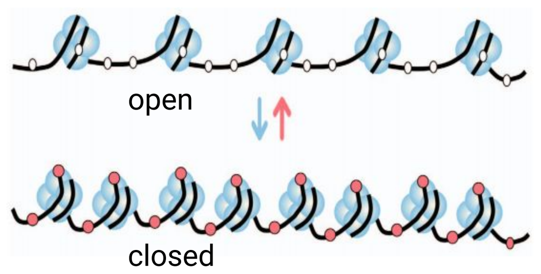
Non-monotonicity of Gene Regulation Functions

Sophie Woodward, advised by Dr. Rosa Martinez-Corral
Gunawardena group, Systems Biology, Harvard Medical School

Overview

Gene regulation, which determines how genes are expressed, is a fundamental process of every living cell. In eukaryotes, gene regulation consists of many stages which require energy. The function of this energy, however, is not well understood. In particular, I want to know how energy expenditure influences the monotonicity of the gene regulation function (GRF), which relates transcription factor (TF) concentration to gene expression. At equilibrium, average binding GRFs are proven to be monotonic, but away from equilibrium, average binding GRFs may be non-monotonic.



Assumptions

- Two TF binding sites, pairwise cooperativity
- Two conformations (open, closed chromatin)
- Average binding (expression of microstate proportional to #sites bound by TF)
- Following the Linear Framework (Gunawardena 2012)[1]

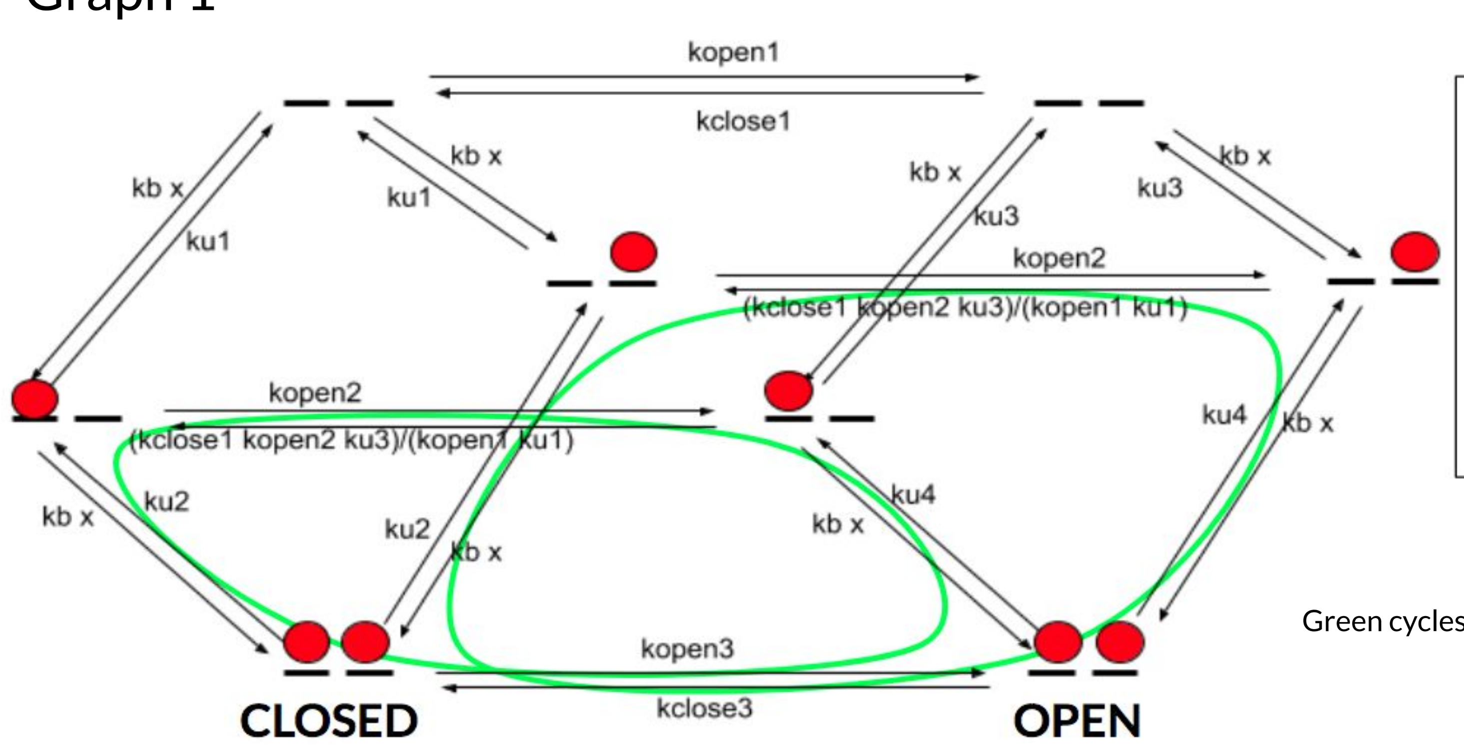
1. Gunawardena J (2012) A Linear Framework for Time-Scale Separation in Nonlinear Biochemical Systems. PLoS ONE 7(5): e36321. https://doi.org/10.1371/journal.pone.0036321

