AN EXPLORATION IN MATHEMATICAL BIOLOGY
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Goals and Purpose

This summer, I worked with Aaron Fogelson in the field of mathematical biology. We read books and papers pertaining to the subject of control of cellular processes in order to learn about regulation of these processes, including cellular maturation, cellular apoptosis, imperfect adaptations, homeostatic responses, and the other processes which are components of the cell cycle. We worked through Tyson's paper, consisting of 10 relatively simple prototypical biochemical networks and saw how it was possible to construct networks with different characteristic features (e.g. toggle switch). Each of these models was implemented in Matlab and studied with regards to their time-dependent behavior as well as their steady state behavior as variables were changed. By studying these things, I learned how mathematical modeling has been applied to understanding these regulatory systems, and gained experience in modeling and relating mathematical tools by reproducing the mathematical work in these works. Our long-term goal is to develop original mathematical models of some aspects of cell biology and physiology.

Experimentation, Modeling, and Analysis (Reaction diagrams by J.J. Tyson. All other figures produced in Matlab)

The following experiments are based off of the results of Tyson's paper regarding cell signaling mechanisms. These models are relatively simple but occur as "motifs" throughout the cell cycle and other biochemical processes.
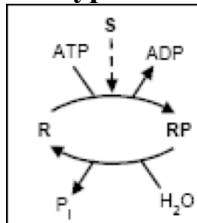
1a.Linear Response
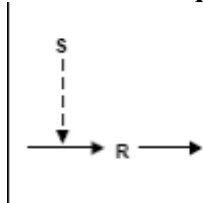
The signal-response curve is linear, suggesting that the response varies directly with the signal.
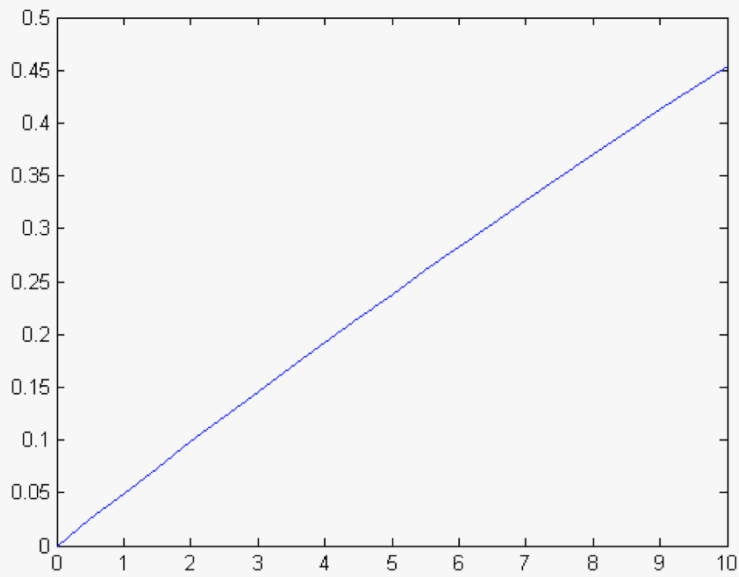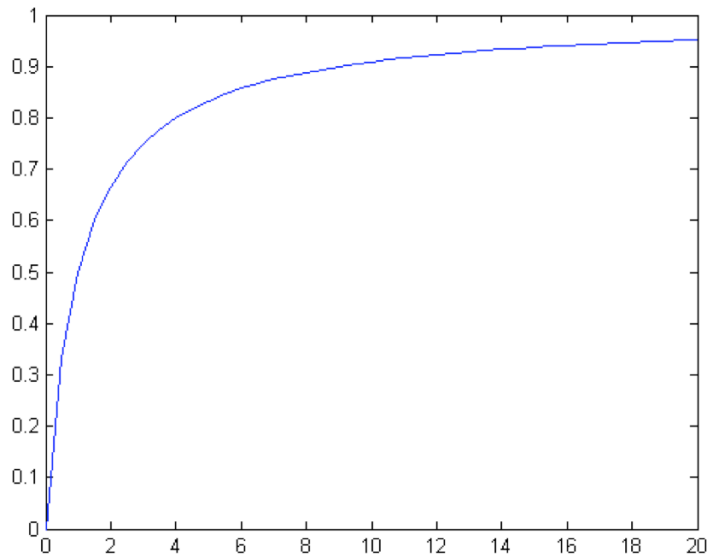
This type of curve is common in models of simple protein synthesis and degradation.
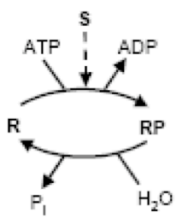
1b. Hyperbolic Response

