Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Microbiology

# From systems biology to metabolically engineered cells — an omics perspective on the development of industrial microbes

Judith Becker and Christoph Wittmann

Green routes are indispensable for a sustainable production of energy, chemicals and materials, and health and nutrition products from renewable resources. Naturally, microbes are capable to conduct many of the desired biochemical conversions involved, however, only at rather low efficiency. It is therefore essential to metabolically engineer them towards efficient cell factories, which enable a high product titer, yield and productivity, exhibit a good process robustness and a broad substrate spectrum, and are safe to be used, to name a few prominent points from the wish list for industrial bioproduction. Such optimization of a microbial cell typically involves the implementation of several up to multiple traits into its genome, which then mediate the desired phenotype. While the genetic modification step itself is straightforward due to the much advanced genome editing methods, the selection of what exactly has to be optimized out of the manifold possibilities is still a challenge. Here we will discuss, how systems biology can offer guidance to orchestrate the hundreds to thousands of biochemical conversions of a microbe into a concert of desired performance. To this end, we will highlight recent success stories, where systems biology approaches have enabled next-level cell factories and bioprocesses.

**Address**
Institute of Systems Biotechnology, Universität des Saarlandes, Germany

Corresponding author:
Wittmann, Christoph (christoph.wittmann@uni-saarland.de)

