Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Systems Biology

# New opportunities for optimal design of dynamic experiments in systems and synthetic biology

Nathan Braniff and Brian Ingalls

**Abstract**

Recently developed dynamic experimental techniques offer new opportunities for the use of model-based experimental design in the construction and refinement of predictive models of cellular behaviour. Specifically, novel optogenetic and microfluidic tools have been made accessible by the distribution of low-cost, automated hardware designs that rely on readily available components and inexpensive construction processes. Experimental design methods can be applied to these platforms to identify time-varying input signals that generate maximally informative system responses. We review these developments and illustrate how the convergence of these approaches facilitates the construction of accurate biological models of both natural and engineered cellular systems.

**Addresses**

Department of Applied Mathematics, University of Waterloo, 200 University Ave W., Waterloo, Ontario, Canada

Corresponding author: Ingalls, Brian (bingalls@uwaterloo.ca)

**Current Opinion in Systems Biology** 2018, ■:1–7

This review comes from a themed issue on **Mathematical modelling (2018)**

Edited by **Leah Edelstein-Keshet** and **William Holmes**

For a complete overview see the Issue and the Editorial

Available online xxx

https://doi.org/10.1016/j.coisb.2018.02.005



**Keywords**

Model-based design of experiments, Optimal experimental design, Mathematical modeling, Systems biology, Synthetic biology, Optogenetics, Microfluidics, Dynamic experiments, Cybergenetics.

## Introduction

Quantitative characterization of the dynamic (time-varying) behavior of cellular systems is central to systems and synthetic biology. In systems biology, mathematical models are used to generate testable hypotheses and to provide insight into the behavior of natural systems. In synthetic biology, predictive models are increasingly needed to guide design, in the tradition of more established engineering disciplines. Unfortunately, biological models are often poorly constrained. This is, in part, due to a lack of appropriate data (e.g. time-series), the collection of which has traditionally required specialized commercial equipment or laborious protocols.

We review a maturing set of accessible techniques for precise dynamic perturbation and observation of cellular systems, and the low-cost, automated equipment that enable their implementation. These techniques can generate a wide range of dynamic excitations not previously achievable, and thus raise the question: what excitation profiles should be applied? Model-based design of experiment (MBDOE) tools can be used to answer this question. These tools provide a framework in which researchers can formalize their experimental goals and identify time-varying stimuli to accomplish them. We begin this brief review with a survey of recent innovations in experimental devices and protocols that facilitate the generation of broad classes of dynamic stimuli. We then provide an overview of model-based experimental design methods and review examples demonstrating their practical use for dynamic experimental design. Together these advances offer an effective work-flow, shown in Figure 1, for the design and implementation of dynamic biological experiments.

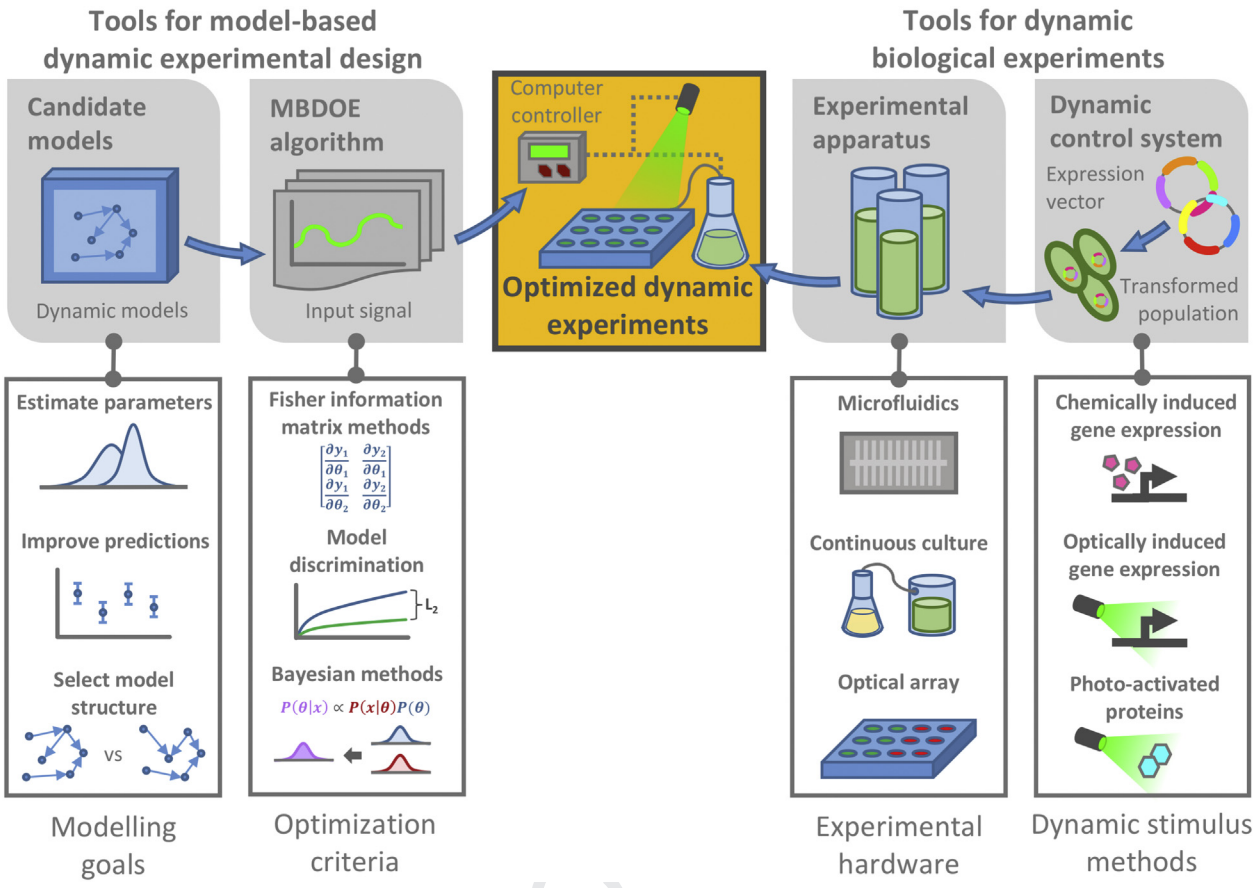
## Time-varying control of cellular systems