The signal-response curve increases in a nonlinear fashion, finally leveling out to a steady state response value. This graph considers the system where signal S induces the transform of R to Rp, which in turn changes into R. The ODEs are constructed using the Law of Mass Action.

This type of curve can be used to describe protein phosphorylation and dephosphorylation.

1c.Sigmoidal Response

The signal-response curve increases in a nonlinear fashion, finally leveling out to a steady state response value. This graph considers the system where signal S induces the transform of R to Rp, which in turn changes into R. The ODEs are constructed using Michaelis-Menton kinetics.
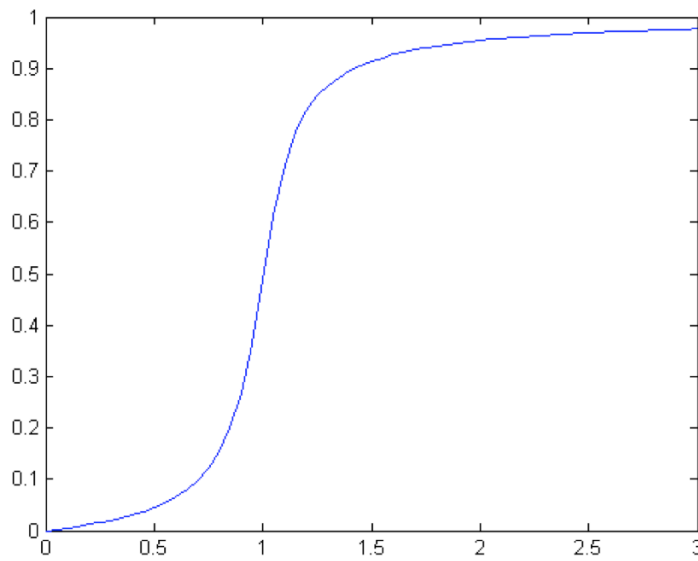
The situation described below is the same as that in 1b, simply analyzed with the laws of Michaelis-Menton kinetics.

1d.Perfect Adaptation
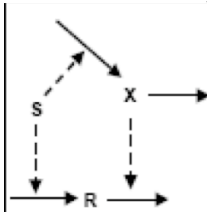
As signal S is increased in a stepwise motion over time, a second signaling pathway of X (blue) increases in a stepwise hyperbolic fashion and response(red) follows a repetitive skewed bell curve with a general trend, with increasing time(and hence signals S and X), towards a steady state response of 1. Despite repeated stimuli, the system continues to adapt perfectly to its original steady state.
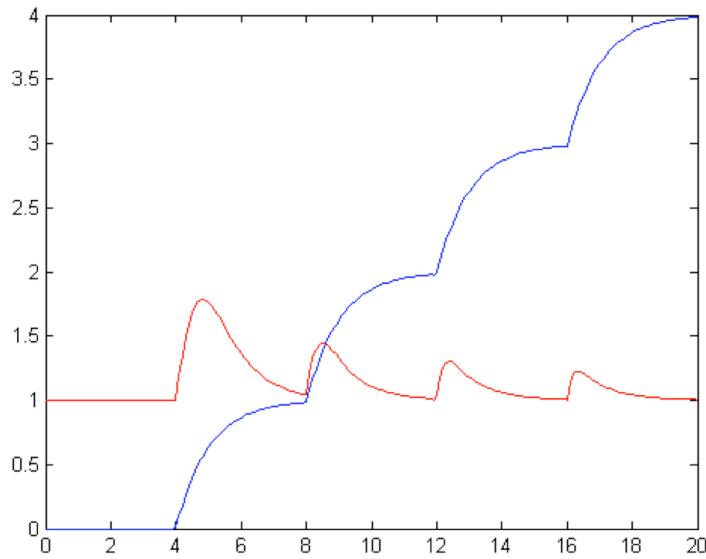
This system mimics the signaling system of processes such as the human immune system's neutrophils.

