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ChemE 7770

Prelim 1

1.

a) 1 mL @ OD600 = 0.1 $\Rightarrow$ $N_c = 1\times10^8$ cells/mL

$V = 1$ mL

From BioNumbers, $B = 280\times10^{-15}\ \frac{\text{gDW}}{\text{cell}} \times 1\times10^{8}\ \frac{\text{cells}}{\text{mL}} \times 1\ \text{mL} = 280\times10^{-7}$ gDW

$\langle n\rangle\ [\ ]\ \frac{\text{mRNA}}{\text{cell}} \Rightarrow \frac{\text{mRNA}}{\text{cell}} \times \frac{1\ \text{mol}}{6.02\times10^{23}\ \text{mRNA}} \times \frac{10^{9}\ \text{nmol}}{1\ \text{mol}} = \frac{\text{nmol}}{\text{cell}}$

To get $\frac{\text{nmol}}{\text{gDW}}$,

$$\frac{\text{nmol}}{\text{gDW}} = \frac{\text{nmol}}{\text{cell}} \times \underbrace{\frac{1\times10^{8}\ \text{cells}}{\text{mL}}}_{N_c} \times \underbrace{1\ \text{mL}}_{V} \times \underbrace{\frac{1}{280\times10^{-7}\ \text{gDW}}}_{1/B}$$

(see attached table for corrected values)

b) $\dot{m}_i = r_{x,i}\bar{u}_i - (\mu + \theta_{m,i})m_i$, where $\underline{r_{x,i} = k_{E,i} R_{x,T}\left(\frac{G_i}{\tau_{x,i}K_{x,i} + (\tau_{x,i}+1)G_i}\right)}$

To find K_x:

s.s $\Rightarrow$ $0 = r_{x,i}\bar{u}_i + (\mu + \theta_{m,i})m_i$

$m^* = \frac{r_x\bar{u}}{\mu + \theta_{m^*}} = K_x\bar{u}$, where $\underline{K_x = \frac{r_x}{\mu + \theta_m^*}}$

$$\Rightarrow \boxed{m^* = K_x(G,\theta)\,\bar{u}(I,K), \text{ where } K_x = \frac{r_x}{\mu + \theta_{m^*}},\quad r_x = \underbrace{k_{E,i}}_{\text{elongation}}\overbrace{R_{x,T}}^{\text{RNAP}}\left(\frac{G_i}{\underbrace{\tau_{x,i}K_{x,i}}_{\text{saturation}} + (\tau_{x,i}+1)G_i}\right),\quad \bar{u} = \frac{w_1 + w_2 f_I}{1 + w_1 + w_2 f_I},\ f_I = \frac{I^n}{K^n + I^n}}$$

c) $$m^* = f(I) = K_x\,\bar{u}(I) = K_x\frac{w_1 + w_2\left(\frac{I^n}{K^n+I^n}\right)}{1 + w_1 + w_2\left(\frac{I^n}{K^n+I^n}\right)}$$

Fitting the above model to the data (using MATLAB's Curve Fitting Tool), we find the following parameters:

$$\boxed{\begin{aligned} K_x &= 0.4347\\ w_1 &= 0.2642\\ w_2 &= 520.9\\ K &= 0.4285\\ n &= 1.532\end{aligned}}$$

d) (Look at attachment for MATLAB plot)

With the fitted parameters, the model replicates the data quite well ($R^2 = 0.9984$

2.

