Development of new chemical-producing microbial cell factories is an iterative trial-and-error process, and to screen candidate cells at high throughput, genetic biosensor systems are appealing. Each biosensor has distinct biological parameters, making modular tuning networks attractive. However, all synthetic gene systems -- including the target metabolic pathways themselves -- represent a possible fitness burden to the cell and thus constitute a threat to strain stability.

In this thesis, several studies served to develop genetic systems for optimizing cell factory development and understanding the common error modes leading to loss of stable metabolic productivity during long-term microbial fermentation.

A molecular buffer system in Saccharomyces cerevisiae was designed and engineered to tune the signals of a known tetracycline-responsive RNA switch (riboswitch). Generalizable and based on split transcription factors, the system e.g. allowed shift of ligand sensitivity and inversion of the output signal from OFF to ON -- without changing the riboswitch or output gene. The system was i.a. characterized by green fluorescent protein (GFP), for which a recombination-stabilized multimeric GFP was developed. Overcoming cellular autofluorescence, this multimer enabled detection of weak promoter signals in S. cerevisiae. The concept of split transcription factors was further applied in S. cerevisiae as a tool to enable selection for three DNA fragments under a single selectable phenotype. This enabled quick introduction of a three-step polyketide pathway and may also serve to challenge the current paradigm of "one selectable trait -- one selection gene", as was demonstrated in plasmid and chromosomal gene introduction. Despite of genetic selection, the load of all synthetic systems can challenge the stability of strain designs. A metabolite--producing Escherichia coli strain was long-term cultured to study production stability and the dynamic effects of mutations within the cell population. A genetic error landscape of pathway disruptions was identified including particular, recurring error modes. Driven by a gain in fitness, these errors within 70 generations led to a transformation of the strain to a population of genetic non-producer cells. Knowledge about these mechanisms and the applied simple mathematical model may likely serve to realize more stable microbial cell factories in future.