

# When activators repress and repressors activate: a qualitative analysis of the Shea-Ackers model

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Synthetic biology suggests the possibility of developing organisms with different functional abilities. Producing such organisms may require a deep understanding of signal transduction/gene regulatory network designs. Despite recent successes of synthetic biology, much remains to be understood.

On the network level Alon [2] provides a compelling framework for understanding the design principles of biological circuits as it relates local models for transcriptional regulation and network design to phenomenological function of the system. The local model uses the concept of regulated recruitment [4], wherein the rate of transcription of mRNA is determined by concentrations of regulatory proteins, often referred to as activators and repressors. As the names suggest activators enhance and repressors decrease the rate of transcription. For the most part, Hill functions are used in [2] to model the transcription rate. These are monotone functions of the regulatory protein  $r$ .

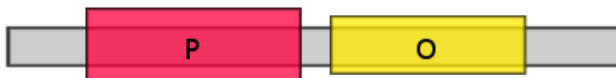


Figure 1: Simple Regulatory Region

The assumption of monotone regulatory interaction is widespread. The most common representation of a regulatory network is a graph with vertices corresponding to the chemical

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species or genes and edges corresponding to reactions. Each reaction is usually labelled with a positive or a negative sign corresponding to up- or down-regulation. Considerable effort has been spent deducing dynamics and function from such representations of a network [2]. The theory of motifs is a result of such activity.

Assuming chemical equilibrium Shea and Ackers [1] construct a nonlinear model for the rate of transcription. It starts with a concept of a state  $s$  of the promoter whose probability of occurrence is

$$\mathbb{P}(s) = \frac{K_B(s)[P]^{\alpha_s}[r_1]^{\alpha_s^1}[r_2]^{\alpha_s^2}\dots[r_m]^{\alpha_s^m}}{Z},$$

where  $Z$  is a partition function,  $[r_i]$  is the concentration of the  $i$ -th regulator,  $[P]$  is the concentration of RNAP, and  $K_B(s)$  is a rate constant. The exponents  $\alpha_s^i$  indicate the number of  $r_i$  molecules bound to the regulatory region in state  $s$ . If  $k(s)$  is the rate of transcription initiation for state  $s$ , then the Shea-Ackers function is given by  $f([P], [r_1], \dots, [r_m]) = \sum_{s \in \mathcal{S}} k(s)\mathbb{P}(s)$ .

The Shea-Ackers model provides a broadly accepted quantitative framework and has been experimentally validated for a variety of gene networks. Since the Hill function is derived from the assumption of equilibrium binding of one transcription factor to the promoter, the Shea-Ackers nonlinearity is a generalization of the Hill function that naturally allows for multiple binding factors.

Given a state  $s$  its *binding dependence constant* is defined by  $\beta_s := \frac{K_B(s)}{\prod_{i=1}^m K_B(s_i)}$  where  $s_i$  are the corresponding elementary states in which only one regulatory protein is bound. The value  $\beta_s > 1$  indicates cooperative binding. Similarly,  $\phi_s$  is the *normalized transcription initiation constant* is  $\phi_s := \frac{k(s)}{k_P}$ . Again,  $\phi_s > 1$  infers cooperative transcription initiation.

The association constants and the initiation rate constants are the fine levers by which the cell controls transcription and they can be measured. Of course, what is of interest to systems biologists is the effect of particular regulators on transcription. A regulatory protein  $r$  is a *phenomenological activator (repressor)* for a gene if the transcription rate of this gene always increases (decreases) with the concentration of  $r$ , that is,  $\frac{\partial f}{\partial [r]} > 0$  ( $\frac{\partial f}{\partial [r]} < 0$ ) for all  $[r] \geq 0$ .

In this contribution, we show that the correspondence between  $\phi_s > 1$  or  $\beta_s > 1$  and phenomenological activation holds only for the simplest of the promoters (see Figure 1) which consists of a single binding site of a regulator and a single binding site for RNAP. For this promoter, the regions in  $\beta_s, \phi_s$  space where the regulator is an activator or repressor are depicted in Figure 2. The nonlinear character of this relationship leads us to define a new regulatory constant  $\rho_r := \frac{\phi_r \beta_r (1 + K_P [P])}{1 + \beta_r K_P [P]}$  which defines a transparent relationship between regions of monotonicity. Indeed for a simple regulatory region the regulatory protein  $r$  is a phenomenological activator (repressor) if and only if  $\rho_r > 1$  ( $r < 1$ ). (See figure 2)

The regulatory constant  $\rho_r$  also simplifies considerably the characterization of activation verses repression for more complicated promoters. We analyze a single binding site with multiple regulatory proteins, a promoter with one regulatory protein that has two possible binding sites, and finally a gene with two regulators and two binding sites. We apply our results to the phage  $\lambda$ , *lac* operon and many other operons.

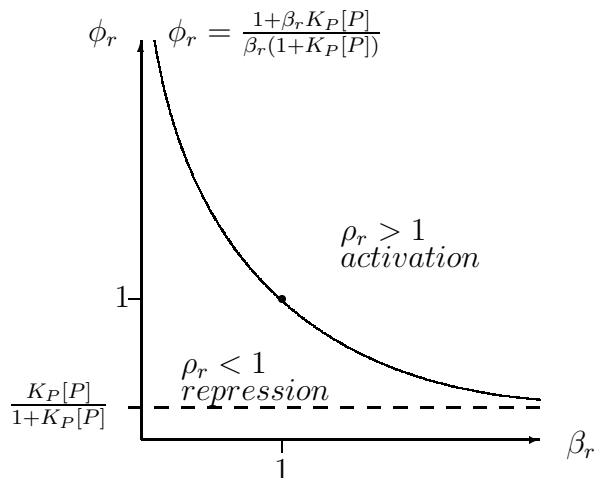


Figure 2: The dependence constant and the normalized transcription initiation constant determine whether a regulator is a phenomenological activator or repressor for a simple promoter.

**Discussion** The mathematical implications of non-monotone reaction functions can be significant. As an example, the global dynamics of cyclic feedback systems with arbitrarily many components with monotone reaction functions exhibits very simple dynamics; asymptotically one can have only equilibria or periodic orbits. However, if the reaction functions are not monotone, then one can have chaotic dynamics [3].

In principle, the lack of monotonicity of the Shea-Ackers function could have an equally significant impact on the conclusions expressed in [2] concerning the design principles of biological circuits. In reality, it is quite possible that the biologically constrained parameters prevent this non-monotonicity. Understanding and design of transcriptional regulation requires the ability to easily identify the appropriate constraints on the set of states, their association constants, and their initiation rate constants.

## References

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