a) $S \longrightarrow X \rightleftarrows Z$

$$\boxed{\begin{aligned} \frac{d\tilde{X}}{d\tilde{t}} &= \frac{\tilde{\alpha}_x + \tilde{\beta}_x S}{1 + S + (\tilde{Z}/\tilde{Z}_x)^{n_{zx}}} - \tilde{\delta}_x \tilde{X} \\ \frac{d\tilde{Z}}{d\tilde{t}} &= \frac{\tilde{\alpha}_z}{1 + (\tilde{X}/\tilde{X}_z)^{n_{xz}}} - \tilde{\delta}_z \tilde{Z} \end{aligned}}$$

derived using basic Hill function regulation

$\tilde{X}, \tilde{Z}$ = conc. of protein

S = signal

$\tilde{\alpha}_x, \tilde{\alpha}_z$ = basal rates of production

$\tilde{\delta}_x, \tilde{\delta}_z$ = rates of degradation

$\tilde{X}_z, \tilde{Z}_x$ = strength of repression

n_{zx}, n_{xz} = cooperativity of repression

b) Measuring time in terms of degradation of X:

$\delta_z = \frac{\tilde{\delta}_z}{\tilde{\delta}_x}$, $t = \tilde{t}\,\tilde{\delta}_x$ (this should be dimensional time $\Rightarrow$ typo in paper)

Measuring rates and concentrations in terms of $\tilde{\delta}_x$ and $\tilde{\alpha}_z$:

$\alpha_x = \frac{\tilde{\alpha}_x}{\tilde{\alpha}_z}$, $\beta_x = \frac{\tilde{\beta}_x}{\tilde{\alpha}_z}$

$X_z = \frac{\tilde{X}_y \tilde{\delta}_x}{\tilde{\alpha}_z}$, $Z_x = \frac{\tilde{Y}_x \tilde{\delta}_x}{\tilde{\alpha}_z}$

$X = \frac{\tilde{X}\tilde{\delta}_x}{\tilde{\alpha}_z}$, $Z = \frac{\tilde{Z}\tilde{\delta}_x}{\tilde{\alpha}_z}$

$$\Rightarrow \frac{d\left(X\tilde{\alpha}_z/\cancel{\tilde{\delta}_x}\right)}{d\left(t/\cancel{\tilde{\delta}_x}\right)} = \frac{\alpha_x\tilde{\alpha}_z + \beta_x\tilde{\alpha}_z S}{1 + S + \left(\frac{Z\tilde{\alpha}_z/\tilde{\delta}_x}{Z_x\tilde{\alpha}_z/\tilde{\delta}_x}\right)^{n_{zx}}} - \cancel{\tilde{\delta}_x}\left(X\frac{\tilde{\alpha}_z}{\cancel{\tilde{\delta}_x}}\right)$$

$$\cancel{\tilde{\alpha}_z}\frac{dX}{dt} = \cancel{\tilde{\alpha}_z}\left(\frac{\alpha_x + \beta_x S}{1 + S + (Z/Z_x)^{n_{zx}}}\right) - \cancel{\tilde{\alpha}_z}X$$

$$\boxed{\frac{dX}{dt} = \frac{\alpha_x + \beta_x S}{1 + S + (Z/Z_x)^{n_{zx}}} - X}$$

$$\Rightarrow \frac{d\left(Z\tilde{\alpha}_z/\cancel{\tilde{\delta}_x}\right)}{d\left(t/\cancel{\tilde{\delta}_x}\right)} = \frac{\tilde{\alpha}_z}{1 + \left(\frac{X\tilde{\alpha}_z/\cancel{\tilde{\delta}_x}}{X_y\tilde{\alpha}_z/\cancel{\tilde{\delta}_x}}\right)^{n_{xz}}} - \delta_z\cancel{\tilde{\delta}_x}\left(\frac{Z\tilde{\alpha}_z}{\cancel{\tilde{\delta}_x}}\right)$$

$$\tilde{\alpha}_z\frac{d}{dt} = \tilde{\alpha}_z\left(\frac{1}{1 + (X/X_z)^{n_{xz}}}\right) - \cancel{\tilde{\alpha}_z}Z\delta_z$$

$$\boxed{\frac{dZ}{dt} = \frac{1}{1 + (X/X_z)^{n_{xz}}} - \delta_z Z}$$

(Look at attachments for MATLAB plots)

c)

