

INTERNATIONAL INSTITUTE OF  
INFORMATION TECHNOLOGY, HYDERABAD



SYSTEMS BIOLOGY

ADAPTATION MECHANISMS IN PHOSPHORYLATION CYCLES

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## Project Notes

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November 24, 2020

# Introduction

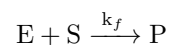
The project is based on the paper 'Adaptation mechanisms in phosphorylation cycles by allosteric binding and gene autoregulation'. The aim of this paper was to study adaptation mechanics in a class of phosphorylation cycles under regulation by allosteric binding and gene autoregulation methods.

## Mass Action Kinetics

The paper has done all the math using the mass action kinetics which is described below.

### Definition 0.1

For the reaction



The rate of reaction ( $v$ ) is given by :

$$\begin{aligned} v &= \frac{d[P]}{dt} \\ &= k_f[E][S] \end{aligned}$$

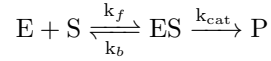
This is known as the mass action kinetics.

## Michaelis-Menten Kinetics

The project attempts to replicate the paper using Michaelis-Menten kinetics, which is defined as below.

**Definition 0.2**

For the reaction



The rate of reaction ( $v$ ) is given by :

$$\begin{aligned} v &= \frac{d[P]}{dt} \\ &= V_{max} \frac{[S]}{[S] + K_d} \end{aligned}$$

In this, the definitions are as follows :

$$\begin{aligned} V_{max} &= k_{cat}[E]_0 \\ K_d &= \frac{k_b}{k_f} \end{aligned}$$

This is known as the Michaelis–Menten kinetics.

## Limitations of Michaelis–Menten Kinetics

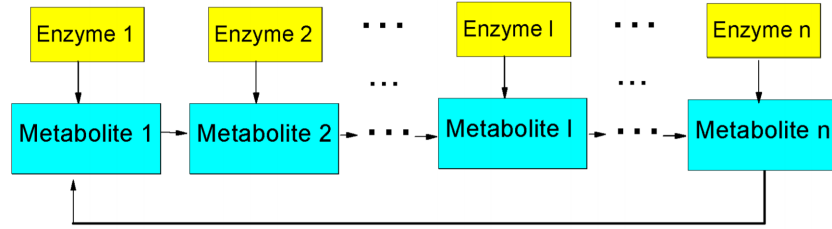
This is a different result as compared to mass action kinetics. The Michaelis–Menten kinetics operate under the assumption that  $K_d \ll 1$ , and in general operate under the rule that the second reaction is non reversible, which is applicable under the condition that  $[S] \gg [P]$  or  $\Delta G \ll 0$ .

Thus, the conditions under which Michaelis–Menten kinetics operate are :

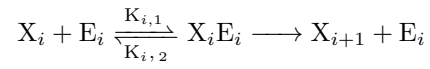
- $K_d \ll 1$
- $[S] \gg [P]$
- $\Delta G \ll 0$

## Results of the Original Paper

The original paper does mathematical analysis of the phosphorylation system given below :



This system is described by the following set of equations :



The paper then uses multiple Lemmas and Propositions to describe the behavior of the system. The following analyses are done on the system :

- Robustness Analysis
- Stability Analysis
- Adaptation to Biological Rhythms

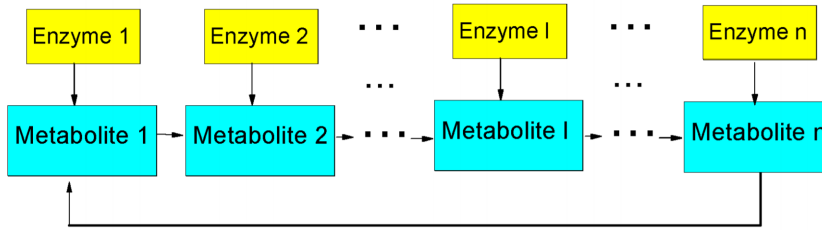
The aim of the project is to replicate results of the above analysis using Michaelis–Menten kinetics.

# Original Results

This chapter contains all the analysis done in the original paper and the conclusions that it came up with. This is very similar to the original paper itself but is redone again to make the compare and contrast easier to understand and make the steps followed easier to understand.