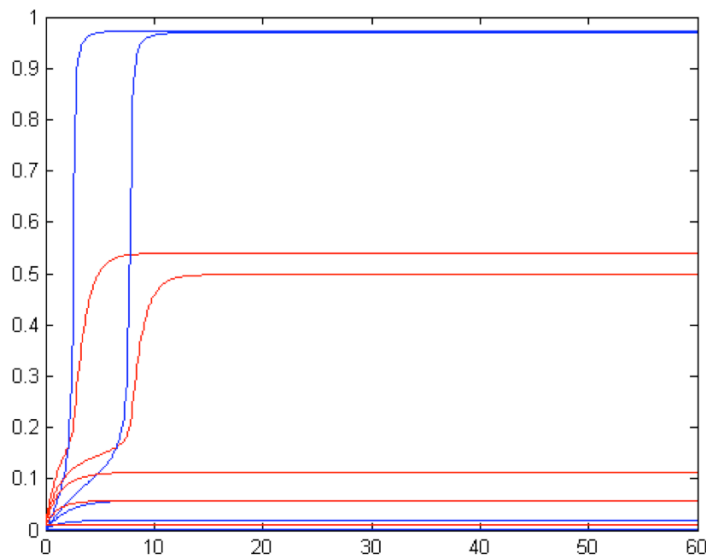### 1e. Mutual Activation (One-way Switch)
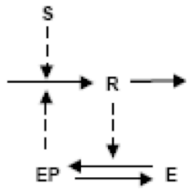
The tables and graphs given below correspond to values found in a mutual activation system where response changes drastically when signal strength passes through a critical value. In this situation, R and E mutually activate each other.
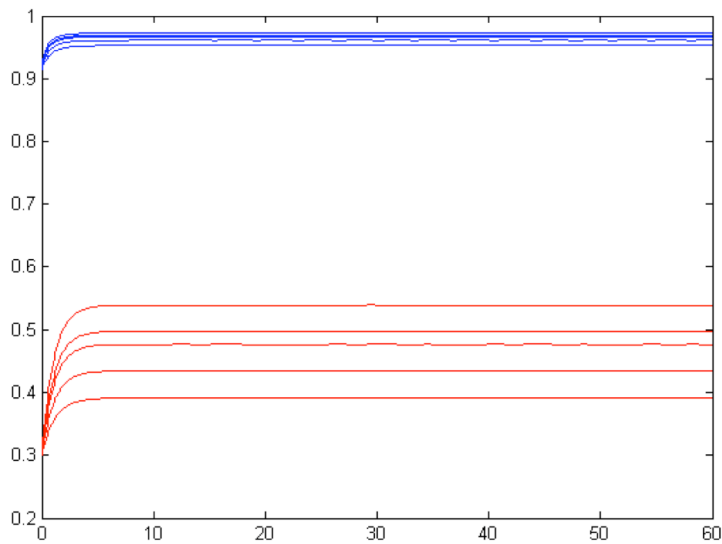
R0=.3

S	Rss
1	.38
5	.43
9	.47
11	.5
15	.54

R0=.01

| S	Rss
1	.011
5	.057
9	.115
11	.5
15	.54

This system is highly reminiscent of the processes such as apoptosis, where the cell's development passes a critical value from which there are no reversing effects.

