Explore design principles of signaling networks with *in silico* evolution of rule-based models

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***Short Abstract* — Systems and synthetic biologists aim to decipher the structure and dynamics of cellular networks underpinning specific responses, then to alter existing networks or engineer de novo ones. Both tasks could benefit from study of which structural and dynamic features can emerge from evolutionary processes, through which intermediary steps these arise, and whether they constitute key "design principles". Here, we present a design approach that focuses on *discovering* a range of possible signalling circuits with a given response dynamics. This approach combines *in silico* evolution and rule-based modelling of signalling proteins and their interactions. In particular, we evolve ultrasensitive and bistable signalling circuits that display both known and hereto unknown design features.**

***Keywords* — Design Principles, Signalling Networks, Evolution *in silico*, Rule-based Models, Computational Design**

I. Introduction

SIGNALING networks allow organisms to sense and process environmental information and thereby implement phenotypic behaviors that enable survival. It is of fundamental interest to understand the structure and dynamics of these cellular networks. In particular, systems biologists hope to be able to define common structural and dynamical features of networks that can be seen as "design principles" that are re-used in diverse systems, while synthetic biologists aim to utilize such design principles for reliable and modular engineering of biology [1]. One approach for understanding the evolutionary processes that lead to existing network elements, and for exploring the space of possible solutions, is to re-create the evolutionary dynamics of cellular networks *in silico*. Here, we present a design approach based on a novel combination of *in silico* evolution with a specific rule-based modeling of signaling proteins called Allosteric Network Compiler (ANC) [2]. The use of rule-based models allows us to define biochemical features of signaling proteins in detail, while overcoming the combinatorial explosion in model structure that arises from evolving protein interactions [3]. At its core, the rule sets in the ANC framework allows us to define any number of signaling proteins, each with a number of domains, and their interactions, i.e. a complete signaling circuit. Combining the ANC with an *in silico* evolutionary algorithm, we are able to evolve such signaling circuit models according to a user-defined fitness function [4].

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II. Results

We applied this approach to explore signaling circuit design exhibiting switch-like (i.e. ultrasensitive) and bistable response dynamics. These types of response dynamics are particularly important in information processing and decision-making in cells [5,6].

For signaling circuits with ultrasensitive response dynamics emerged from evolutionary simulations, approximately half of them utilize the zero-order sensitivity to get ultrasensitivity [6]. More interestingly, some evolved circuits displayed bistability, while, from previously reported works, the only suggested cases for bistability in phosphorylation based signaling networks were multi-site phosphorylation and positive feedback loops where phosphorylated proteins acted upon their own, upstream kinases [5,6,7]. The evolved bistable circuits we find displayed neither of these features. To better understand the role of allosteric regulation, we analyzed the simplest found circuit with bistability and further reduced its complexity by removing reactions from it. This led to a minimal design for bistability, in which we had a protein with a single phosphorylation site that is phosphorylated by an allosteric kinase.

III. Conclusion

This analysis demonstrates the power of an *in silico* evolution approach in designing signaling networks as well as the potentials for discovering design principles of ultrasensitive and decision making in cells.

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