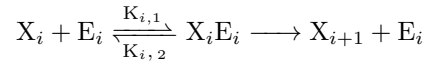
## System Description

The following phosphorylation system is used for studying :



## Rate Equations

This corresponds to the following set of reactions :



Which then corresponds to the following rate equations :

$$\begin{aligned} \frac{d[X_i]}{dt} &= -K_{i,1}[X_i][E_i] + K_{i,2}[X_i E_i] + K_{i-1,3}[X_{i-1} E_{i-1}] \\ \frac{d[E_i]}{dt} &= -K_{i,1}[X_i][E_i] + (K_{i,2} + K_{i,3})[X_i E_i] \\ \frac{d[X_i E_i]}{dt} &= K_{i,1}[X_i][E_i] - (K_{i,2} + K_{i,3})[X_i E_i] \end{aligned}$$

As the amount of enzyme remains constant in the system, the equations can be rewritten as follows :

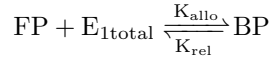
$$\begin{aligned}\frac{d[X_i]}{dt} &= -K_{i,1}[X_i][X_iE_i] + K_{i,2}[X_iE_i] + K_{i-1,3}[X_{i-1}E_{i-1}] + K_{i,1}[X_i][E_i]_0 \\ \frac{d[E_i]}{dt} &= -K_{i,1}[X_i][X_iE_i] + (K_{i,2} + K_{i,3})[X_iE_i] + K_{i,1}[X_i][E_i]_0 \\ \frac{d[X_iE_i]}{dt} &= K_{i,1}[X_i][X_iE_i] - (K_{i,2} + K_{i,3})[X_iE_i] - K_{i,1}[X_i][E_i]_0\end{aligned}$$

This is due to the fact that  $[E_i]_0 = [E]_i + [X_iE_i]$ , which can be used to eliminate the  $[E_i]$  term from the equations.

## Allosteric Binding and Negative Autoregulation

The paper then goes on to describe the phosphorylation cycle with allosteric binding and negative autoregulation. The reaction taken to exhibit this phenomenon is the DNA  $\longrightarrow$  mRNA  $\longrightarrow$  Proteins, where negative autoregulation is described.

The paper assumes that autoregulation is done by a reversible binding/releasing of free and bound promoters, which is described below.

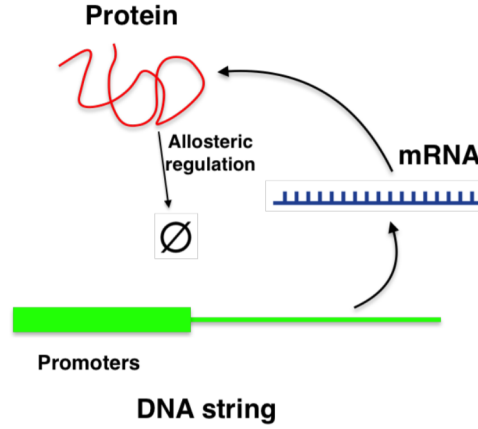


In this  $FP$  is the free promoter and  $BP$  is the bound one. The assumption that number of binding sites on promoters is very small as compared to concentration of proteins, to neglect the effect of binding/releasing reaction on the dynamics of the enzyme, is also made.

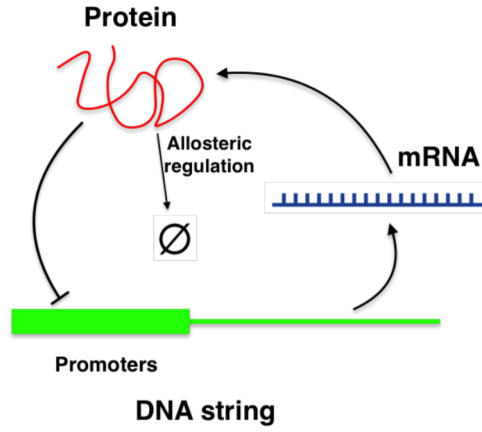
The state equations for these reactions are as follows :

$$\begin{aligned}\frac{d[FP]}{dt} &= K_{rel}([FP]_{max} - [FP]) \\ \frac{d[mRNA]}{dt} &= K_{pro}[FP] - K_d[mRNA] \\ \frac{d[E1]_{total}}{dt} &= K_{tran}[mRNA] - K_{allo} \frac{[X_l][E1]_{total}}{K_{half} + [E1]_{total}}\end{aligned}$$

These equations are for the following reaction :



Another mechanism with negative autoregulation is also described by the paper, which is given as follows :



This system is described by the following equations :

$$\begin{aligned}\frac{d[FP]}{dt} &= K_{rel}([FP]_{max} - [FP]) - K_{auto}[E_1]_{total}[FP] \\ \frac{d[mRNA]}{dt} &= K_{pro}[FP] - K_d[mRNA] \\ \frac{d[E_1]_{total}}{dt} &= K_{tran}[mRNA] - K_{allo} \frac{[X_l][E_1]_{total}}{K_{half} + [E_1]_{total}}\end{aligned}$$

In these,  $[FP]_{max}$  is the total concentration of all the promoters.