1f.Mutual Inhibition(Toggle Switch)
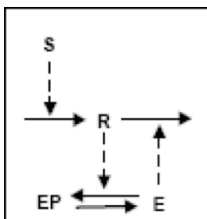
The tables and graphs given below correspond to values found in a mutual inhibition system where response changes drastically when signal strength passes through a critical value. In this situation, R and E are mutually inhibitive and the entire system follows a toggle switch.
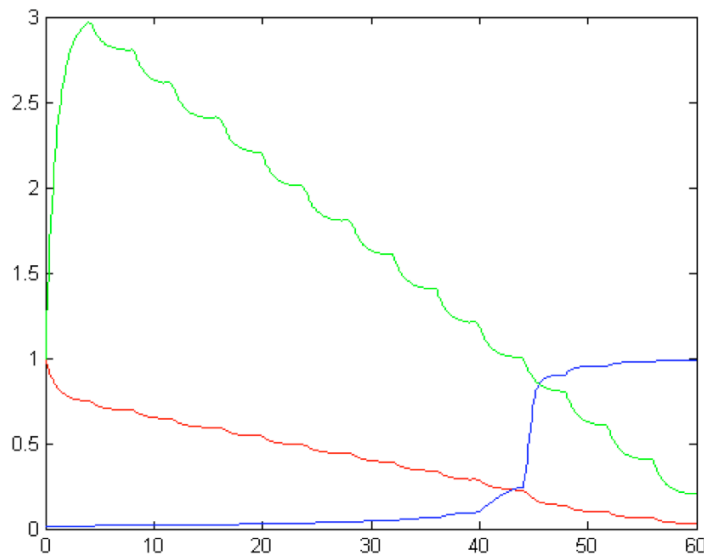
The processes described by this system include the activation of M (mitosis) phase Promoting Factor in frog eggs.

1g. Homeostatic Response
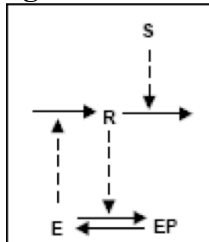
Signaling mechanism S induces a drop in R levels. E induces an increase in the level of R, but R changes E to Ep, which decreases the amount by which E increases R. As a result, the system's total response levels out to a maintained level, shown here as .5.
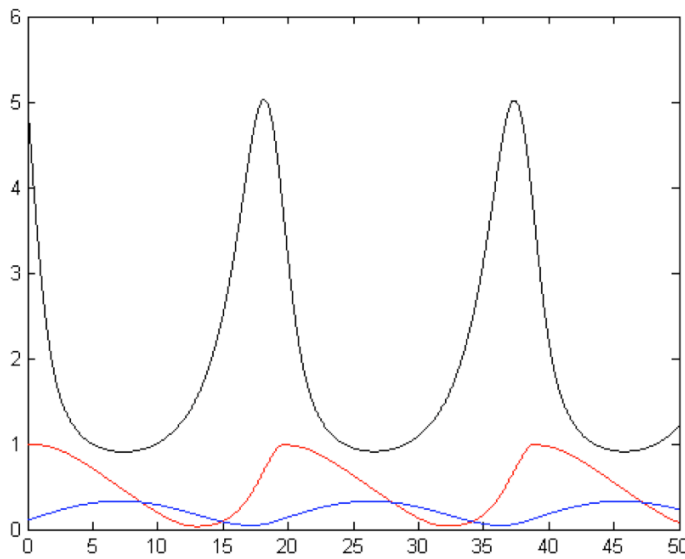
The fascinating circadian rhythms common in earth's creatures, including the human sleep cycle, are often described by homeostatic systems.
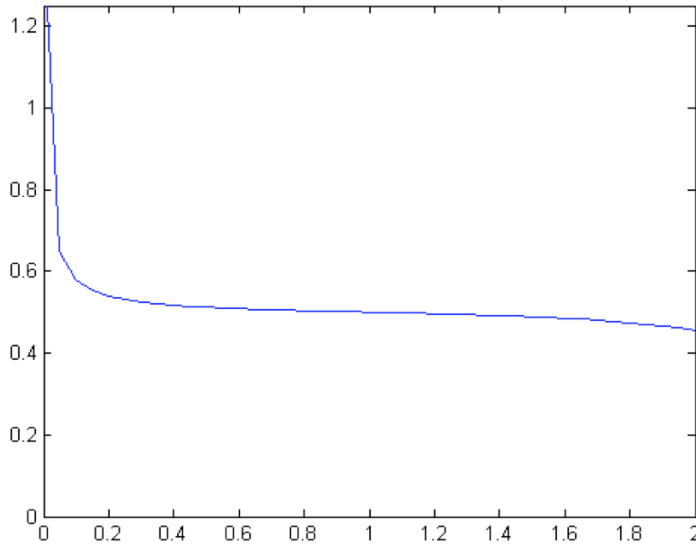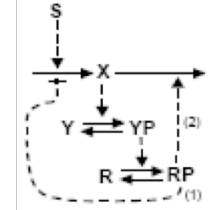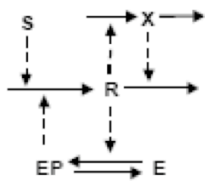
Signal S increases X, which changes Y to Yp, which changes R to Rp, which decreases X. Due to these interactions, X, Rp, and Yp tend to oscillate over time.