$\alpha_x = 1.5$

$\beta_x = 5$

$z_x = 0.41$

$n_{zx} = 2.7$

$x_z = 1.5$

$n_{xz} = 2.7$

$\delta_z = 1.0$

First, check for S.S. solutions:

$$0 = \frac{\alpha_x + \beta_x S}{1 + S + (Z/z_x)^{n_{zx}}} - X$$

$$0 = \frac{1}{1 + (X/x_z)^{n_{zx}}} - \delta_z Z$$

Second, check for stability of each S.S. solution:

$$f(X,Z) = \frac{\alpha_x + \beta_x S}{1 + S + (Z/z_x)^{n_{zx}}} - X$$

$$g(X,Z) = \frac{1}{1 + (X/x_z)^{n_{zx}}} - \delta_z Z$$

$$\frac{\partial f}{\partial x} = -1 \qquad \frac{\partial f}{\partial z} = \frac{-\frac{n_{zx}}{z_x^{n_{zx}}} \cdot Z^{n_{zx}-1} (\alpha_x + \beta_x S)}{(1 + S + (Z/z_x)^{n_{zx}})^2}$$

$$\frac{dg}{dx} = \frac{-\frac{n_{zx}}{x_z^{n_{zx}}} X^{n_{zx}-1}}{(1 + (X/x_z)^{n_{zx}})^2} \qquad \frac{\partial g}{\partial z} = -\delta_z$$

$$\Rightarrow J = \begin{bmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial z} \\ \frac{\partial g}{\partial x} & \frac{\partial g}{\partial z} \end{bmatrix}$$

$\det(J - \lambda I) = 0 \Rightarrow \underline{\lambda_{real} < 0}$

d) Look at attachments for MATLAB plots

(ODE's were solved using ode45 for the given initial conditions and values of S as well as the parameters presented in Table S.1)

e) For Hopf bifurcation, one obvious stable steady-state solution can be found at low S, such as $\underline{S = 1}$.

S.S. values for X, Y, Z:

(Using parameter values from Table S.1) $\Rightarrow$

$$0 = \frac{\alpha_x + \beta_x S}{1 + S + (Z/z_x)^{n_{zx}}} - X$$

$$0 = \frac{\alpha_y + \beta_y S}{1 + S + (X/x_y)^{n_{xy}}} - \delta_y Y$$

$$0 = \frac{1}{1 + S + (X/x_z)^{n_{xz}} + (Y/y_z)^{n_{yz}}} - \delta_y Z$$

(solved using MATLAB) $\Rightarrow$

$$\boxed{\begin{aligned} X_{ss} &= 0.0022 \\ Y_{ss} &= 0.5430 \\ Z_{ss} &= 0.0004 \end{aligned}}$$

(Look at attachments for MATLAB plots)

Oscillations are asychronous $\Rightarrow$ $\underline{\text{incoherent}}$

For saddle node bifurcation, a stable steady state solution can be found at high S, such as S = 1000.

S.S. values for X, Y, Z:

(Using previous equations to solve using MATLAB) ⟹

$$\boxed{\begin{aligned} X_{ss} &= 0.1065 \\ Y_{ss} &= 0.2529 \\ Z_{ss} &= 0.0015 \end{aligned}}$$

(Look at attachments for MATLAB plots)

Oscillations are synchronous and overlap with one another ⟹ coherent

The differences in coherence result from the different gene expression states relative to the oscillatory spiral center of the gene circuit. For Hopf bifurcation, transient states start close to this unstable spiral center, so a small perturbation leads to large differences in the final oscillation phase and larger amplification of small initial differences. For a saddle node bifurcation, initial states occur very far away from the oscillatory region, so small differences in initial values are preserved from a perturbation until the trajectory enters the oscillatory region. In this manner, expression is sychronous and doesn't result in incoherence.

