheater" mutants, which are deficient in exoenzyme production and benefit from the product provided by the "cooperating" cells. This can be simulated by game-theoretical models.

As in every field of science, also the (current) limitations of Systems Biology should be discussed and assessed. This concerns, among others, the difficulty to measure large amounts of kinetic data and the computational complexity of genome-scale models.