Using Synthetic Biology to Identify a Human Papillomavirus Infection

Lactoguard

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Introduction

1. What is IGEM?
2. Identify a problem.
3. Research potential solution using a Genetic Machine.
4. Devise a mathematical model.
5. Build the machine.

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Contents

Introduction to Machine

- What does it do?
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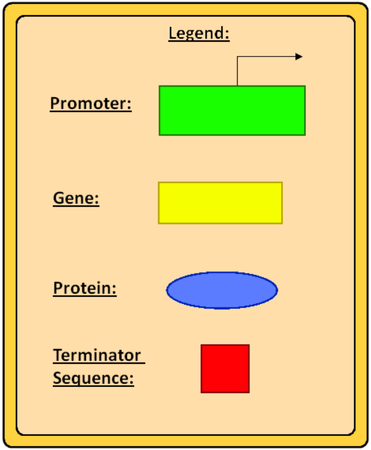
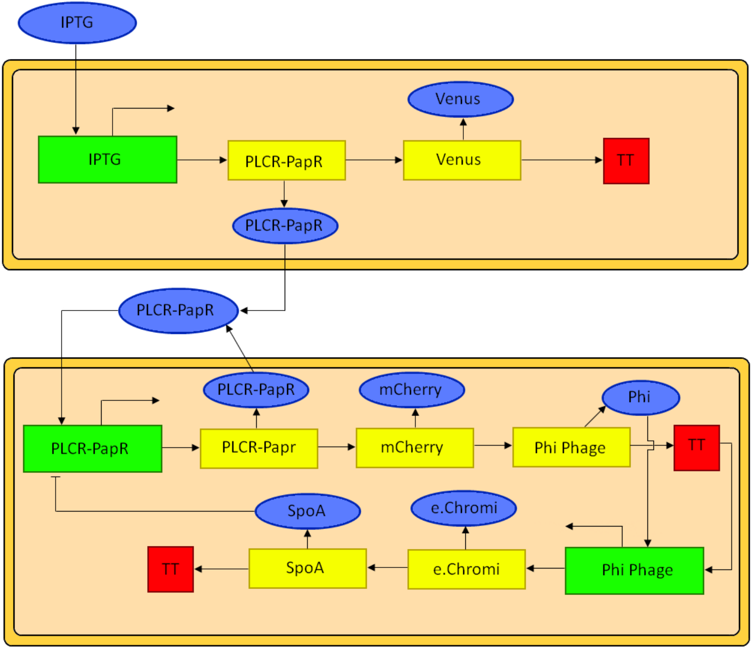
Legend for Genetic Circuit




IPTG
Venus
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PLCR-PapR
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TT
PLCR-PapR
PLCR-PapR
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mCherry
Phi
PLCR-PapR
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Importance of the Model

- Saves valuable resources, every revision of the machine need not be built.
- Allows insights into what biology may or may not work, aiding in the selection of biological components. Leaky promoters for example.
- The benefits of modelling reach far beyond a theoretical understanding of a system. Models allow us to determine how we hope a system will behave. From this and experimental findings we can go on to determine where assumptions and simplifications made are critically important, whether it be positively or negatively.

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Assumptions

- The total occupied and unoccupied receptors, is constant.
- Our system reaches a quasi-steady state.
- The number of input molecules is much greater than the number of receptors, this implies that the receptors are always operating at maximal capacity, so they are virtually never unoccupied.

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Activation

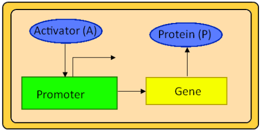


Figure: Genetic Circuit Illustrating Activation.

- Activation Kinetic

$$\frac{d[P]}{dt} = i\frac{[A]^n}{K_h+[A]^n} + b$$

where $[A]$ is the concentration of activator,
$[P]$ is the concentration of the protein,
n is the Hill cooeefficient, (A measure of cooperative binding)
K_h is the concentration relating to half the maximal rate of expression,
i is the increase in output from basal rate to maximal rate,
b is the basal rate of transcription.

Activation Kinetic Graph

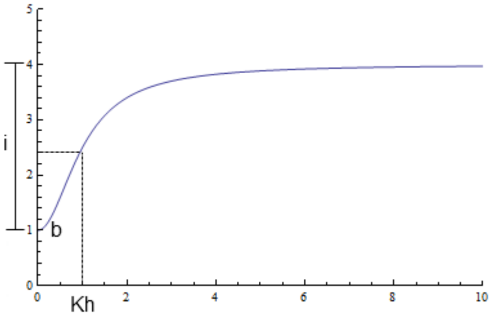


Figure: Activation Kinetic, i=3, Kh=1, b=1, n=2.

Activation Kinetic Graph

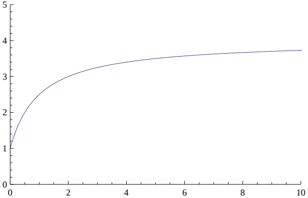


Figure: Activation Kinetic, i=3, Kh=1, b=1, n=1.

