Discrete-Time L1 Adaptive Controller to Regulate In Vivo Protein Expressions

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Abstract: The application of DNA nanotechnology to interface with cellular environment provides tremendous opportunities to expand the synthetic biological circuits. The current application of DNA nanotechnology spans smart therapeutics (Douglas et al, Science 2012), drug delivery (Perrault, Shih, ACS Nano 2014), imaging (Choi et al, ACS Nano 2014), and probes for cell biology (Shaw et al, Nat Methods 2014). The excellent programmability of nucleic-acid-based parts would enlarge the space of complex functionalities realized in synthetic biological circuits. Building on our earlier works on DNA strand displacement circuits to regulate DNA tweezers driven by transcriptional oscillators, we show how discrete-time L1 adaptive controller can be used to deliver drugs *in situ* in response to cellular condition. For this, we replace the model predictive controller used (Menolascina et al, PLOS CB 2014). Our controller automatically regulates the administration of inducer molecules to the cells by comparing the actual protein expression level in the cell population with the desired expression level. We intend to use in the automated platform of (Menolascina et al, PLOS CB 2014) which is based on a microfluidic device, a time-lapse microscopy apparatus, and a set of motorized syringes, all controlled by a computer. They have tested the platform to force yeast cells to express a desired fixed, or time-varying, amount of a reporter protein over thousands of minutes. Here, the computer automatically switched the type of sugar administered to the cells, its concentration and its duration, according to the control algorithm. Our discrete-time L1 adaptive controller facilitates superior results on controlling expression of any protein, fused to a fluorescent reporter, provided that an external molecule known to (indirectly) affect its promoter activity is available.

Conceptually, our controller is also compatible to work with optogenetic systems that allow one to generate desired perturbations in the intracellular concentration of a specific protein in microbial cell culture. As light can be easily added and removed, this enables an easier dynamic control of protein concentration in culture than would be possible with long-lived chemical inducers. Implementation of this closed-loop control scheme is achieved by sampling individual cells from the culture apparatus, imaging and quantifying protein concentration, and adjusting the inducing light appropriately. The culturing apparatus can be operated as a chemostat, allowing one to precisely control microbial growth and providing cell material for downstream assays. Apart from the obvious applications in phenotype regulations, this method of specifically perturbing the concentration of a single protein and measuring the downstream signaling and transcriptional responses will allow experimentalists to make more informative perturbations to better elucidate the kinetics and architecture of biological networks for disease diagnosis and drug delivery.

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