Methods

- Sampled parameters (kb, ku1,...) uniformly at random from logscale (-3,3).
- Discarded parameter sets that do not follow constraints.
- Generated one million non-monotonic parameter sets per graph.

Graphs

Graph 1



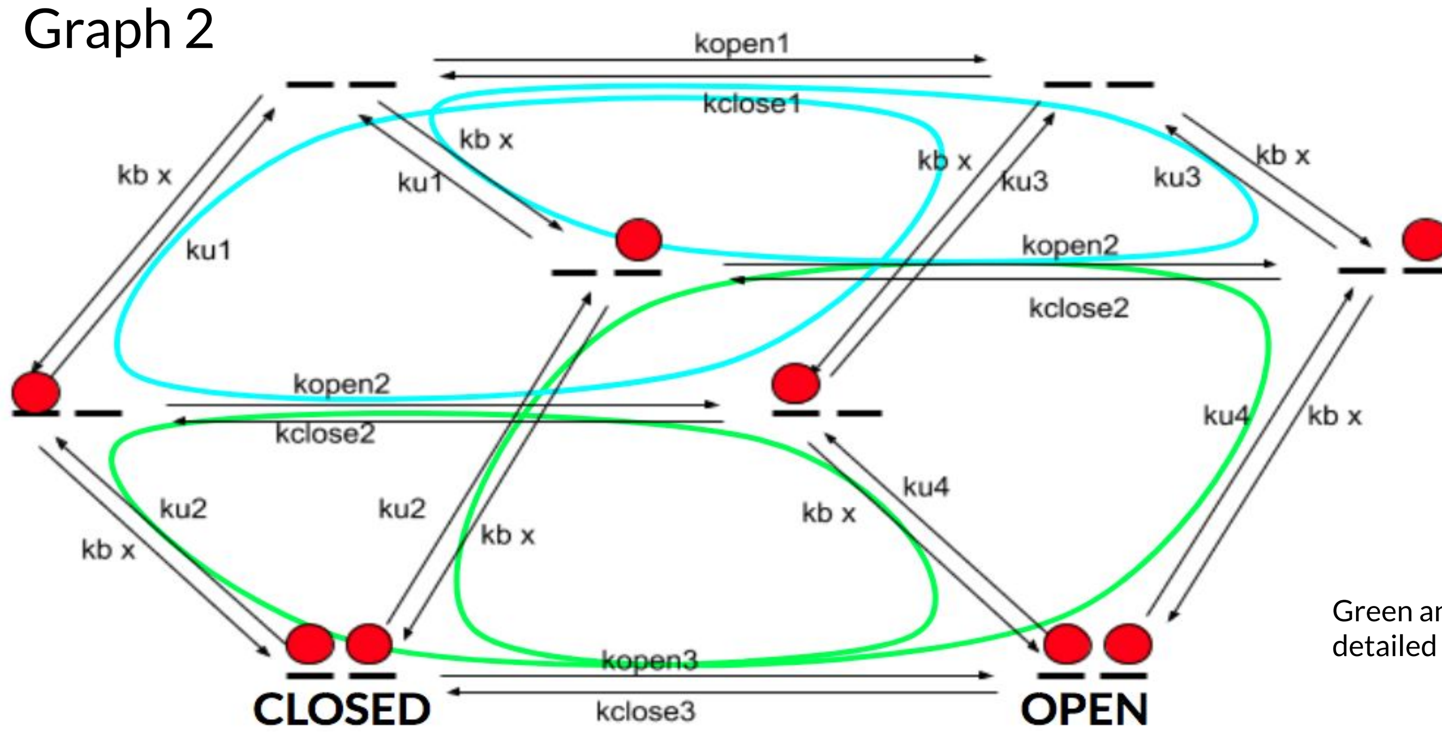
CONSTRAINTS

- kopen2>kopen1
- kopen3>kopen2

- ku2<ku1
- ku3<ku2
- ku4<ku3

Green cycles break detailed balance

Graph 2



CONSTRAINTS

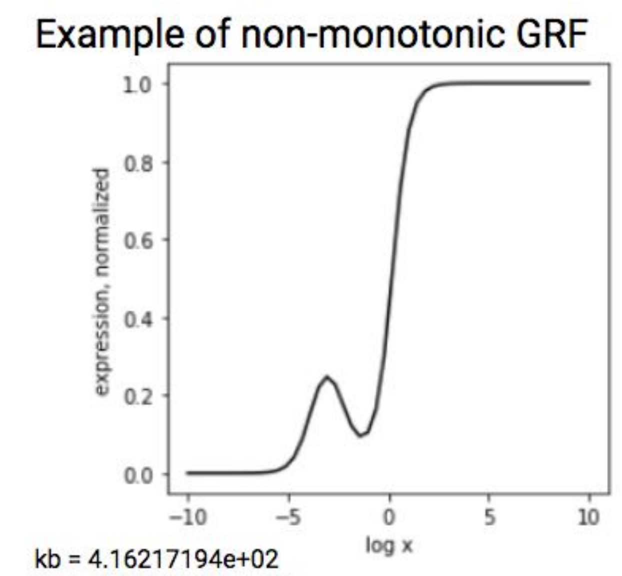
- kopen2>kopen1
