Patterns of Activation and Repression for a Single Transcription Factor with Multiple Binding Sites

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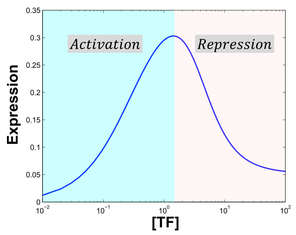
Abstract

We seek to understand how a single type of transcription factor regulates gene expression (in eukaryote) by studying the previously introduced linear framework-based model of the gene regulation function (GRF), which employs higher-order cooperativities of transcription factors (TFs) and DNA polymerase. We looked at whether it is possible to have multiple windows of "activation" and "repression" and the necessary mechanisms, such as numbers of sites or forms of higher-order cooperativity, to achieve such pattern.

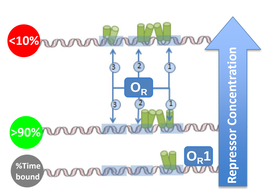
Introduction

The molecular complexity of eukaryotic gene regulation has made it difficult to study gene products, which are processed from DNA sequences. We built mathematical models of gene expression based on the established linear framework. In this project, we want to know how complicated the gene expression profile can be when a single type of transcription factor binds to multiple sites. The lambda phage repressor is a classical example of an actual gene that has both “activation” and “repression.”

More Complicated Pattern



The Lambda Repressor



We investigate the parameters of the gene regulation functions (GRFs), such as higher-order affinity binding and cooperativity of TFs and polymerase. We gained insights to the GRFs’ behavior though (1) random exploration, (2) clustering parameters based on the characteristics of the GRFs, and (3) modular exploration.

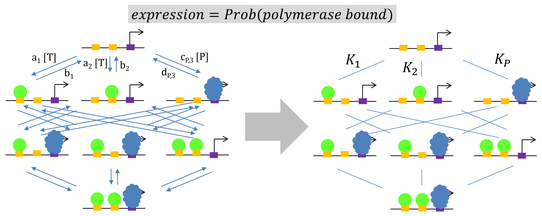
The Model

Parameters of the model:

$$K_{i,S}=\frac{a_{i,S}}{b_{i,S\cup t}},\qquad \omega_{i,S}=\frac{K_{i,S}}{K_{i,\emptyset}},\qquad \kappa_i=\frac{K_{i,\emptyset}}{K_{1,\emptyset}},$$

$$K_{P,S}=\frac{c_S}{d_S},\qquad \omega_{P,S}=\frac{K_{P,S}}{K_{P,\emptyset}}.$$

$expression = Prob(polymerase\ bound)$



$state\ probability = p(\boldsymbol{a}, \boldsymbol{b}, [T])$ $\qquad$ $state\ probability = P(\boldsymbol{K}, \Omega, [T])$

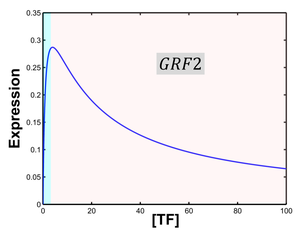
A gene regulatory function that outputs the rate of gene expression as a function of TF concentration, x, is

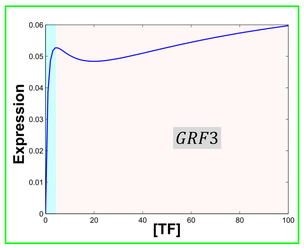
$$\frac{d[mRNA]}{dx} = \frac{\text{microstates where transcription is occuring}}{\text{all microstates}} = \frac{p_1x+p_2x^2+\cdots+p_nx^n}{c_0+c_1x+c_2x^2+\cdots+c_nx^n}$$

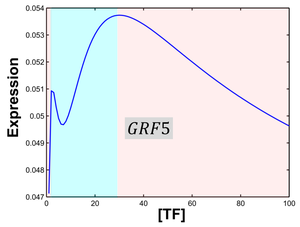
The coefficient p_k collects microstates with the polymerase bound and the coefficient c_k collects all microstates with k sites bound by TF.

