Tryptophan Synthesis in Various Organisms

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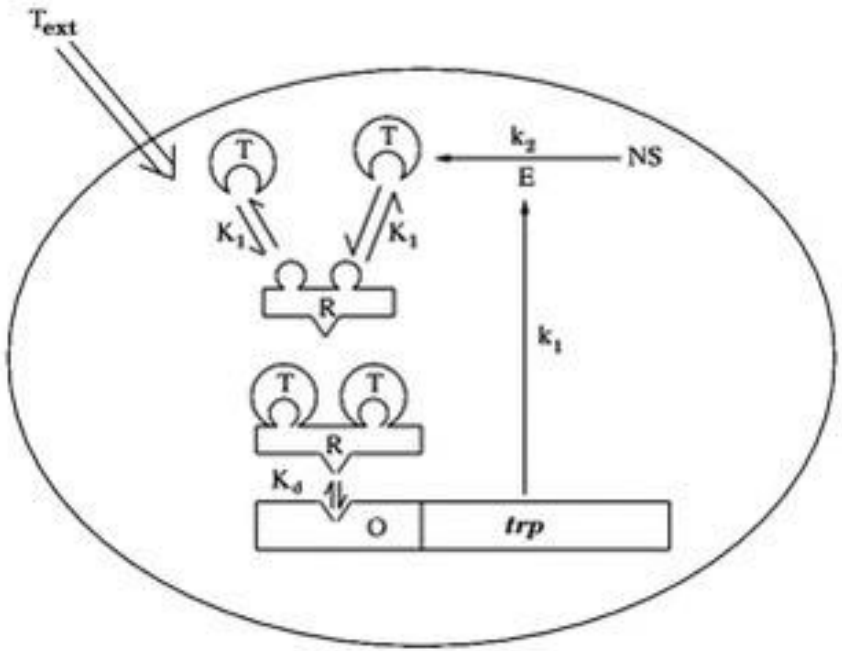
Introduction

- Tryptophan is an important amino acid.
- The system can act as negative feedback.
- Input is the Tryptophan concentration.
- Output is the enzyme concentration.
- Great example of homeostasis despite perturbations.



Differential Equations

$$\frac{\mathrm{d}}{\mathrm{d}t}(O_{\mathrm{R}}) = k_1 O_t C_1(T) - k_{d1} \cdot O_{\mathrm{R}} - \mu \cdot O_{\mathrm{R}},$$

$$\frac{\mathrm{d}}{\mathrm{d}t}(\mathrm{mRNA}) = k_2 O_{\mathrm{R}} C_2(T) - k_{d2} \cdot \mathrm{mRNA} - \mu \cdot \mathrm{mRNA}$$

$$\frac{\mathrm{d}}{\mathrm{d}t} E = k_3 \cdot \mathrm{mRNA} - \mu E$$

$$\frac{\mathrm{d}}{\mathrm{d}t} T = k_4 C_3(T) E - g \frac{T}{T + K_{\mathrm{g}}} - \mu T$$

$$C_1(T) = \frac{K_{i,1}^{\eta_{\mathrm{H}}}}{K_{i,1}^{\eta_{\mathrm{H}}} + T^{\eta_{\mathrm{H}}}},$$

$$C_2(T) = \frac{K_{i,2}^{1.72}}{K_{i,2}^{1.72} + T^{1.72}},$$

$$C_3(T) = \frac{K_{i,3}^{1.2}}{K_{i,3}^{1.2} + T^{1.2}}.$$

Constant Values

	Parameter	Value
Kinetic rate constants for synthesis of free operator, mRNA transcription, translation, and tryptophan	k_1	50 min^{-1}
	k_2	15 min^{-1}
	k_3	90 min^{-1}
	k_4	59 min^{-1}
Total concentration of free operator	O_t	3.32 nM
Degradation rate constants of free operator	k_{d1}	0.5 min^{-1}
	k_{d2}	15 min^{-1}

