Automated design of ligand responsive RNA devices

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Synthetic biology is revolutionizing the field of metabolic engineering by providing novel tools and technologies to rewire metabolism in a standardized way with a view to optimally converting renewable resources into a broad range of bio-products, bio-materials and bio-energy. Since rational methods for pathway optimization are seriously flawed for example by the fragmentary knowledge of the various regulatory mechanisms affecting the flux through the pathway, (semi-)combinatorial approaches are popularly applied to address such multi-variate optimization questions. One major prerequisite, which considerably hinders the generic character of these combinatorial approaches, is the availability of efficient, reliable and high-throughput screens enabling the identification of improved phenotypes from massive combinatorial libraries. In this context, the development of a generic RNA-based biosensor could be of interest due to its versatile and programmable nature.

Here, we propose a framework for the automated design and construction of riboswitches. These genetic switches are completely folded RNA molecules which control gene expression in response to changes in metabolite concentrations. In a first phase, a model and automated optimization algorithm was developed to design riboswitches configurations with the desired properties. Next, the various designs were tested in vivo to determine their performance. In a second phase, the generated data is used to conduct data-driven optimization of the model. Ultimately, this approach can be used for the design of tailor made riboswitches with excellent performance.