- kopen3>kopen2

- ku2<ku1
- ku3<ku2
- ku4<ku3

Green and blue cycles break detailed balance

Non-monotonics of Graph 1

Example of non-monotonic GRF

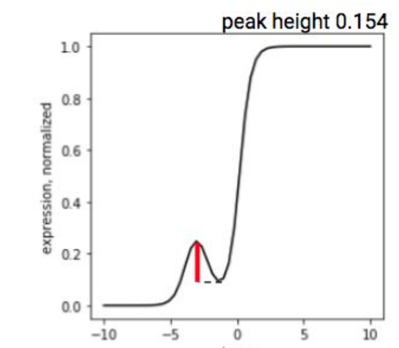


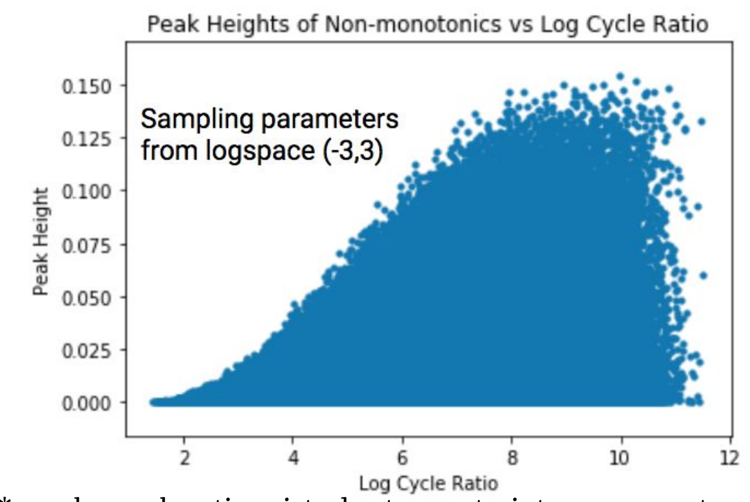
kb = 4.16217194e+02
ku1 = 7.98626645e+02
ku2 = 6.67969941e+02
ku3 = 1.53739409e-01
ku4 = 1.58984643e-02
kopen1 = 1.41480075e+00
kclose1 = 2.25156386e-01
kopen2 = 3.58383587e+01
kopen3 = 7.51160369e+01
kclose3 = 5.12093262e+02