	Parameter	Value
Specific growth rate of E. Coli	μ	0.01 min^{-1}
Kinetic Constant	g	25 μM min^{-1}
Half-saturation constant for uptake of tryp. for protein synthesis	K_g	0.2 μM
Half-saturation constants	$K_{i,1}$	3.35 μM
	$K_{i,2}$	0.04 μM
	$K_{i,3}$	810 μM
Sensitivity of genetic regulation	η_H	1.92

Linearization

$$\frac{d}{dt}[T] = k_4 C_3(T)[E] - \frac{g[T]}{[T] + K_g} - \mu[T]$$

$$C_3(T) = \frac{K_{i,3}^{1.2}}{K_{i,3}^{1.2} + T^{1.2}}$$

Jacobian: $\left[\frac{d}{dT}\dot{T} \quad \frac{d}{dE}\dot{T}\right] = \left[\left(-\frac{6EK_{i,3}^{1.2}k_4T^{0.2}}{5\left(T^{1.2}+K_{i,3}^{1.2}\right)^2} - \frac{g}{T+K_g} + \frac{gT}{\left(T+K_g\right)^2} - \mu\right) \quad \left(\frac{K_{i,3}^{1.2}k_4}{T^{1.2}+K_{i,3}^{1.2}}\right)\right]$

Evaluated at a zero steady state: $\left[\left(-\frac{g}{K_g} - \mu\right) \quad \left(\frac{K_{i,3}^{1.2}k_4}{K_{i,3}^{1.2}}\right)\right]$

Linearization: $\left[\left(-\frac{g}{K_g} - \mu\right) \quad \left(\frac{K_{i,3}^{1.2}k_4}{K_{i,3}^{1.2}}\right)\right] * \begin{bmatrix}\tilde{T}\\ \tilde{E}\end{bmatrix}$

$$\frac{d}{dt}\tilde{T} \approx -125\tilde{T} + 59\tilde{E}$$

Laplace Transform,Transfer Function, and Bode Plot

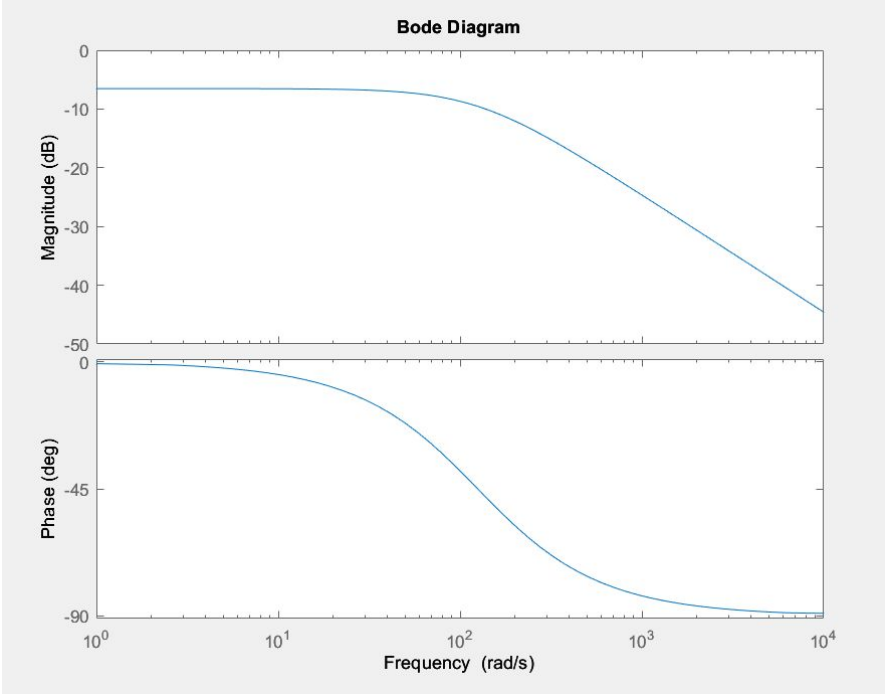
Linearized Equation: $\frac{d}{dt}\tilde{T} = -125\tilde{T} + 59\tilde{E}$

Take Laplace Transform: $s\tilde{T}(s) - \tilde{T}(0) = 59\tilde{E}(s) - 125\tilde{T}(s)$