**Current Opinion in Microbiology** 2018, **45**:180–188

This review comes from a themed issue on **Microbial systems biology**

Edited by **Terence Hwa** and **Uwe Sauer**

https://doi.org/10.1016/j.mib.2018.06.001



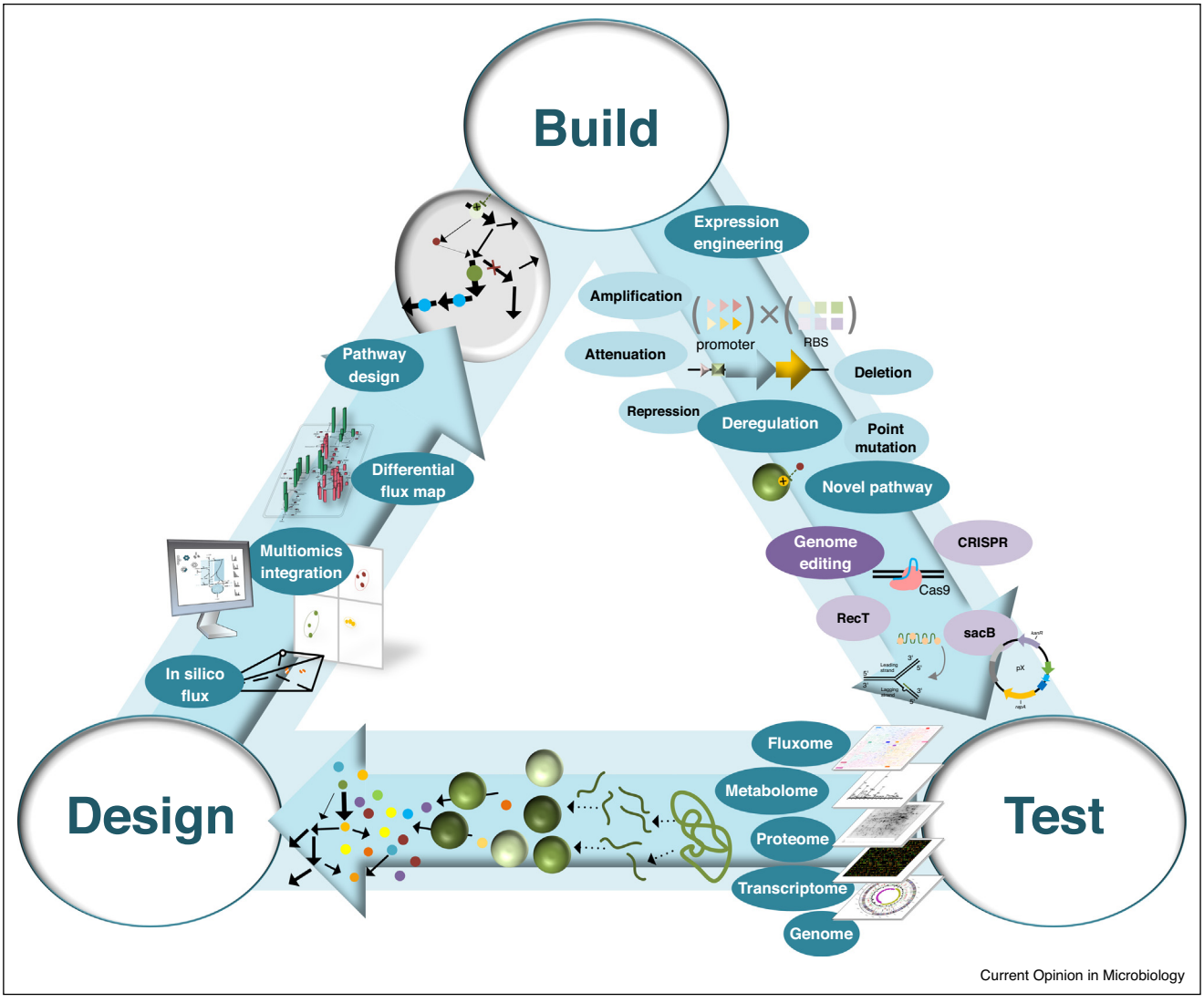
## Introduction

The technological breakthrough in omics-based analysis has enabled quantitative insights into cellular systems at a new level of detail and survey. Systems biology continuously and substantially deepens our understanding of biology and additionally provides a powerful toolbox to re-design existing cellular functions and create new ones. The sequencing of entire genomes and the quantification of cellular components and their interaction at a global level (transcripts, proteins, metabolites, and fluxes) are major drivers of design-based systems metabolic engineering [1,2]. Whole-genome sequencing of microbes and metagenome analysis [3,4] unravels the genetic repertoire of an organism and has laid the foundation for genome breeding [5], genome mining [4–7], and genome-scale metabolic modelling [8,9]. In the post genomic research, systems-wide profiling of transcriptome, proteome, metabolome, and fluxome has proven valuable to better understand network operation and regulation on a global scale [1,2]. Embedded into an iterative design-built-test cycle (Figure 1), omics technologies meanwhile open the door to create tailored cell factories for numerous products provided by Natures treasure chest and derive novel attractive industrial processes [3]. Their particular value lies in the guidance of researchers to select the most promising combinations of genetic traits for a desired phenotype out of the manifold possibilities, or to conduct fine-tuned changes to the industrial process environment. Guided by knowledge, strains with impressive performance were developed within a comparably short time period, providing traditional bio-based products such as the amino acids L-lysine [10], L-threonine [11], L-arginine [12] and L-valine [13], but also completely new ones, including diaminopentane [14,15], aminovalerate [16,17], artemisinin [18–20] and other high-value molecules [21–24]. In this review, we will highlight prominent examples of very recent studies that used the analysis of transcriptome, proteome, metabolome, fluxome, and combinations thereof for industrial strain and process optimization.

### Transcriptomics-based metabolic engineering

A breakthrough in DNA sequencing technology promoted the development of transcriptome analysis already about 20 years ago. Pioneering methods such as microarrays and RT-PCR are meanwhile complemented by RNA sequencing, substantially increasing throughput and additionally targeting RNA species, not captured by previous methods [25]. In the past years, transcriptome profiling has proven valuable to support rational strain design.

**Figure 1**




Iterative Design-Build-Test cycle for the creation of optimized producer strains for industrial application through systems metabolic engineering. Systems biology technology platforms (omics) are used to decipher genome, transcriptome, proteome, metabolome, and fluxome. Through comprehensive data integration, computational modelling and simulation, a metabolic blueprint is designed and then translated into a 'genetic engineering language' for genome editing of the desired phenotypes.

In a recent example, microarray-based transcriptomics, combined with *in silico* flux modelling, was used to improve heterologous production of the polyketide 6-deoxyerythronolide (6dEB) in *Escherichia coli* [26]. Polyketides are natural products with a tremendous value for the pharmaceutical industry, but their heterologous production in workhorses such as *E. coli* remains challenging, related to the complex biosynthetic enzyme cluster, often incompatible with the host's physiology [21]. In particular, the comparative analysis of 6dEB-producing and non-producing cells identified pentose phosphate pathway and nucleotide metabolism as relevant pathway modules to be engineered. For these, *in silico* prediction and transcriptome data were most divergent, for example, genes were upregulated, whereas the flux model suggested to reduce pathway activity. The down-regulation of all 25 identified targets was then addressed using synthetic antisense RNAs [26]. Combinatorial repression of beneficial targets increased 6dEB production by almost 300% (Figure 2a) up to a remarkable titer of 210 mg/L [26].

Transcriptome studies were also successfully applied to optimize the fermentative production of bulk chemicals. During succinate production in *Corynebacterium glutamicum*, elevated product levels had detrimental effects on glucose consumption and succinate production rate, as well as cellular fitness [27•]. Expression profiling, again