
Model-based robust design of synthetic designer cells with minimum load for the host cell

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Abstract

By expressing pre-designed biological circuits, synthetic designer cells can detect disease markers and express therapeutic proteins on demand. During the past years, synthetic biologists started to assemble simple circuits into larger systems, in order to obtain more complex circuit behaviours with controlled features such as switches, amplifiers and pulse generators. Unfortunately, sub-modules characterized in different contexts often failed to operate as predicted when they were combined.

One reason for this lack of predictability is that synthetic genetic circuits are integrated into a host organism that has its own signalling circuitry and a limited amount of resources. Current design approaches most often aim to avoid influences of the host signalling on the synthetic circuit by designing orthogonal components, but unexpected interactions might still occur, and the interaction of a resource-consuming circuit with the host physiology cannot be avoided. For alternative designs of signalling systems, one could take advantage of endogenous pathways, which often show remarkable properties such as amplification and dose response alignment; totally synthetic signalling pathways with such properties would represent a huge load for the cell. However, current approaches that rewire endogenous pathways to desired synthetic inputs and outputs all disable the pathways' natural functions.

Here, we describe an alternative strategy to synthetic signalling systems that uses a few synthetic components to multiplex an endogenous signalling pathway to synthetic signals with minimal perturbation of the endogenous function of the pathway. We develop a proof-of-principle with the mating pathway in yeast. We combine systems biology inspired computational methods and state-of-the-art yeast experimental synthetic biology to design robust and minimal circuits able to achieve maximal insulation of the synthetic signalling pathway from the natural pheromone sensing - mating function, while both circuits share the same pathway. Our computational analysis suggests that with only five constructs we could encode the two input signals with different kinetics and decode these signals downstream, thereby achieving kinetic insulation of the two circuits. Topological filtering with efficient exploration of parameter spaces enables to further design and rank various minimal circuit topologies which achieve this goal and exhibit a maximal robustness, thus increasing the probability of

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success of the future experimental construction.

This proof-of-principle could pave the way towards a more integrative and host-aware synthetic biology. From a reverse engineering perspective, it could also unravel mechanisms explaining the cells' surprising ability to use always the same few pathways for many different functions.

Keywords: host, aware integrative modeling computational synthetic circuits multiplexing robustness mating pathway yeast