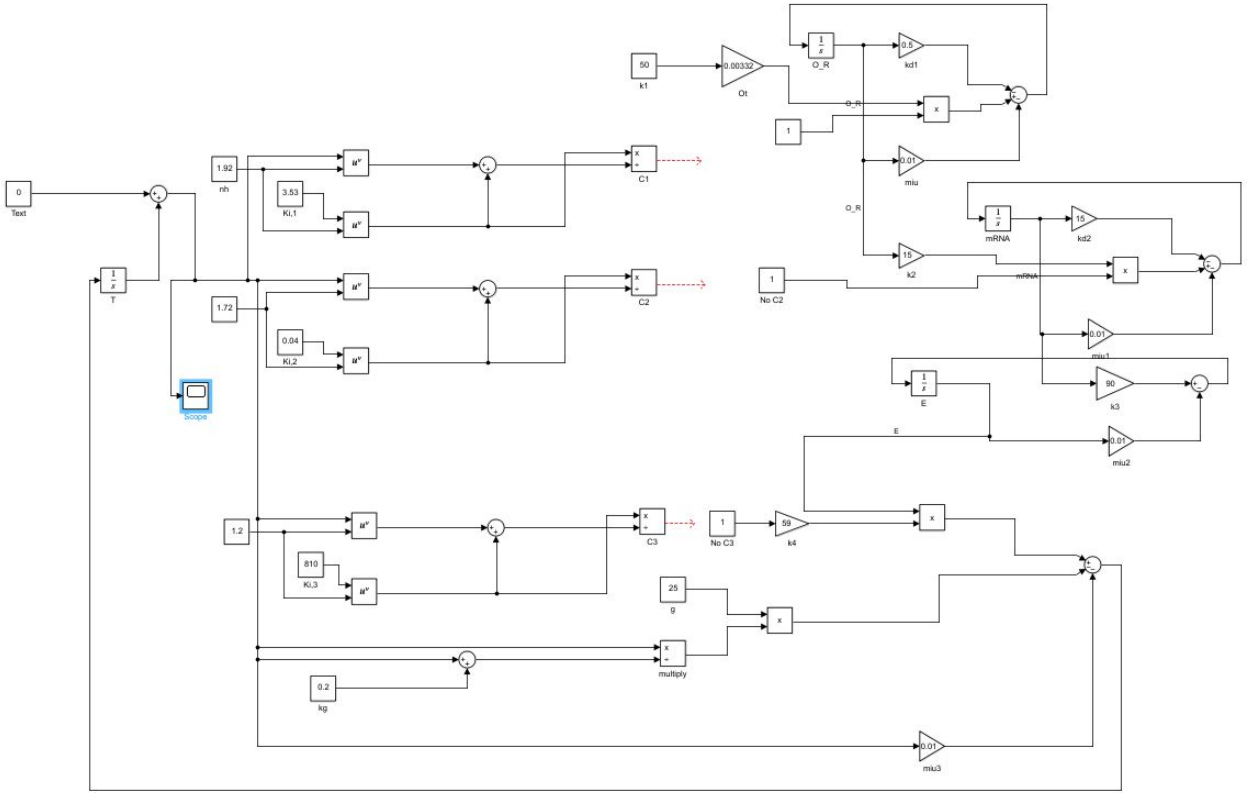
Isolate $\tilde{T}(s)$: $s\tilde{T}(s) + 125\tilde{T}(s) = 59\tilde{E}(s)$