f) The S.S. values for S = 105 can be found as the following:

$X_{ss} = 0.0213 - 0.0236i$

$Y_{ss} = -0.0126 + 0.3536i$

$Z_{ss} = -0.0009 + 0.0001i$

These S.S. values give rise to asynchronous oscillations following a perturbation of $\Delta S_2 = 5$

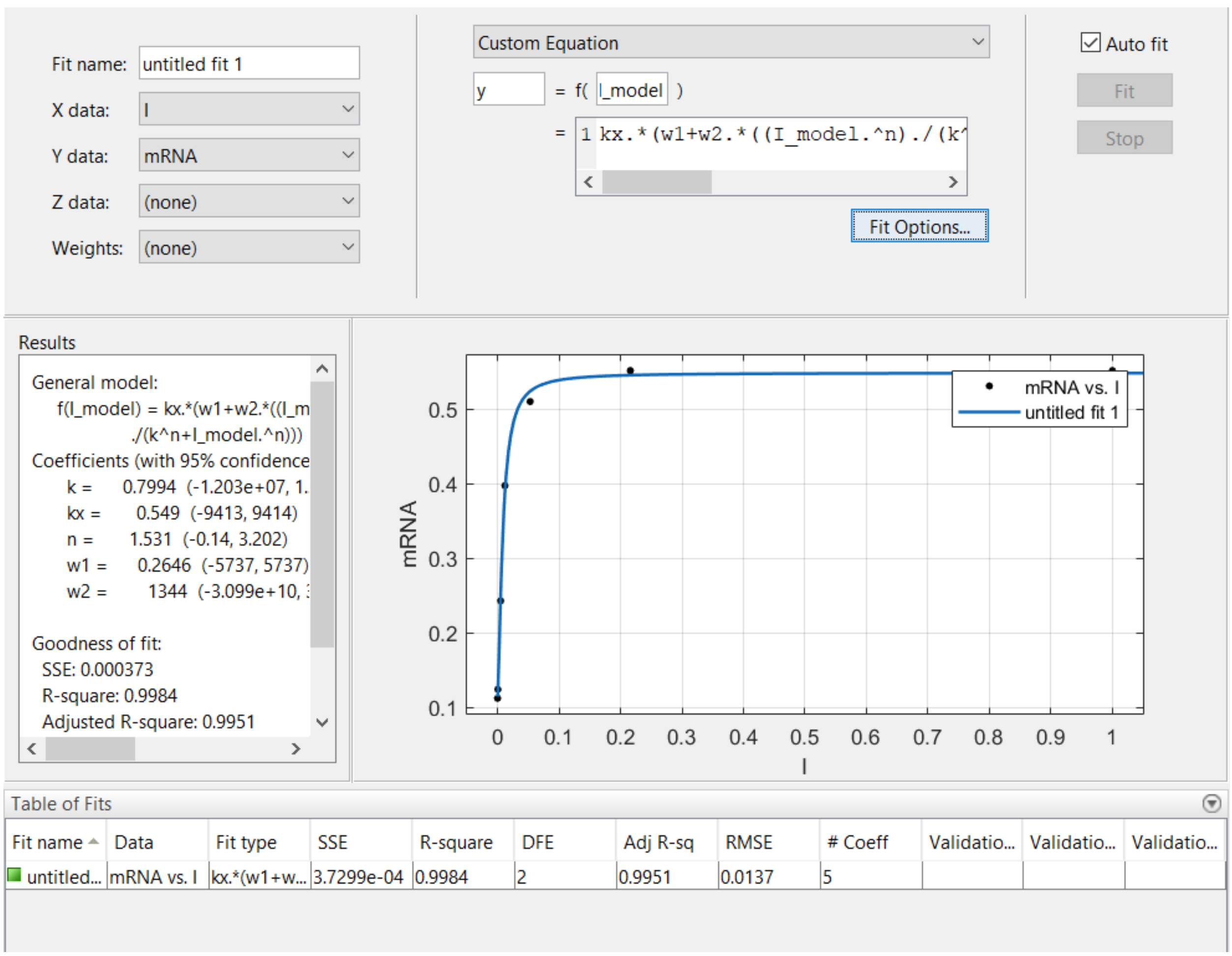
Therefore, we can conclude that the authors must have used different parameters to obtain their results.