Non-monotonics maintain the "cycle ratio inequality": around the green cycle, Clockwise product of edge labels> counterclockwise product of edge labels.

I.e. kopen2 kb kclose3 ku2 > (kclose1 kopen2 ku3)/(kopen1 ku1) kb kopen3 ku4
Simplifies to: **kclose3 ku2 ku1 kopen1 > kopen3 ku4 ku3 kclose1**

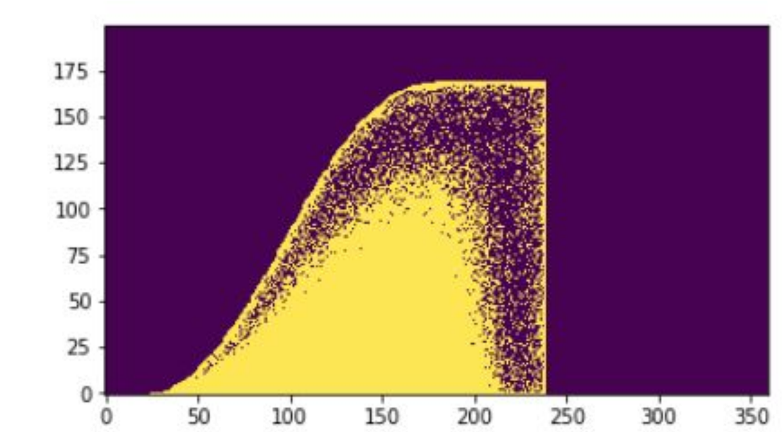
peak height of non-monotonic GRF as a primitive way of quantifying non-monotonicity





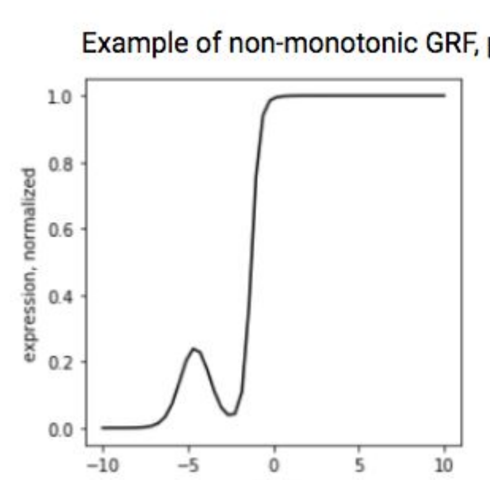
*max log cycle ratio exists due to constraints on parameters

