

Week 2 Writeup

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June 14, 2017

1 Overview

This week, I focused on finishing the gene circuit model for curli production. To do so, I will continue from where I left off in last week's writeup.

2 Mass Action Kinetics

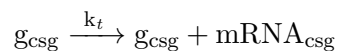
Mass Action Kinetics state that the rate of a reaction is the product of a rate constant (k) and the mass of the substrate (S). Several assumptions will be made in the following model:

1. Some of the molecular interactions, like polymerase or ribosome binding, will be ignored, as these would greatly increase the complexity of the model.
2. Transcription factor binding achieves equilibrium much faster than transcription, translation, and protein accumulation, so it can be considered to be at steady state on the time scale of proteins.
3. Spatial parameters, heat and diffusion gradients, transport times, etc. will not be considered to avoid partial differential equations.

In the case of curli fibers, the main reactions are transcription, translation, secretion, nucleation, and polymerization.

3 Transcription

Reactions



Degradation



3.1 Gene Regulation

The rate of transcription can be regulated by either activators or repressors. Thus, we must modify our differential equations to take this into account. We will define rate of transcription, α , to be

$$\alpha = Bf(x)$$

where B is the basal, or maximum, expression rate when the gene is "on", and $f(x)$ represents the probability of expression, a function of the concentration of x . This function $f(x)$ can be described by the Hill function model:

$$f(x)_{\text{activation}} = \frac{x^n}{x^n + K^n}$$

$$f(x)_{\text{repression}} = \frac{1}{1 + (\frac{x}{K})^n}$$

Here, x is the level of activator or repressor, n is the Hill coefficient, and the K is the value of x where the probability $f(x) = 0.5$. The Hill coefficient is context dependent and represents the cooperativity of the transcription factor. In other words, it describes the switch-like behavior of the transcription factor, increasing the nonlinearity of the function. The parameter K defines the functional concentration range of x .

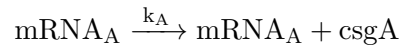
3.2 Transcript Stability

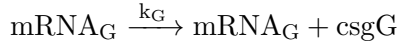
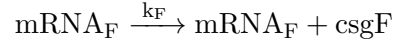
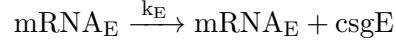
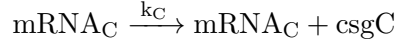
Need to take barcodes and switches into account.

4 Translation

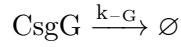
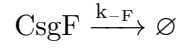
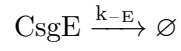
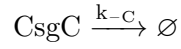
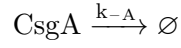
Since the genes coding for each *csg* protein is controlled by a different RBS and are translated independently of each other, each segment of the mRNA transcript will be treated as a separate gene

Reactions





Degradation



4.1 RBS Effects

4.2 Protein Stability

5 Differential Equations

From these, we derive a system of differential equations to describe the rate of change of mRNA and protein levels over time:

Differential Equations

$$\frac{d[mRNA_{csg}]}{dt} = k_t[g_{csg}] - k_{-t}[mRNA_{csg}]$$

$$\frac{d[CsgA]}{dt} = k_A[mRNA_{csg}] - k_{-A}[CsgA]$$

$$\frac{d[CsgC]}{dt} = k_C[mRNA_{csg}] - k_{-C}[CsgC]$$

$$\frac{d[CsgE]}{dt} = k_E[mRNA_{csg}] - k_{-E}[CsgE]$$

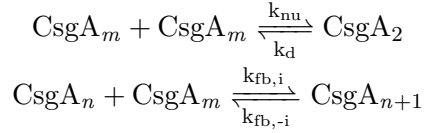
$$\frac{d[CsgF]}{dt} = k_F[mRNA_{csg}] - k_{-F}[CsgF]$$

$$\frac{d[CsgG]}{dt} = k_G[mRNA_{DEFG}] - k_{-G}[CsgG]$$

6 Protein Secretion

7 Fiber Formation

The main reactions involved in the fibril formation is nucleation of monomers (k_{nu} and k_d) and elongation of fibrils ($k_{fb,i}$ and $k_{fb,-i}$). These two steps proceed until the species involved reach an equilibrium. These are described by the following reactions:



$CsgA_m$ represents the monomer and $CsgA_n$ represents an oligomer containing n monomers, respectively. Although fibril entanglement has been reported, the ends of the fibers are assumed to be the only active chemical sites, and thus fibers of all lengths are treated equally.

Nucleation is considered the rate limiting step in amyloid formation (Chapman 2008)

8 References

Csicsery, Nick and O’Laughlin, Ricky. (2013). *A Mathematical Model of a Synthetically Constructed Genetic Toggle Switch*.