

Problem 1

$$\rho_{lac} = \text{promotor} \quad \text{specific volume} = \frac{\langle n \rangle}{\rho}$$

(a) Assuming $\text{OD}_{600} = 0.1 \sim 1 \times 10^8 \text{ cells/mL}$

$$\beta = \langle m_c \rangle \hat{N}_c V \quad \langle n \rangle \rightarrow \beta$$

$V = 1 \text{ mL}$

$$\langle n \rangle = \frac{\text{lacZ messenger RNA copy \#}}{\text{cell}} \quad \langle m_c \rangle = \frac{\text{gDW}}{\text{cell}} \quad \hat{N}_c = \frac{\# \text{cells}}{\text{mL}}$$

water fraction
Mass of e.coli cell

$$\beta = \frac{2.8 \times 10^{-13} \text{ gDW}}{\text{cell}} \left(\frac{1 \times 10^8 \text{ cell}}{\text{mL}} \right) (1 \text{ mL}) = 2.8 \times 10^{-5} \text{ gDW}$$

$$\langle n \rangle = \frac{\text{lacZ mRNA}}{\text{cell}} \left(\frac{\text{mol}}{6.022 \times 10^{23} \text{ molecules}} \right) \left(\frac{10^9 \text{ nmol}}{1 \text{ mol}} \right)$$

converted $\langle n \rangle$	IPTG (nm)
1.12682E-09	0
1.24543E-09	5E-10
2.43156E-09	0.000000005
3.97353E-09	0.000000012
5.10035E-09	0.000000053
5.51549E-09	0.000000216
5.51549E-09	0.000001

See excel sheet for calculations.

(b)

$$\dot{m}_i = \underbrace{r_{xi,i} \bar{U}_i}_{\frac{\text{nmol}}{\text{gDW hr}}} - (\mu + \theta m_i) m_i \quad \text{promotor activity function}$$

rate of transcription
of gene i

show that $m^* = K_x (G, P) \bar{U}_i (I, K)$

\uparrow $\frac{\text{nmol}}{\text{gDW}}$ \downarrow $\frac{\text{lacZ gene abundance}}{\text{parameters}}$

$$\text{S.S. } 0 = r_{xi,i} \bar{U}_i - (\mu + \theta m^*) m^*$$

$$m^* = \frac{r_{xi,i} \bar{U}_i}{\mu + \theta m^*} = \left(\frac{r_{xi,i}}{\mu + \theta m^*} \right) \bar{U}_i$$

$\underbrace{\qquad\qquad\qquad}_{K_x} \qquad \bar{U}_i (I, K)$

$$K_x = \frac{r_{xi,i}}{\mu + \theta m^*}$$

$$\bar{U}_i = \frac{w_1 + w_2 f_i}{1 + w_1 + w_2 f_i} \quad f_i = \frac{1^n}{K_d^n + 1^n}$$

$$r_x = k_f^x R_{x,T} \left(\frac{G}{T_x K_x + (T_x + 1) G} \right) \quad (\text{Eqn 26 LN})$$

(c)

We need: k_f^x
 $R_{x,T}$
 G
 T_x
 K_x

we have:
 $\text{IPTG} = \text{inducer concentration } (I)$
 $\mu = \frac{1}{t_{\text{half}}}$ (LN2)

k_f^x : elongation rate constant = $\frac{\text{transcription elongation rate}}{\text{gene length}}$ $K_I = 1/\text{characteristic initiation time}$
 T_I characteristic initiation time (initiation limited)

$$K_x = \frac{k_- + k_+}{k_+}$$

$$n(I) = \frac{W_1 + W_2 f_2}{1 + W_1 + W_2 f_2} \quad f_2 = \frac{I^n}{K_D + I^n} \quad K_D = 49600 \text{ nM}$$

$$0.049$$

At $\text{IPTG} = 0$:
 $M^* = K_{\text{gmax}} \bar{U} \longrightarrow 1.13 \times 10^7 = 2.05 \times 10^7 \quad \bar{U} = 0.38$
 $K_2 = K_I \quad k_- = k_{-1} \quad k_1 = k_+$
 $\frac{W_1}{1 + W_1} = \bar{U}$ $K_I = \frac{4 \times 10^{-2}}{s} = \frac{1}{k_{on}} \quad K_m = 25 \quad 0.1 \times 10^6 \frac{1}{M \cdot s} \left(\frac{1 M}{10^9} \right) = 0.009$
 $2 \times 10^8 = \frac{4 \times 10^{-2}}{k_{off}}$