Results of Boundary Finder algorithm, performed on O2 HMS cluster

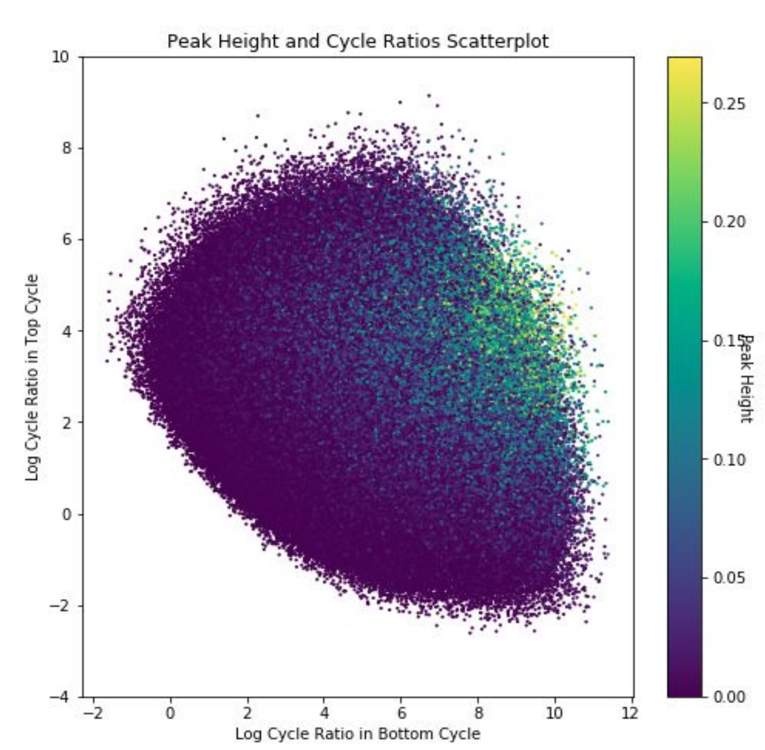


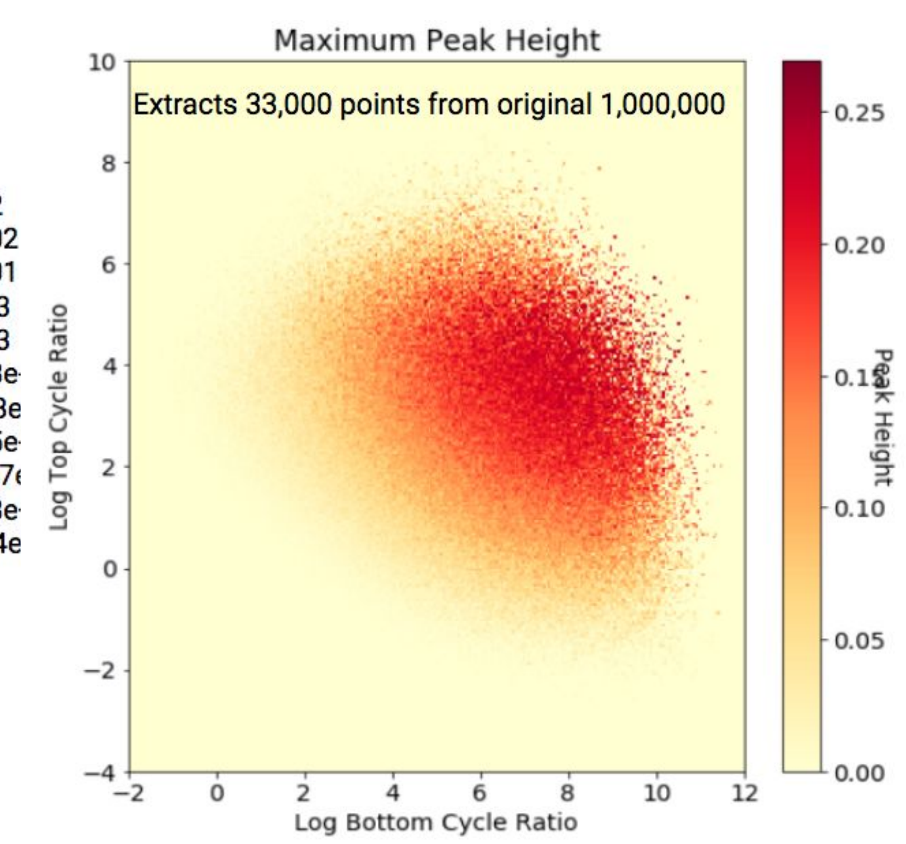
Non-monotonics of Graph 2

Example of non-monotonic GRF, peak height 0.203



kb = 8.47922280e+02
ku1 = 4.46388647e+02
ku2 = 2.32461913e+01
ku3 = 4.59410868e-03
ku4 = 3.74849009e-03
kopen1 = 8.94715808e
kclose1 = 1.02488688e
kopen2 = 1.03786855e
kclose2 = 4.76990747e
kopen3 = 1.74883388e
kclose3 = 3.89451164e





