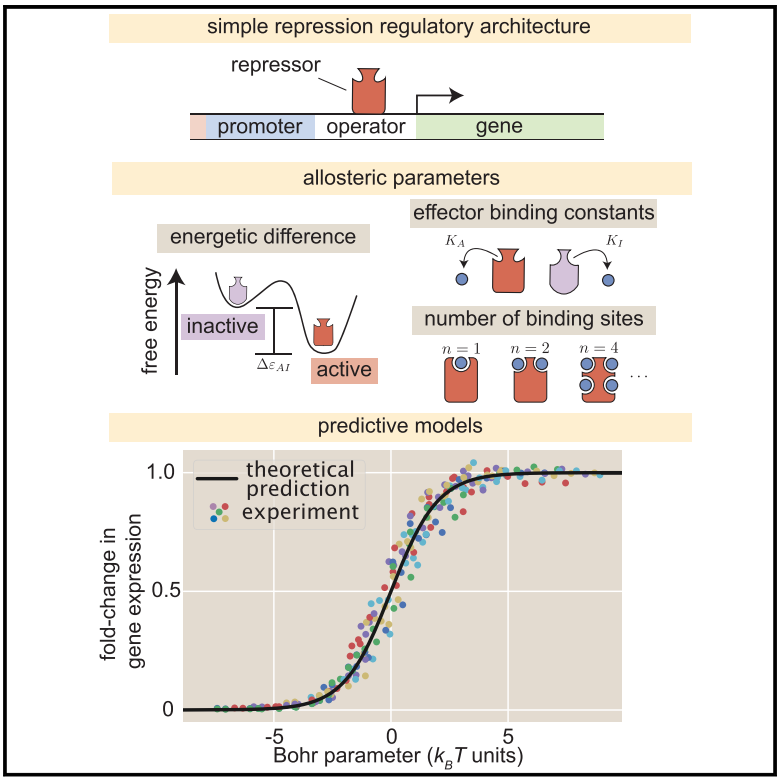
Article

Cell Systems

Tuning Transcriptional Regulation through Signaling: A Predictive Theory of Allosteric Induction

Graphical Abstract



Highlights

- The MWC model is used to understand allosteric transcription factor regulation
- Properties of predicted gene expression profiles are validated using LacI
- The data points collapse as a function of a key combinations of parameters

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In Brief

Allosteric regulation is found across all domains of life, yet we still lack simple, predictive theories that link the experimentally tunable parameters of such systems to their input-output response. We present a general theory of allosteric transcriptional regulation that is rigorously tested using a well-characterized regulatory system in bacteria. Our model not only accurately captures our data, but also enables us to derive analytic expressions for key phenotypic properties and is broadly applicable to other regulatory systems in bacteria.

Razo-Mejia et al., 2018, Cell Systems 6, 1–14
April 25, 2018
https://doi.org/10.1016/j.cels.2018.02.004

CellPress

Please cite this article in press as: Razo-Mejia et al., Tuning Transcriptional Regulation through Signaling: A Predictive Theory of Allosteric Induction, Cell Systems (2018), https://doi.org/10.1016/j.cels.2018.02.004

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Tuning Transcriptional Regulation through Signaling: A Predictive Theory of Allosteric Induction

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SUMMARY

Allosteric regulation is found across all domains of life, yet we still lack simple, predictive theories that directly link the experimentally tunable parameters of a system to its input-output response. To that end, we present a general theory of allosteric transcriptional regulation using the Monod-Wyman-Changeux model. We rigorously test this model using the ubiquitous simple repression motif in bacteria by first predicting the behavior of strains that span a large range of repressor copy numbers and DNA binding strengths and then constructing and measuring their response. Our model not only accurately captures the induction profiles of these strains, but also enables us to derive analytic expressions for key properties such as the dynamic range and [EC_{50}]. Finally, we derive an expression for the free energy of allosteric repressors that enables us to collapse our experimental data onto a single master curve that captures the diverse phenomenology of the induction profiles.

INTRODUCTION

Understanding how organisms sense and respond to changes in their environment has long been a central theme of biological inquiry. At the cellular level, this interaction is mediated by a diverse collection of molecular signaling pathways. A pervasive mechanism of signaling in these pathways is allosteric regulation, in which the binding of a ligand induces a conformational change in some target molecule, triggering a signaling cascade (Lindsley and Rutter, 2006). One of the most important examples of such signaling is offered by transcriptional regulation, whereby a transcription factor's propensity to bind to DNA will be altered upon binding to an allosteric effector.

Despite allostery's ubiquity, we lack a formal, rigorous, and generalizable framework for studying its effects across the broad variety of contexts in which it appears. A key example of this is transcriptional regulation, in which allosteric transcription factors can be induced or corepressed by binding to a ligand. An allosteric transcription factor can adopt multiple conformational states, each of which has its own affinity for the ligand and for its DNA target site. *In vitro* studies have rigorously quantified the equilibria of different conformational states for allosteric transcription factors and measured the affinities of these states to the ligand (Harman, 2001; Lanfranco et al., 2017). Despite these experimental observations, the lack of a coherent quantitative model for allosteric transcriptional regulation has made it impossible to predict the behavior of even a simple genetic circuit across a range of regulatory parameters.

The ability to predict circuit behavior robustly—that is, across both broad ranges of parameters and regulatory architectures—is important for multiple reasons. First, in the context of a specific gene, accurate prediction demonstrates that all components relevant to the gene's behavior have been identified and characterized to sufficient quantitative precision. Second, in the context of genetic circuits in general, robust prediction validates the model that generated the prediction. Possessing a validated model also has implications for future work. For example, when we have sufficient confidence in the model, a single dataset can be used to accurately extrapolate a system's behavior in other conditions. Moreover, there is an essential distinction between a predictive model, which is used to predict a system's behavior given a set of input variables, and a retroactive model, which is used to describe the behavior of data that has already been obtained. We note that even some of the most careful and rigorous analysis of transcriptional regulation often entails only a retroactive reflection on a single experiment. This raises the fear that each regulatory architecture may require a unique analysis that cannot carry over to other systems, a worry that is exacerbated by the prevalent use of phenomenological functions (e.g., Hill functions or ratios of polynomials) that can analyze a single dataset but cannot be used to extrapolate a system's behavior in other conditions (Setty et al., 2003; Poelwijk et al., 2011; Vilar and Saiz, 2013; Rogers et al., 2015; Rohlhill et al., 2017).