$$T_{\text{obs}} = 400$$

$$D_{\text{obs}} = \frac{1}{K_I} + \underbrace{\left(\frac{k_- + K_I}{K_+ K_I} \right)}_{\frac{K_x}{K_I}} \frac{1}{R_{x,T}}$$

slope $0.12 \text{ } \mu\text{M} \cdot \text{s}$
intercept 25 s

$$f_2 = \frac{I^n}{49600 + I^n}$$

↑
ignore my random
scratch work

$$K_m = 4 \times 10^{-4}$$

$$\bar{G} = \frac{\text{copies}}{\text{cell}}$$



-cell

Bionumbers:

$$K_d = 49.4 \times 10^{-8}$$

$$K_x = 5.15 \times 10^{-9}$$

$$\text{Background} = \frac{W_1}{1+W_1} = 0.22$$

$$W_1 = 0.28$$

$$m^+ = K_x \bar{u} \quad @ \text{fully induced transcription } \bar{u}=1 \quad m^+ = K_x (u=1)$$

$$\begin{matrix} \text{background} \\ \text{lowest value} \end{matrix} \rightarrow 1.127 \times 10^{-9} = 5.15 \times 10^{-9} \bar{u} \Rightarrow u = 0.22$$

↳ gain

I struggled to solve n and W₂ simultaneously, so I am estimating n=1.5 for the sake of finishing this problem → $n=1.5$

$$\frac{u(I) = 0.28 + W_2 \left[\frac{I^n}{K_d^n + I^n} \right]}{1 + 0.28 + W_2 \left[\frac{I^n}{K_d^n + I^n} \right]} = \frac{m^+}{K_{\text{gain}}}$$

↓ plugging in I and $\frac{m^+}{K_{\text{gain}}}$ value into Wolfram Alpha

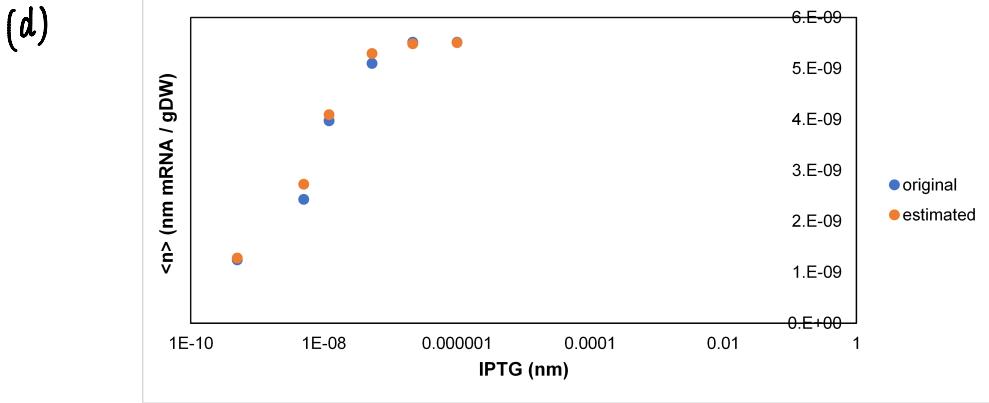
$$W_2 = 191.74$$

$$\text{Eqn for estimated values: } m^+ = K_{\text{gain}} \left[\frac{W_1 + W_2 \left(\frac{I^n}{K_d^n + I^n} \right)}{1 + W_1 + W_2 \left(\frac{I^n}{K_d^n + I^n} \right)} \right]$$

I started out finding a bunch of parameters to solve for K_x, But I could never get the units to match up when solving for u (to get w₁), since u is between 0 and 1. I ended up basing my K_x value from my graph of the converted data. At fully induced transcription, u=1 so I used the same logic as the lecture notes.

$$\downarrow \quad \begin{matrix} \text{kinetic limit} = \\ S \times 10^{-9} \frac{\text{nmoL}}{\text{gDW}} \end{matrix}$$

$$m^+ = K_x (u=1)$$



Originally, my model did not fit at ALL. My first Kd value was 49600, and I believe that I just converted my units wrong. However, I think my Kd value is wrong overall. For the sake of getting my curve to fit, I just played around with each value to see how it affected the graph, and then from there I could determine what values were wrong in my model.