$$\tilde{T}(s)[s + 125] = 59\tilde{E}(s)$$

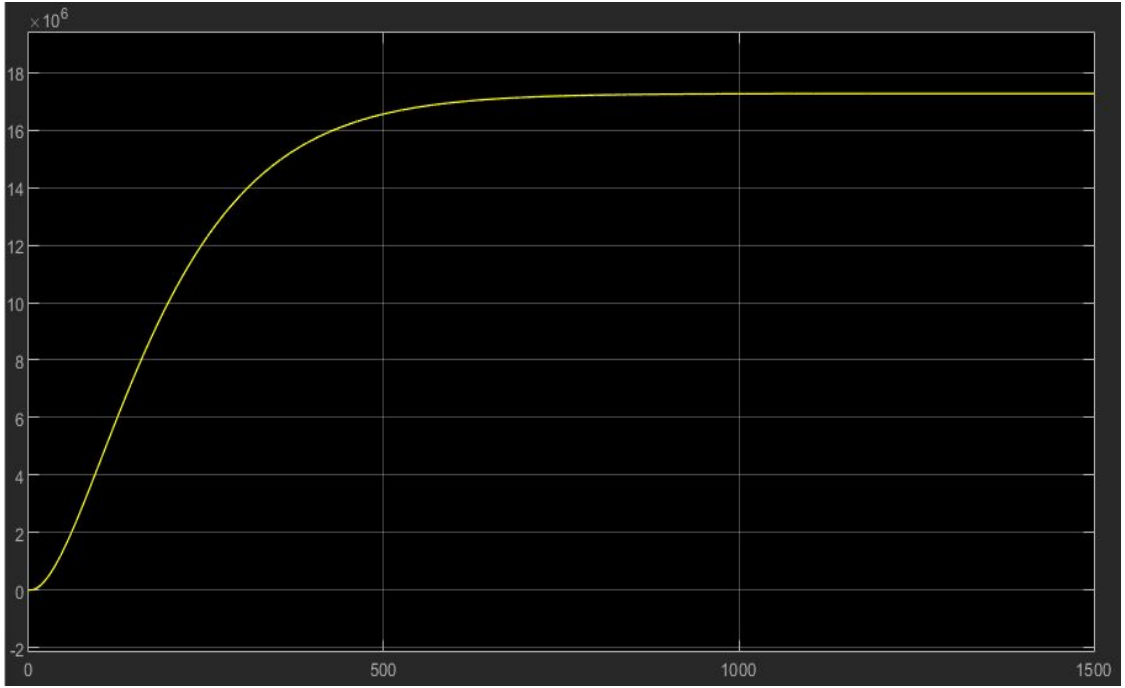
Transfer function $\frac{\tilde{T}(s)}{\tilde{E}(s)} = \frac{59}{s+125}$



If we go with (a): no controller



Results of no controllers:



Stable System

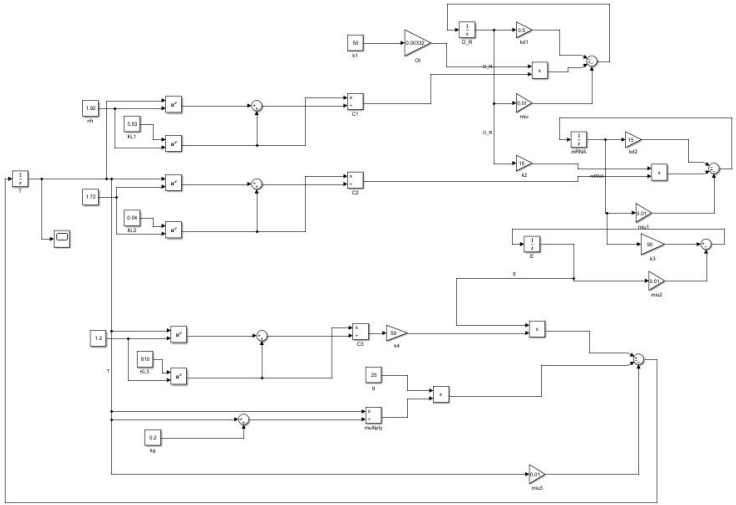
Steady state concentration:

~1.73*10^7 μM

Rising time: about 395 min

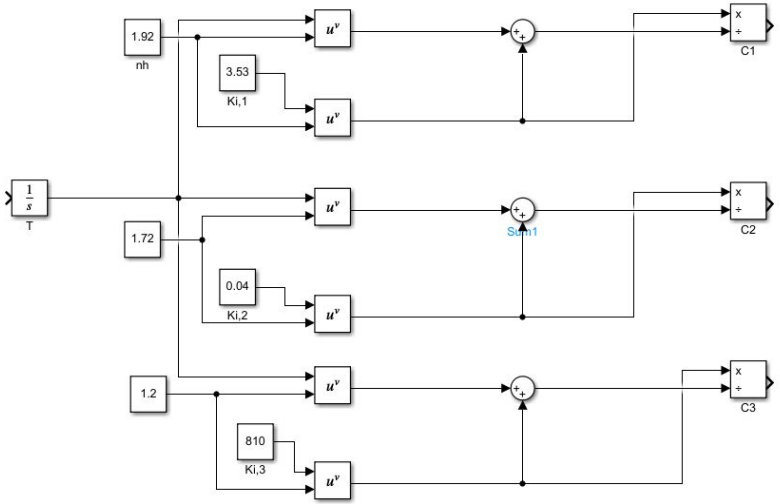
With no overshoot

If we go with (b)

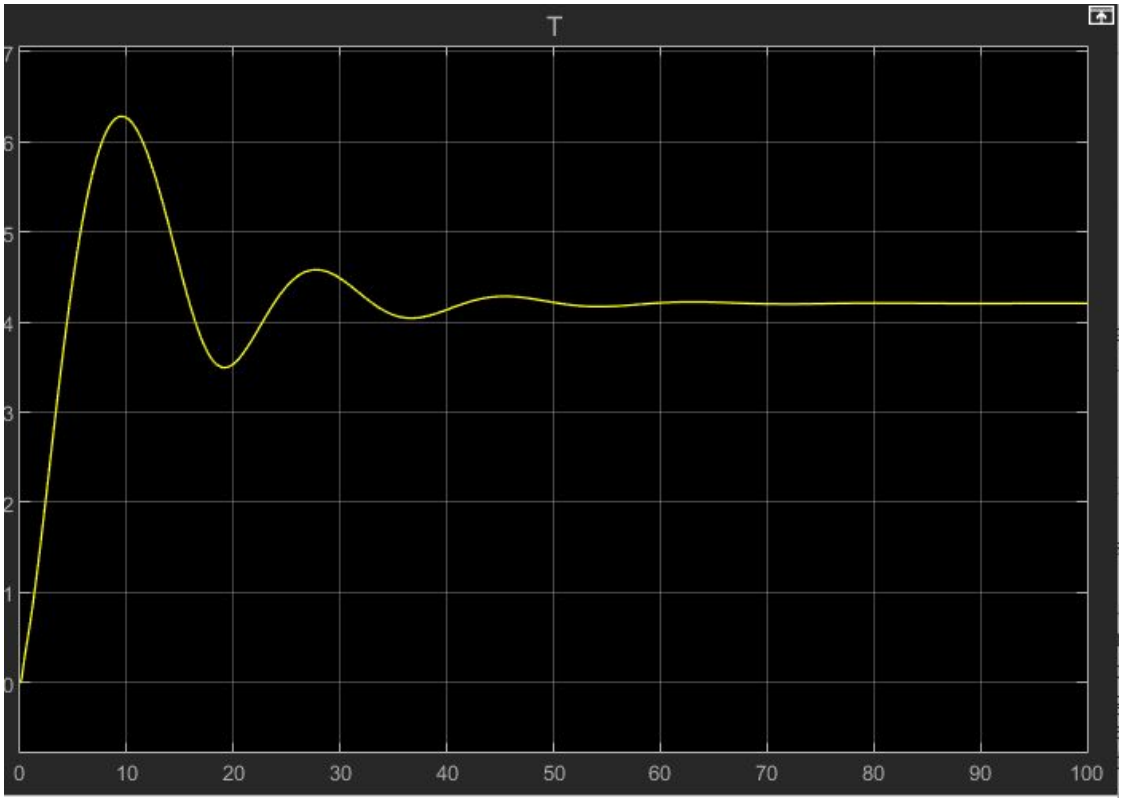


Modeled by Michaelis_menten Equation:

$$v = \frac{\mathrm{d}[\mathrm{P}]}{\mathrm{d}t} = V_{\max} \frac{[\mathrm{S}]}{K_\mathrm{M} + [\mathrm{S}]}$$



Results of with 3 controllers:



Stable System

Steady State concentration:

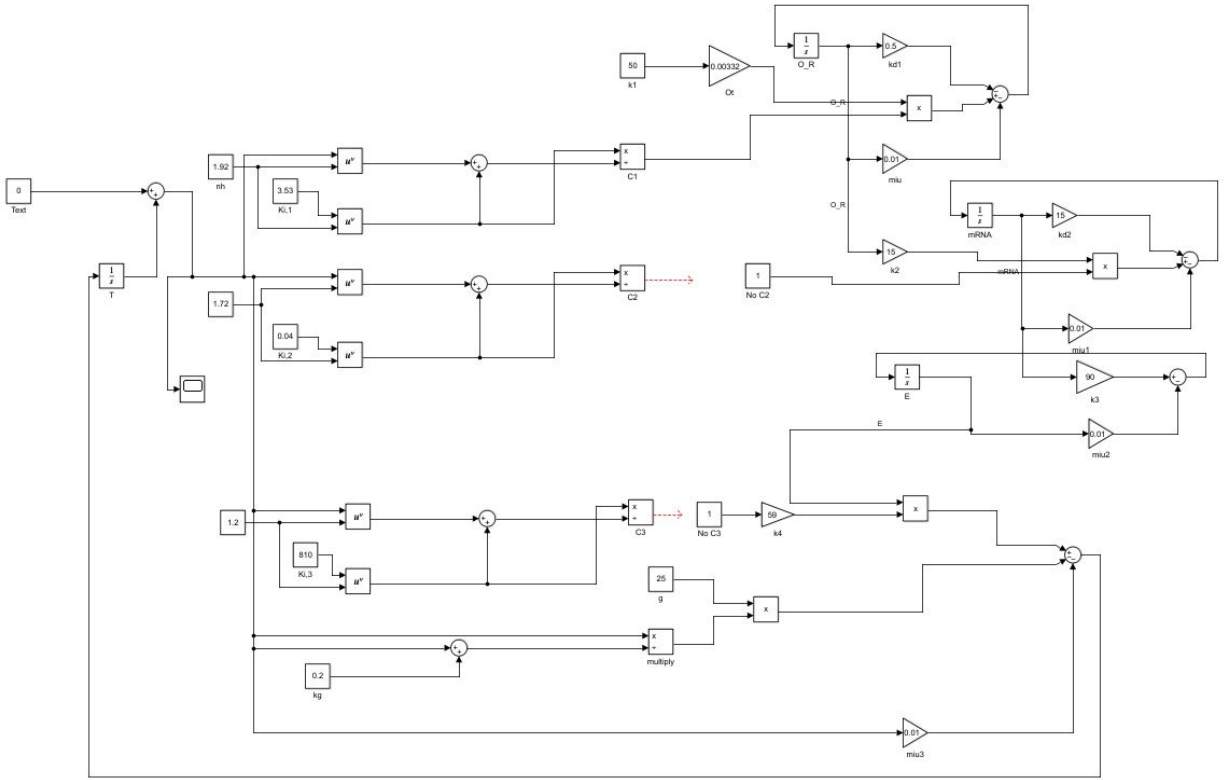
~4.2 μM

Rising time: ~6.8 min

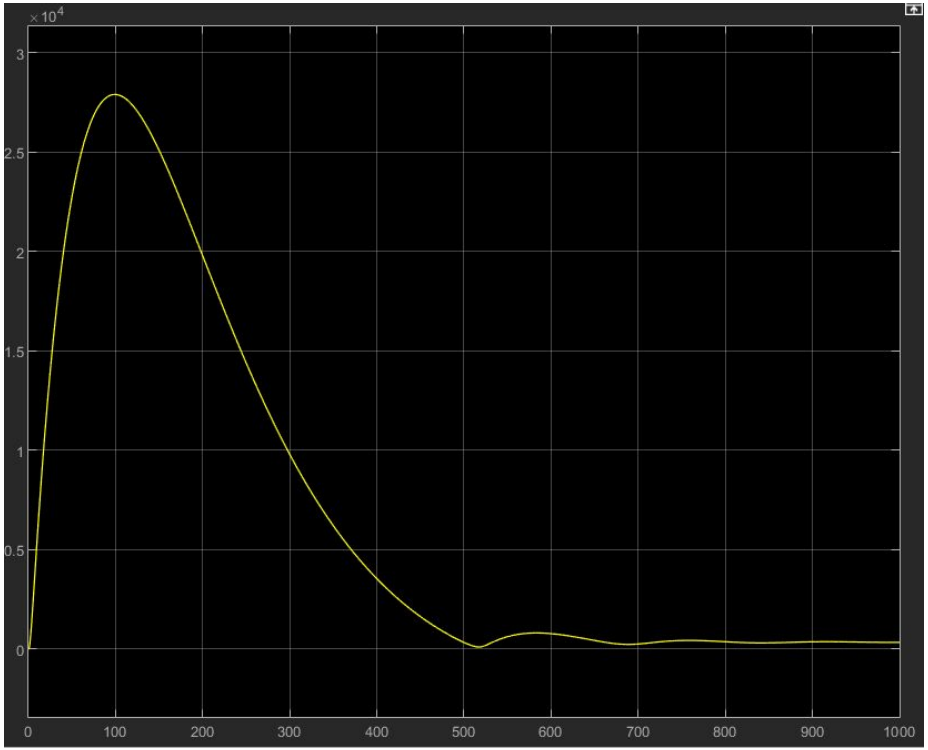
Settling time: ~32 min

Overshoot detected

If we go with (c)



Results of no attenuation and no inhibition



Stable System

Steady State concentration:

Back to ~0

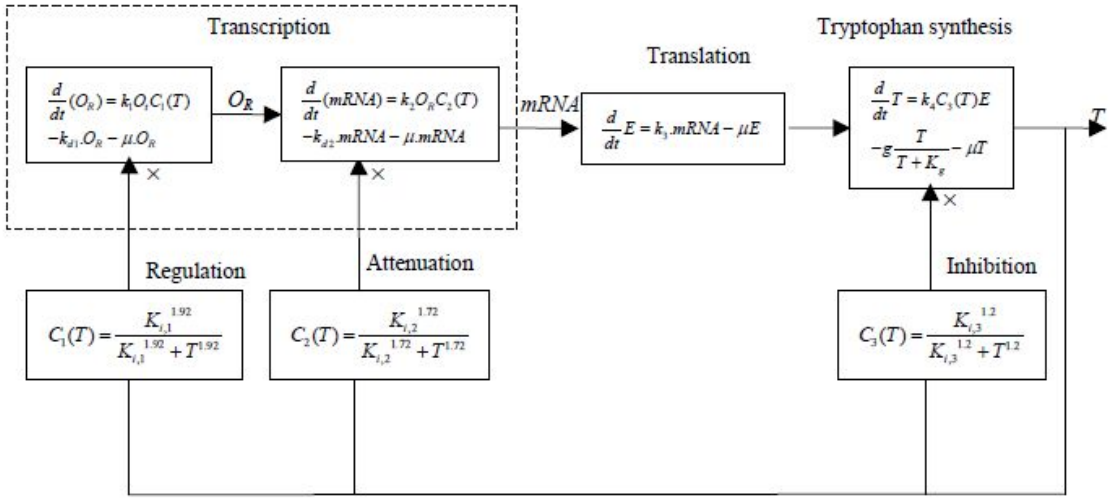
Rising Time: ~62 min

Settling Time: ~750 min

A large overshoot detected

Conclusion

- Hypertryptophanemia and Hartnup disease
  - Build up of tryptophan.



Conclusion

- Simulation over actual experiment?
  - Pros
    - Less money to operate
    - Tighter control over the system, especially with the C1,C2, and C3 equations
  - Cons
    - Lack of experimental data
    - Less control over unforeseen external factors

Resources

Bhartiya, Sharad. “Dynamic Model of Escherichia Coli Tryptophan Operon Shows an Optimal Structural Design.” *PubMed.gov*, June 2003, pubmed.ncbi.nlm.nih.gov/12787031.

Bhartiya, Sharad. “Multiple Feedback Loop Design in the Tryptophan Regulatory Network of Escherichia Coli Suggests a Paradigm for Robust Regulation of Processes in Series.” *PubMed.gov*, 22 June 2006, pubmed.ncbi.nlm.nih.gov/16849267.