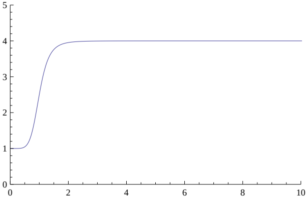


Figure: Activation Kinetic, i=3, Kh=1, b=1, n=6.

Repression

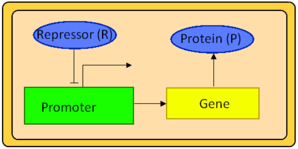


Figure: Genetic Circuit Illustrating Repression.

- Repression Kinetic

$$\frac{d[P]}{dt} = \frac{b}{1+K_e[R]^n}$$

where $[R]$ is the concentration of repressor,
$[P]$ is the concentration of the protein,
K_e is the equilibrium rate of cooperative binding.
b is the basal rate of transcription,

Repression Kinetic Graph

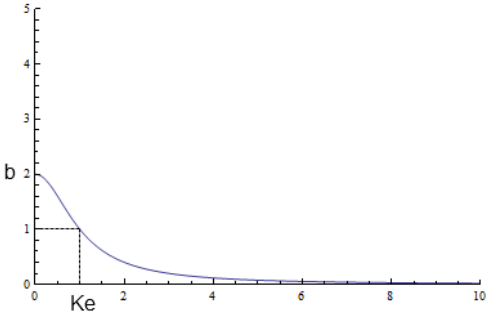


Figure: Repression Kinetic, Ke=1, b=2, n=2.

Repression Kinetic Graph

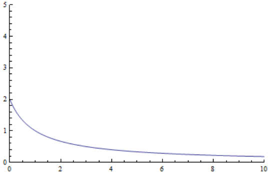


Figure: Repression Kinetic, Ke=1, b=2, n=1.

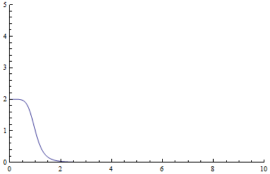
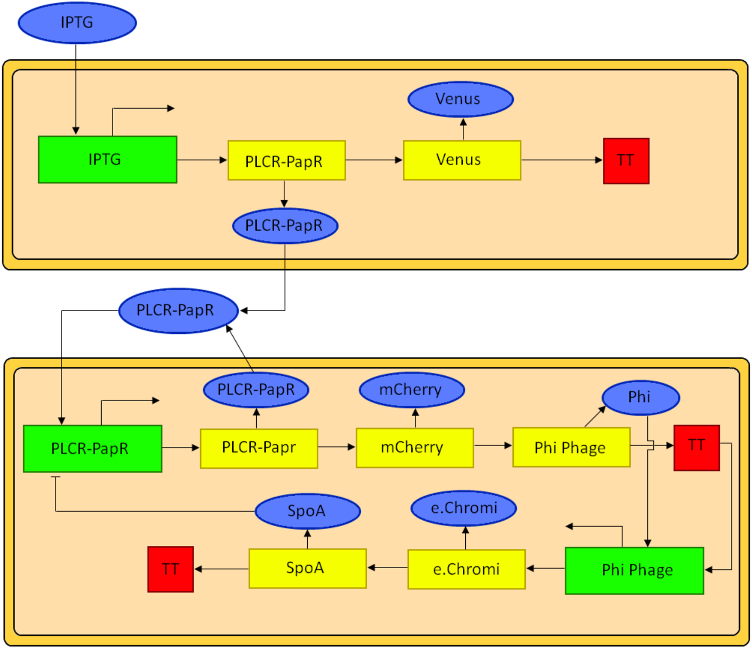


Figure: Repression Kinetic, Ke=1, b=2, n=6.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Model

$$\frac{d[\text{PLCR-PapR}]}{dt} = b_1 + \frac{k_{M1}[\text{IPTG}]^{n1}}{k_{h1}+[\text{IPTG}]^{n1}} - l_1[\text{PLCR-PapR}]$$

$$\frac{d[\text{Venus}]}{dt} = b_2 + \frac{k_{M2}[\text{IPTG}]^{n1}}{k_{h2}+[\text{IPTG}]^{n1}} - l_2[\text{Venus}]$$

$$\frac{d[\text{PLCR-PapR}]}{dt} = \left(b_3 + \frac{k_{M3}[\text{PLCR-PapR}]^{n2}}{k_{h3}+[PLCR-PapR]^{n2}}\right)\left(\frac{1}{1+c_1[SpoA]^{n3}}\right) - l_3[\text{PLCR-PapR}]$$

$$\frac{d[\Phi Act]}{dt} = \left(b_4 + \frac{k_{M4}[\text{PLCR-PapR}]^{n2}}{k_{h4}+[PLCR-PapR]^{n2}}\right)\left(\frac{1}{1+c_2[SpoA]^{n3}}\right) - l_4[\Phi Act]$$

$$\frac{d[\text{SpoA}]}{dt} = b_5 + \frac{k_{M5}[\Phi Act]^{n2}}{k_{h2}+[\Phi Act]^{n2}} - l_5[\text{SpoA}]$$

Preliminary Results

- By making the false assumption that our promoter is not leaky we can exam the results following.
- From these results we can ascertain whether the behaviour and subtle delays in expression are accurate and desirable.