I had to use a very small Kd value (i.e I just divided the original value I found (4.96 M) by factors of 10 until it fit my graph). I ended up using $K_d = 4.96e-7$. That being said, the K_d value has a large impact on the overall shape. I am not sure what the correct value is, but it would be on the order of $1e-7$ from my guess and check method. Additionally, I suck at anything computational so I was unable to solve for n and w_2 simultaneously. I guessed $n=1.5$, which is just the number given in the 1-30-2020 lecture notes. Changing the cooperativity affects the range of the y values, but the shape of the graph remains relatively the same. Changing w_1 and w_2 do affect the range of the graph, but not as drastically as K_d did.

problem 2

(a) 

$$\frac{d\tilde{X}}{dt} = \frac{\tilde{\alpha}_x + \tilde{\beta}_x S}{1 + S + (\tilde{z}/\tilde{x})^{n_{zx}}} - \tilde{\delta}_x \tilde{X}$$

$$\frac{d\tilde{Z}}{dt} = \frac{\tilde{\alpha}_z}{1 + (\tilde{x}/\tilde{z})^{n_{zx}}} - \tilde{\delta}_z \tilde{Z}$$

In the paper, they should have put a tilde over the α_x for eq. 3: $t = \tilde{t} \delta_x$

(b) Nondimensionalize: $\tilde{\delta}_z = \frac{\tilde{\delta}_z}{\delta_x}$ $t = \tilde{t} \delta_x$ $\alpha_x = \frac{\tilde{\alpha}_x}{\tilde{\alpha}_z}$ $\beta_x = \frac{\tilde{\beta}_x}{\tilde{\alpha}_z}$

$$\tilde{z}_x = \frac{\tilde{z}_x \tilde{\delta}_x}{\tilde{\alpha}_z} \quad \tilde{x}_z = \frac{\tilde{x}_z \tilde{\delta}_x}{\tilde{\alpha}_z}$$

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

$$\tilde{\tilde{X}} = \frac{X \tilde{\alpha}_z}{\tilde{\delta}_x} \quad \tilde{\tilde{Z}} = \frac{Z \tilde{\alpha}_z}{\tilde{\delta}_x} \quad \tilde{\tilde{t}} = \frac{t}{\tilde{\delta}_x} \quad \tilde{\tilde{\alpha}}_x = \alpha_x \tilde{\alpha}_z \quad \tilde{\tilde{\delta}}_z = \frac{Z \tilde{\alpha}_z}{\tilde{\delta}_x} \quad \tilde{\tilde{\alpha}}_x = \frac{Z \tilde{\alpha}_z}{\tilde{\delta}_x}$$

Plug in variables:

$$\left(\frac{\tilde{\alpha}_z \tilde{\delta}_x}{\tilde{\delta}_x} \right) \frac{d\tilde{X}}{dt} = \frac{\alpha_x \tilde{\alpha}_z + \beta_x \tilde{\alpha}_z S}{1 + S + \left[\frac{Z \tilde{\alpha}_z}{\tilde{\delta}_x} \right]^{n_{zx}}} - \frac{\tilde{\delta}_x \tilde{X} \tilde{\alpha}_z}{\tilde{\delta}_x}$$

$$\left(\frac{\tilde{\alpha}_z}{\delta_x} \frac{dx}{dt} \right) \frac{dx}{dt} = \frac{\alpha_x \tilde{\alpha}_z + \beta_x \tilde{\alpha}_z S}{1 + S + \left[\frac{Z \frac{\tilde{\alpha}_z}{\delta_x}}{\frac{Zx \frac{\tilde{\alpha}_z}{\delta_x}}{\delta_x}} \right]^{n_{zx}}} - \frac{\delta_x \times \tilde{\alpha}_z}{\delta_x}$$

$$\frac{\tilde{\alpha}_z}{\delta_x} \frac{dx}{dt} = \frac{\alpha_x \tilde{\alpha}_z + \beta_x \tilde{\alpha}_z S}{1 + S + \left(\frac{Z}{Zx} \right)^{n_{zx}}} - X \tilde{\alpha}_z$$

Divide by $\tilde{\alpha}_z$:

$$\frac{dx}{dt} = \frac{\alpha_x + \beta_x S}{1 + S + \left(\frac{Z}{Zx} \right)^{n_{zx}}} - X$$