Results

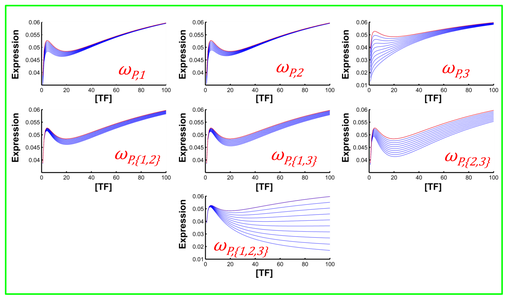
Observed Behaviors



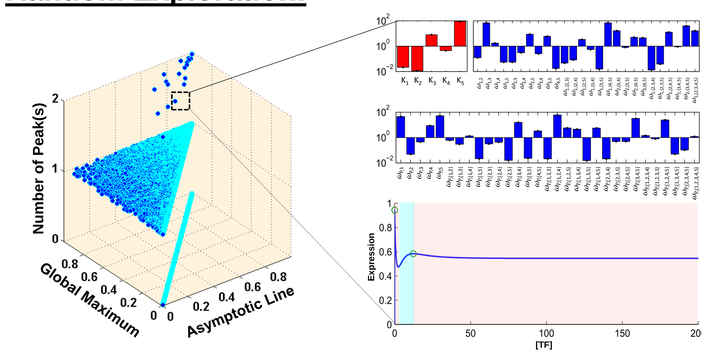




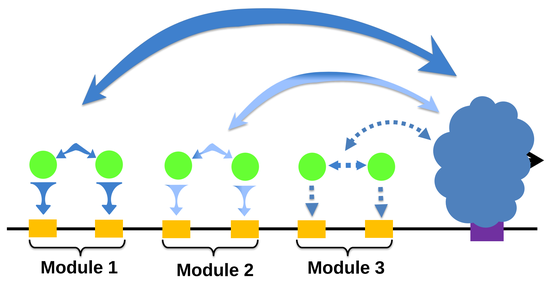
No single parameter controls the peak

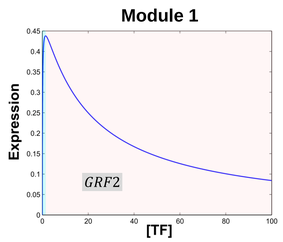


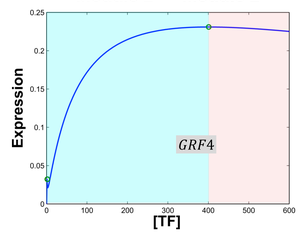
Random Exploration:

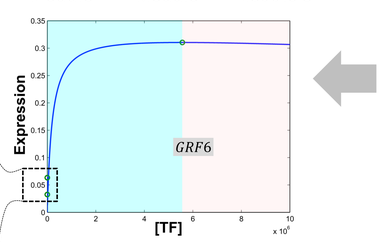


Modular Exploration:

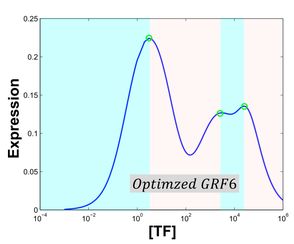








Optimization



Discussion & Conclusion

- The effect of the parameters on the GRFs is global.
- Condition to have a peak: $p_2c_1-p_1c_2<0$, or $\frac{p_2}{c_2}<\frac{p_1}{c_1}$.
- The location of the peak in the case of $n=2$ sites is:
  $$\frac{-p_2c_0+\sqrt{p_2^2c_0^2-4(p_2c_1-p_1c_2)}}{p_2c_1-p_1c_2}.$$
  → hard to control, modular becomes difficult.
- To move peak further → increase c_0 or decrease $|p_2c_1-p_1c_2|$.
  → much of the behavior of the peak depends on $p_2c_1-p_1c_2$.
- Hypothesis: There are $n-1$ possible sign-change(s) for a graph of n vertices.
  → not validated, but fits our examples.

Future Directions

- To make better plots of multiple peaks → optimize the distance between local maxima and adjacent minima.
- To gain more mathematical insights → optimize the area of parameters that gives rise to each peak.
- Vary the non-dimensionalized **[P]** to study its effects on the GRFs.
- Further step: Incorporate multiple TFs with both “activating” and “repressing” higher-order cooperativities.

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Acknowledgements

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