Negatve feedback oscillation is a system model for many processes, including protein synthesis.

## 2b.Activator Inhibitor Oscillator

S is a signal mechanism which increases, inducing the increase of R. As R increases, X increases as well, but the signaling mechanism X induces the decrease of R. Simultaneously, R's increase changes E into Ep, which in turn produces more of R. In

this oscillator, R does things that both creates and destroys itself. The system's steady states are unstable, so the oscillator continues indefinitely.
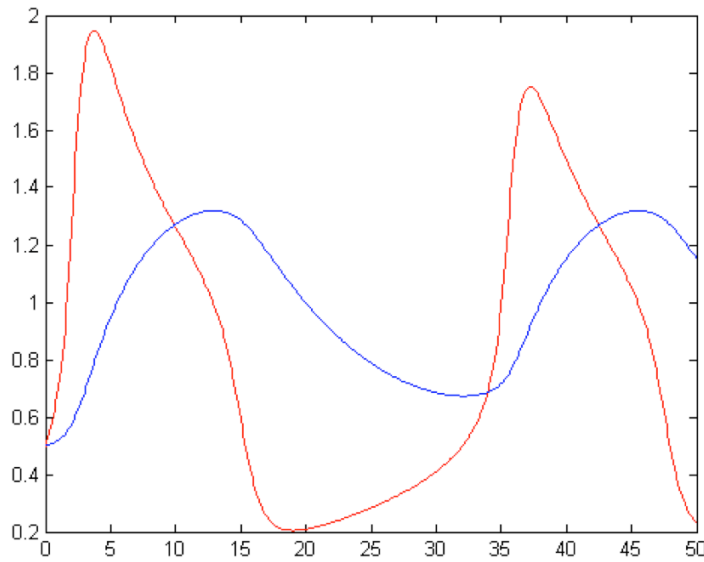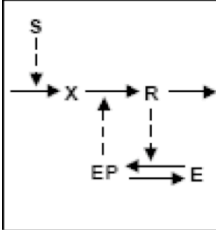