Plug in variables for the Z -equation and divide by $\tilde{\alpha}_z$:

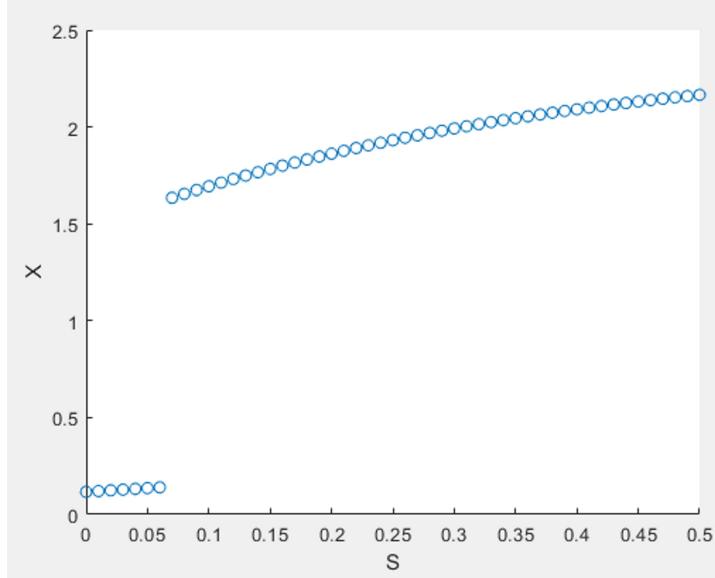
$$\left(\frac{\delta_x \tilde{\alpha}_z}{\delta_x} \frac{dz}{dt} \right) \frac{dz}{dt} = \frac{\tilde{\alpha}_z}{1 + \left[\frac{X \frac{\tilde{\alpha}_z}{\delta_x}}{\frac{Xz \frac{\tilde{\alpha}_z}{\delta_x}}{\delta_x}} \right]^{n_{xz}}} - \delta_z Z \frac{\tilde{\alpha}_z}{\delta_x} \cdot \frac{\tilde{\alpha}_z}{\delta_x}$$

$$\frac{dz}{dt} = \frac{1}{1 + \left(\frac{X}{Xz} \right)^{n_{xz}}} - \delta_z Z$$

(c) Given: $\alpha_x = 1.5$ $Z_x = 0.4$ $X_z = 1.5$ $\delta_z = 1.0$
 $\beta_x = 5.0$ $n_{zx} = 2.7$ $n_{xz} = 2.7$

$$\frac{dx}{dt} = \frac{\alpha_x + \beta_x S}{1 + S + \left(\frac{Z}{Zx} \right)^{n_{zx}}} - X = 0 \text{ @ S.S.}$$

$$\frac{dz}{dt} = \frac{1}{1 + \left(\frac{X}{Xz} \right)^{n_{xz}}} - \delta_z Z = 0 \text{ @ S.S.}$$



The bottom S.S line in the paper is more extended than mine, but I believe it is just an error in my code, and that the figure can be reproduced. I used fsolve, so I'm not sure if this is the reason it won't plot the rest of the bottom line.

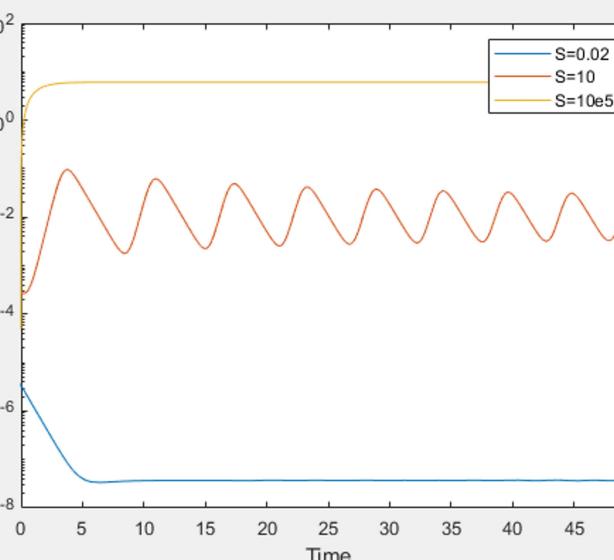
$$(d) \dot{X} = \frac{\alpha_x + \beta_x S}{1 + S + (Z/Z_x)^{n_{zx}}} - X$$