Traditional experimental protocols allow for only a limited selection of temporal perturbation patterns (e.g. steps, sometimes pulses). In contrast, optical inputs and microfluidic delivery enable a wide range of time-varying stimuli. In addition, automated culture systems (turbidostats, chemostats) provide precise environmental control, uncoupling dynamic cellular responses from exogenous effects. For a recent review of developments in this area, see Ref. [1]. Below, we highlight works that exemplify the flexibility and precision of these dynamic techniques. We then survey a range of community-developed automated and accessible hardware for efficient implementation of these experimental approaches.

### Experimental tools for dynamic stimuli

The range of available light-induction systems is growing rapidly [2,3]. Optical stimulus tools have become increasingly popular for precision dynamic perturbation experiments [4]. Toettcher et al. [5] used optically-regulated protein–protein interactions to control the translocation dynamics of signaling proteins. They used automated microscopy measurements and light delivery to implement predefined translocation dynamics, to control population heterogeneity, and to implement robust clamping of targeted intracellular species. Milias-Argeitis et al. [6] demonstrated similar results using an optogenetic system and a computerized

**Figure 1**




*Design and implementation of dynamic biological experiments.* Tools for model-based experimental design (left): Systems biologists often seek to improve a model by more accurately constraining its parameters, its predictions, or its structure. Model-based design of experiment (MBDOE) methods identifies time-varying perturbation stimuli to achieve these goals via a range of optimization criteria. Tools for dynamic biological experiments (right): Temporal perturbation profiles can be realized with a range of emerging biological tools. Low-cost and open-source hardware systems can implement these dynamic experiments efficiently, resulting in informative experiments and improved model accuracy.

feedback circuit to control gene expression in real time. This *in silico* control set-up achieved robust, accurate tracking of reference concentration profiles and was used to mediate growth rates via feedback control of an essential metabolic enzyme [7]. In related work, Melendez et al. employed optogenetic induction in a chemostat system with microfluidic sampling and microscopy to demonstrate precise control of protein expression in a steady state microbial culture [8].

Several groups have made use of the CcaS/CcaR system for optogenetic control in bacteria. This light-responsive cyanobacterial two-component system was cloned into *Escherichia coli* by Tabor et al. [9]. Olson et al. have since developed the CcaS/CcaR system into a precise tool for gene expression control using parallelized delivery of light to an array of culture tubes, enabling more complex experiments and improved dynamic characterization [10]. They determined the response of the CcaS/CcaR system to a range of light stimulus profiles, and further demonstrated precise and predictive model-based control of the system in validation experiments. In complementary work, Davidson et al. characterized the response of the CcaS/CcaR optogenetic system to pulse width modulations [11]. More recently, Chait et al. [12] combined CcaS/CcaR optogenetic induction with microfluidic control of media contents and single-cell microscopy to achieve closed-loop control of single-cell and population-wide gene expression patterns.

Similar optical control strategies have been employed to reveal naturally occurring signaling network behaviour, via a photoactivateable adenylate cyclase stimulating the PKA pathway in yeast [13] and phytochrome-B-PIF activation of Ras/Erk in mammalian cells [14], providing insights into network structure and dynamic response.

Microfluidic approaches allow precise temporal manipulation of media contents [1]. Uhlendorf et al. employed a microfluidic chamber with real-time microscopy to implement a computer-in-the-loop controller of gene expression, resulting in tight regulation of variance in