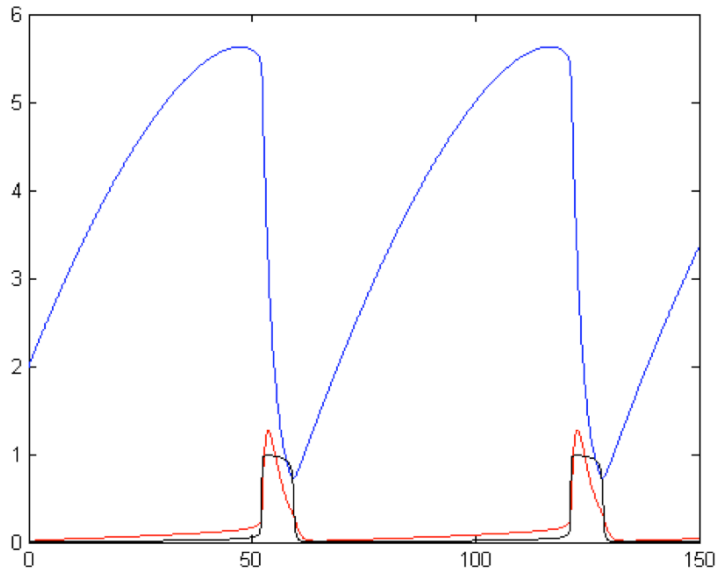This graph shows R as dependent on X.
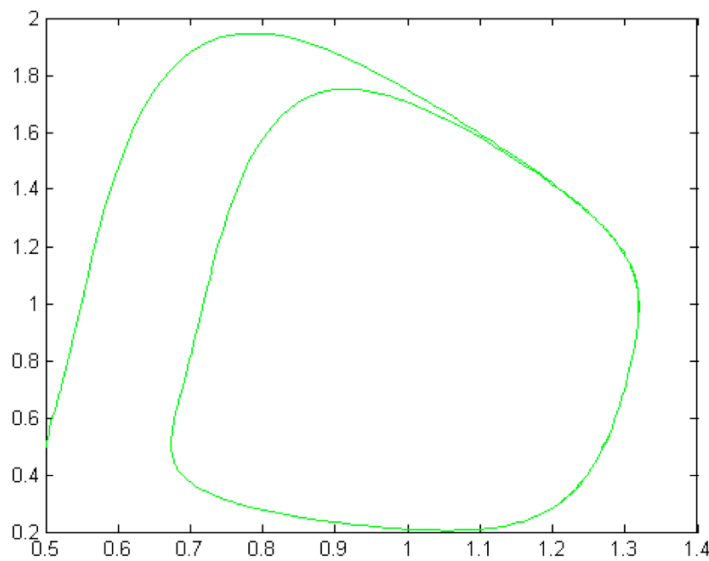
This graph, including the ending hysteresis oscillator, can represent the cyclic AMP production in slime mold.
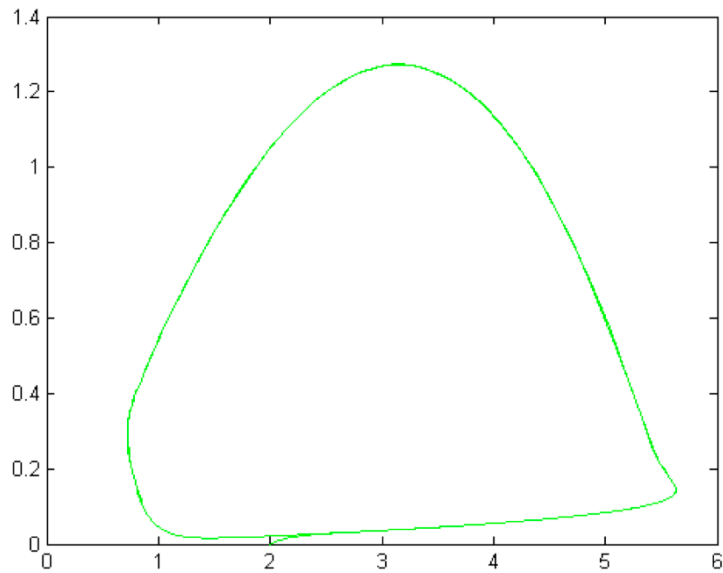
2c. Substrate Depletion Oscillator

The values of X(blue), R(red) and E(black) with respect to time.

This is a graph of R as dependent on X.

This system, which also has a stable limit cycle or hysteresis loop, describes systems such as that of MPF oscillations in frog eggs.

Future Plans

Following our summer explorations into the properties of prototypical simple regulatory networks and their numerical implementation, especially in Matlab, I will work with Dr. Aaron Fogelson to look into more realistic and complex models of the cell cycle that have appeared in the literature. This will involve learning the relevant biology and more about the mathematics of the types of dynamical systems in these models. In addition, I will be looking more closely into "modeling process," that is, how to translate a written or pictorial description of a biological process into mathematics. The goal of this work is to gain sufficient experience to allow me to begin to think about formulating, manipulating, and studying new models of biochemical reaction networks.

Resources

Fogelson, Aaron, Kuharsky, Andrew. Membrane Binding-Site Density Can Modulate Activation Thresholds in Enzyme Systems. Journal of Theoretical Biology; 1998, 193.

Keener, James, and James Sneyd. Mathematical Physiology. New York: Springer-Verlag, 1998.

Strogatz, Steven. Nonlinear Dynamics and Chaos. USA: Addison-Wesley Publishing Company; 1994.

Tyson, John, Chen, Katherine, Novak, Bela. Sniffers, buzzers, toggles, and blinkers: dynamics of regulatory and signaling pathways in the cell. Current Opinion in Cell Biology; 2003, 15.