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Vision article

Future systems and control research in synthetic biology

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ABSTRACT

Synthetic biology is the application of engineering principles to the fundamental components of biology, with the aim of creating systems with novel functionalities that can be used for energy, environment, and medical applications. While the potential impact of this new technology is enormous, there are challenges that we need to overcome before the impact of synthetic biology can be fully realized. Many of these challenges fall beyond the scope of molecular biology and are indeed "system-level" problems, where very little research is being performed. This paper identifies pressing challenges in synthetic biology that can be formulated as systems and control theoretic problems and outlines potentially new systems and control theories/tools that are required to tackle such problems. The aim is to attract more systems and control theorists to collaborate with molecular biologists and biophysicists and help synthetic biology reach its promise. At the same time, engaging the systems and control community more broadly into the rich research opportunities and life-changing applications of synthetic biology may provide added visibility to the field of systems and controls.

Contents

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1. Introduction

Synthetic biology is an emergent interdisciplinary field of research, whose aim is to engineer biomolecular systems to achieve useful functionalities. Synthetic biology provides powerful tools to address many pressing societal needs. For example, in the past decade, researchers in synthetic biology have created engineered bacteria that can produce biofuel (Peralta-Yahya, Zhang, del Cardayre, & Keasling, 2012) and sense heavy metals (van der Meer & Belkin, 2010), genetic circuits that can reprogram cell identity to treat diabetes (Saxena et al., 2016), and engineered immune cells that can track and kill cancer cells (Chakravarti & Wong, 2015). While these efforts, among many others, demonstrate the great impact that synthetic biology can have on society, they also currently remain mostly at the laboratory stage. In fact, most synthetic genetic circuits constructed nowadays rely on lengthy and *ad hoc* design processes that do not yet give predictable outcomes in less controlled environmental conditions. Overall, poor robustness, lack of reliability, and the current inability to predict the emergent behavior of many interacting genetic components are hampering progress in this field.

The origins of these problems can to some extent be traced back to molecular biology issues, such as the reliability and orthogonality of genetic parts, and intense research efforts are underway in this direction (see Arpino et al., 2013; Kosuri et al., 2013, for example). To a large extent, however, issues of robustness, reliability, and predictability are due to the complex dynamic interactions among system components and can be classified as "system-level" problems that fall beyond the scope of molecular biology. Comparatively, in these problems, very little research is being performed. In addition, as we discuss in more detail in Section 3, existing theoretical tools and mathematical frameworks adopted directly from engineering systems are often unsuitable and/or inefficient to deal with the level of complexity in biomolecular systems. The aim of this paper is to provide a perspective on future systems and control research that can help solve a wide range of system-level problems in synthetic biology, with the hope to attract more systems and control engineers to the many interesting open questions in synthetic biology that may have life-changing applications.

This paper is not a comprehensive review of synthetic biology. Instead, it is a vision paper aimed at motivating future theoretical research and new mathematical frameworks that could facilitate the design, analysis, and verification of synthetic genetic circuits and is intended for readers with a background in systems and control theory. Nevertheless, we should clarify that mathematical tools are valuable to synthetic biology only if they are aware of the domain-specific constraints, such as limitations of a biophysical model and the available design parameter space. In fact, many of the problems we describe here reflect such needs. After a brief introduction to synthetic biology, we identify a few pressing system-level challenges that are hampering the development of synthetic biology in Section 3. In particular, the problems of compositionality, stochasticity, and spatial heterogeneity largely limit the scalability and complexity of synthetic biological systems that we can build today. In Section 4, we highlight future research opportunities that can potentially benefit the characterization, design, verification, implementation, and re-design of synthetic biological systems, which can help this nascent field move forward. Some problems may involve adopting existing systems and control theoretic tools to entirely new contexts, while many others require creating novel theories and mathematical frameworks that are complementary to existing ones.

This paper is largely based on the outcome of an AFOSR-funded workshop titled "The Compositionality Problem in Synthetic Biology: New Directions for Control Theory" held on June 26–27, 2017 at MIT. The workshop was co-organized by D. Del Vecchio, R. M. Murray, and E. D. Sontag and was attended by the participants listed in the acknowledgements at the end of this paper.

2. A Glimpse into synthetic biology

The ability of all living organisms to sense, communicate, and make decisions relies on a handful of highly conserved core biological processes such as gene regulation and protein-protein interactions. These, among many others, are used as functional building blocks in the *de novo* creation of genetic circuits (Fig. 1).

2.1. Brief history

The roots of synthetic biology can be traced back to the Nobel winning discovery of the lac operon's regulation in bacteria *E. coli* by Jacob and Monod in the early 1960s (Jacob & Monod, 1961). The fact that a protein (called a transcription factor) can bind the promoter region of the gene of another protein to regulate (i.e., either activate or repress) its rate of synthesis allows us to view the gene expression process as a dynamical system with an input and an output (Fig. 1-A), with a hope that these input/output (I/O) systems can be composed together to build more sophisticated functionalities. The advancement of biotechnology since the late 1960s has enabled time and cost-efficient technological tools to extract, sequence, amplify, and insert foreign DNA elements into cells (Cameron, Bashor, & Collins, 2014). In the year 2000, the first two synthetic genetic circuits were constructed: an oscillator (Elowitz & Leibler, 2000) and a toggle switch (Gardner, Cantor, & Collins, 2000). Although these circuits were built with the aim to understand natural systems, they clearly demonstrated our technological capabilities to create *de novo* functional dynamics through model-based design of gene regulation. In the early 2000s, a number of small-scale synthetic genetic circuits, or functional modules, were constructed (Fig. 1-B), including various forms of logic gates, cell-cell communication modules, cascades, feedback loops, and feedforward motifs (see Cameron et al., 2014; Del Vecchio, Dy, & Qian, 2016; Hsiao, Swaminathan, & Murray, 2018, in press; Qian, McBride, & Del Vecchio, 2018 for more details). The successful assembly of biological parts into functional modules triggered the first wave of applications of synthetic biology, a few noticeable examples include environmental biosensors, *ex vivo* cell type classifiers (Xie, Wroblewska, Prochazka, Weiss, & Benenson, 2011), and biofuel production pathways (Peralta-Yahya et al., 2012) (see more examples in Ruder, Lu, and Collins (2011) and Khalil and Collins (2010)).

In the past decade, research efforts can be roughly categorized as moving along two orthogonal directions. In one direction, efforts concentrated on discovering, creating, and characterizing biological parts and tools (see, for example, Arpino et al., 2013). In the other direction, efforts focused on increasing the complexity of circuits by establishing general approaches to combine available parts and modules into larger systems (Purnick & Weiss, 2009) (Fig. 1-C). This is motivated by the need for sophisticated circuit functionalities in most emerging applications of synthetic biology, such as those in the health industry. For example, in cancer immunotherapy, T cells need to be engineered to sense, track, and attack cancer cells while avoiding side effects to normal cells (Chakravarti & Wong, 2015); when using cell-fate reprogramming to produce insulin-secreting beta cells, the level

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