The authors have committed academic treason of the highest order and deserve to be stripped of their titles and lands (just kidding)

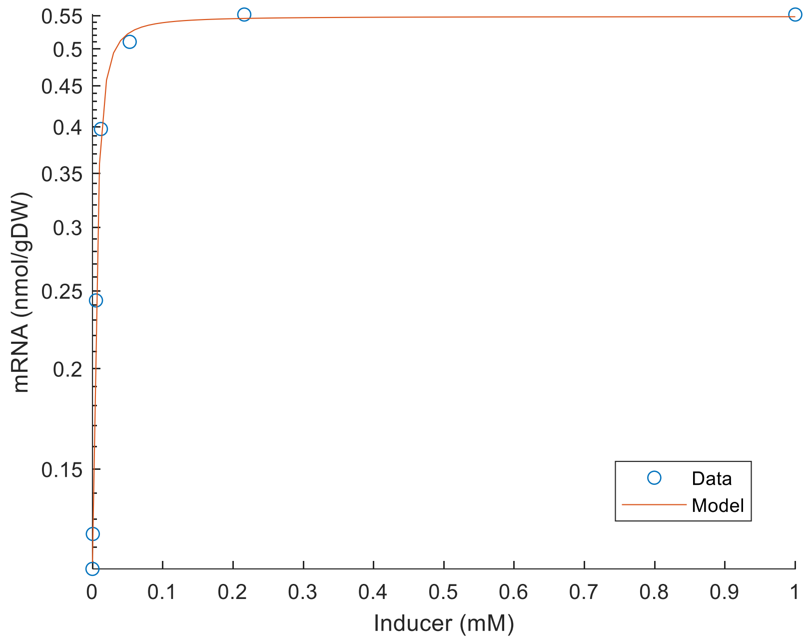
Problem 1a: Converted values

<n> (mRNA/cell)	Converted values (nmol/gDW)
19	0.1127
21	0.1246
41	0.2432
67	0.3975
86	0.5102
93	0.5517
93	0.5517