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No Basal Transcription

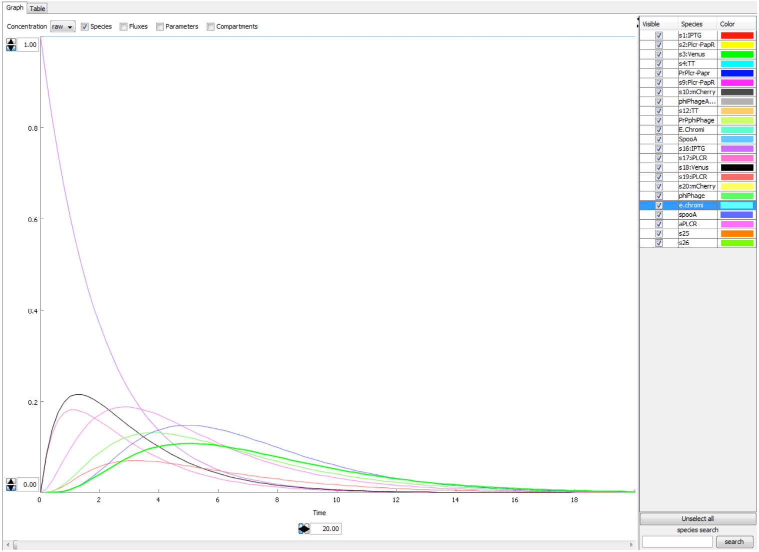

Figure: Solution Plot of System With no Basal Transcription

Reasonable Results

- We now relax our false assumption and incorporate a basal rate of transcription.
- This introduces the problem of identifying correct operation of our machine or ruling out false positives.
- However given the increase in efficacy in production in the presence of an inducer we can regard the basal rates as an acceptable level of noise.

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Non-Zero Basal Rate of Transcription without Activation

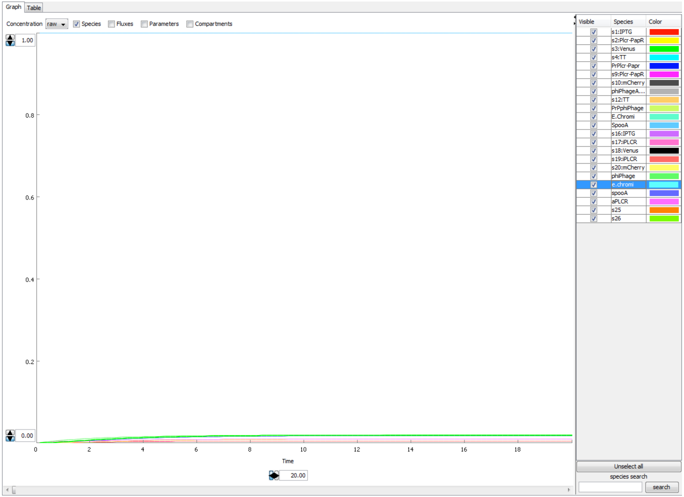

Figure: Solution Plot of System With Basal Transcription but No Input

Non-Zero Basal Rate of Transcription with Activation

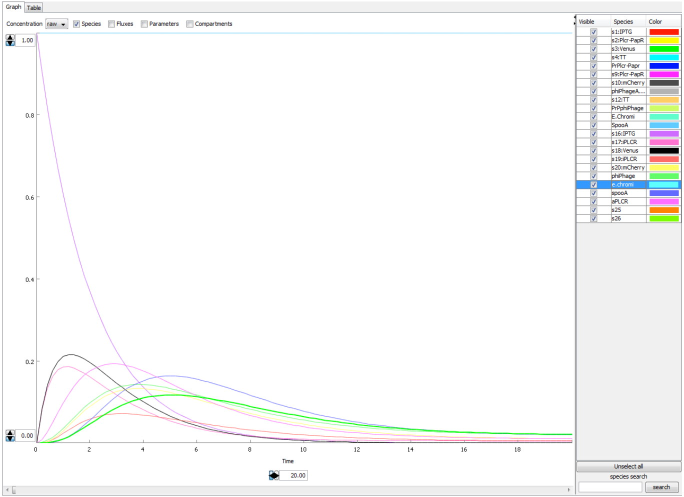

Figure: Solution Plot of System With Basal Transcription

Conclusion

- Although the kinetics used in the model are derived from enzymatic reactions, the biological processes of gene expression and enzyme reactions have parallels that substantiate the use of these models.
- Experimental data from preliminary biological constructs is still pending and hence the accuracy and dependability of the model is still to be determined.
- Next year

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