Control Theory for Synthetic Biology

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Abstract:

About 20 years ago the first two human-made genetic circuits were built in living cells, demonstrating for the first time our ability to perform rational design with biological hardware. A new field was born, called "Synthetic Biology", with a mind-blowing vision in which genetic circuits made of biomolecules could be automatically designed to achieve capabilities such as curing cancer, regenerating damaged tissue, bio-sensing, materials and energy production. Today, despite remarkable successes, we are still largely unable to engineer sophisticated genetic circuits that behave as intended. This is especially due to lack of robustness to changes in extra and intra-cellular environment. Indeed, because a genetic module's input/output behavior changes in unpredictable ways upon inclusion into a larger system, each component is usually redesigned every time a new piece is added. In this talk, I will propose control theoretic approaches to engineer "insulation" of circuit components from its cellular environment. Specifically, I will focus on the problem of resource sharing and introduce a control-theoretic framework to address the insulation question. Within this framework, insulation of a subsystem can be mathematically formulated as a disturbance rejection problem; however, classical solutions are not directly applicable due to bio-physical constraints. I will thus propose a control design architecture that relies on time-scale separation, a key feature of biomolecular ractions, which gives rise to a singular singularly perturbed problem. I will give a solution to this problem based on input-to-state stability concepts; then, using the theory of monotone systems, I will address the stability question for the network of controlled genetic

subsystems that communicate through resource sharing. Based on these control designs, we built genetic resource decoupling devices, in both bacteria and mammalian cells, which effectively insulate any desired genetic module from its environment. These devices aid modularity, facilitate predictable composition of genetic circuits, and show that control theoretic approaches are needed to address pressing challenges in synthetic biology.