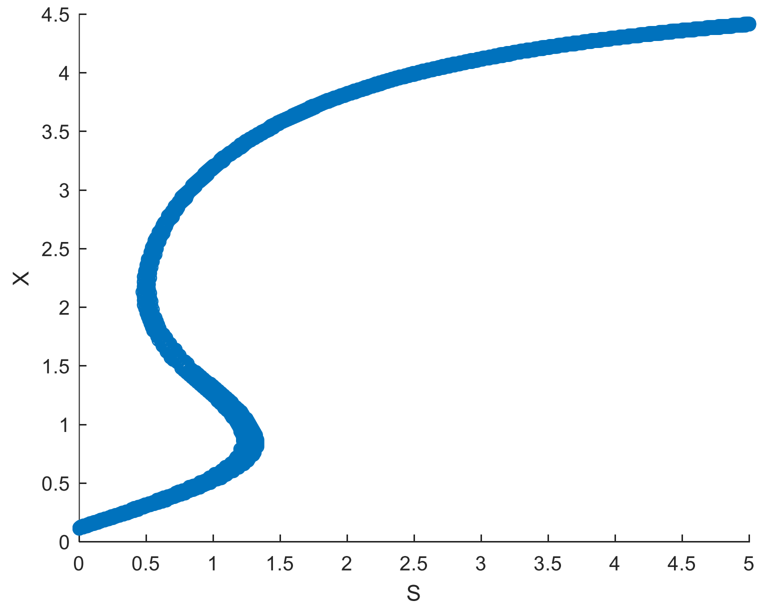
Problem 1c: Parameter fitting



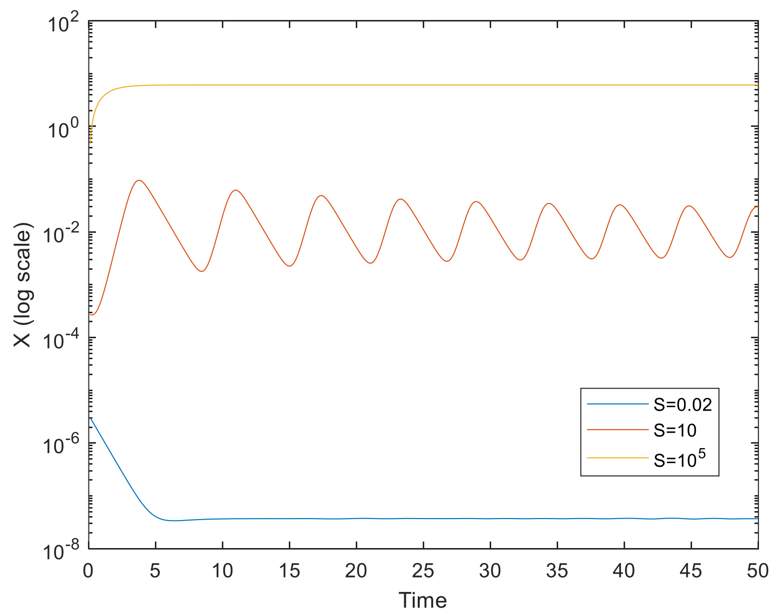
Problem 1d: Data vs Predicted values



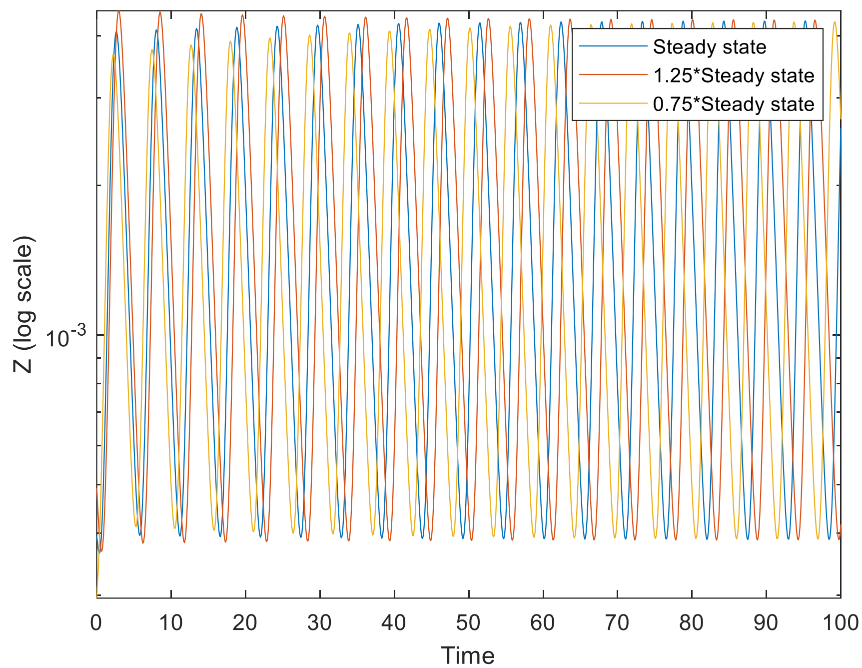
Problem 2c: Plot of S vs. X for Bistable switch



Problem 2d: Plot of X vs. t for different values of S



Problem 2e: Plot of Z vs. t for Hopf Bifurcation



Problem 2e: Plot of Z vs. t for Saddle node bifurcation