1885 nonmon parameter sets broke bottom cycle ratio inequality.
86889 nonmon parameter sets broke top cycle ratio inequality.
No nonmon parameter sets broke both.
(clockwise > counterclockwise in at least one cycle)

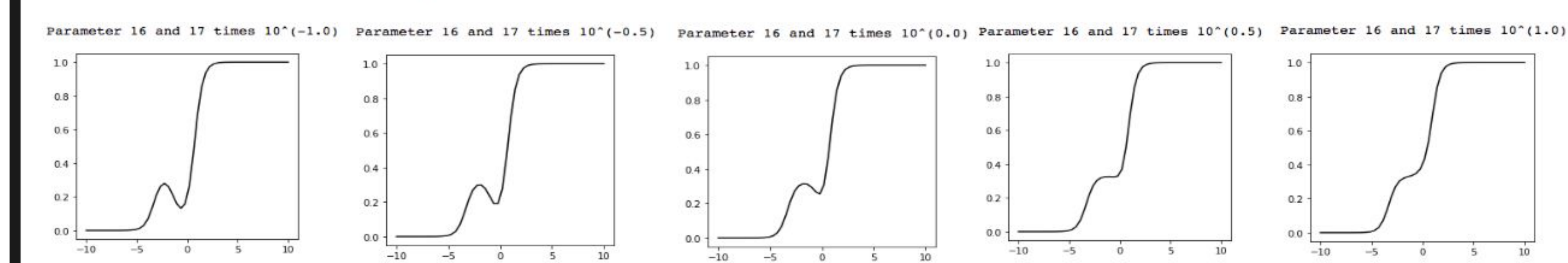
Conclusions and a Caveat

Since the log cycle ratio is tied to energy expenditure, we observed a connection between energy expenditure and the degree of non-monotonicity, quantified by peak height.
This enforces the idea that non-monotonic GRFs are indeed a signature of non-equilibrium conditions.

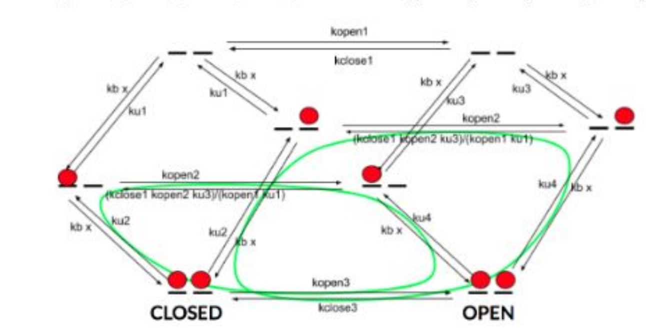
However, it is possible to transform a non-monotonic GRF into a monotonic GRF, and vs versa, without changing cycle ratios (not expending energy).

Transformation of non-monotonic GRF to monotonic GRF, same cycle ratios

Parameter 16 = kopen1, Parameter 17 = kclose1



kb = 1.56837289e+02
ku1 = 9.75025541e+02
ku2 = 7.72064685e+02
ku3 = 2.16454682e-01
ku4 = 1.41187894e-03
kopen1 = 5.15023676e+01
kclose1 =4.63834253e+00
kopen2 = 5.42335665e+01
kopen3 = 7.81857630e+01
kclose3 = 9.23002276e+02



Future Directions

- Attempt to support observations analytically (difficult since the GRF coefficients suffer from a parametric combinatorial explosion)
- Instead of peak height of GRF as a quantifier of non-monotonicity, use most negative derivative
- Use boundary finder to find parameter sets that yield largest non-monotonicity
- Extend to other expression strategies
- Extend to n binding sites, m conformations

Thank you!

A huge thank you to my mentor Dr. Martinez-Corral, Dr. Gunawardena and the lab.