$$I.C: X_0 = Y_0 = Z_0 = 0$$

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

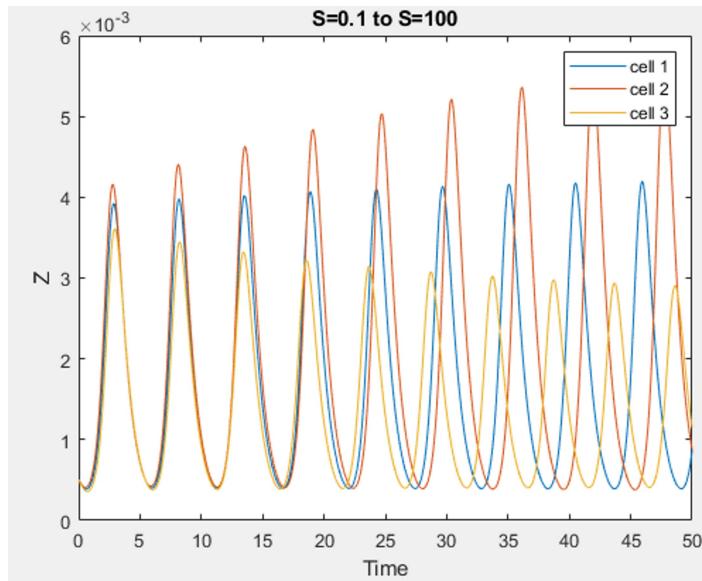
parameter	mode
α_x	3.9×10^{-2}
α_y	4.3×10^{-3}
β_x	6.1
β_y	5.7
δ_y	1.05
δ_z	1.04
Z_x	1.3×10^{-5}
Y_z	11×10^{-3}
X_z	12×10^{-2}
X_y	7.9×10^{-4}
n_{zx}	2.32
n_{xy}	2
n_{yz}	2

Solving for $S = 0.02, 10, 10^5$



- (e) Steady-state for a value of signal, S, near but below the Hopf bifurcation point = 0.1

Corresponding S.S values: X = 0.0001
Y = 0.4839
Z = 0.0005

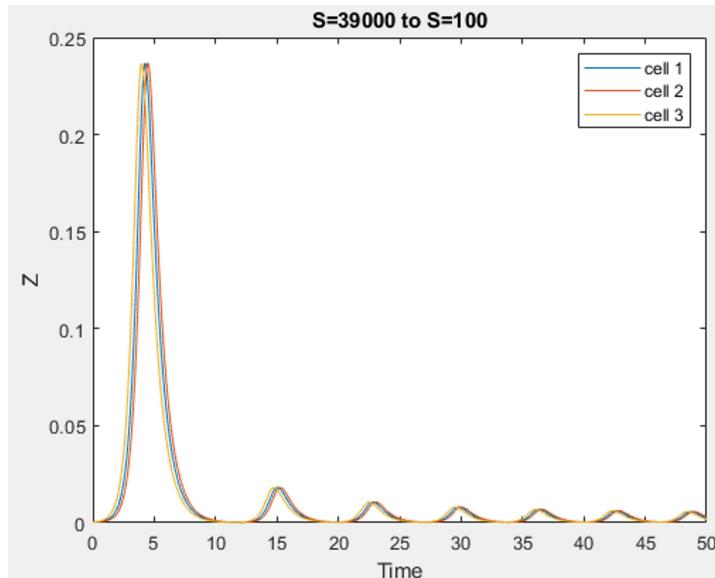


The oscillations are incoherent for an abrupt change from S=0.1 to S=100. They start out coherent, but then lose their coherence like the figure in the paper.

Steady-state for a value of signal, S, near but above the saddle node bifurcation - I started at 10000 and basically just kept guessing large values until I found one that led to one steady state.

S = 40000

Corresponding S.S values: X = 5.6024
Y = 0.0043
Z = 0.0004



The change from S=40000 to S=100 is coherent.

In a Hopf bifurcation, the oscillations occur because a spiral loses stability. The oscillations near this point are already near unsteady centers, so the initial conditions will play a large role in stability and oscillations. For example, the steady-state for a value of signal, S, near but below the Hopf bifurcation point = 0.1 to S=100 is incoherent because small differences in the initial conditions are amplified over time, which is what causes the asynchronous oscillations.

When the cells are passing through the saddle-node bifurcation, they are expressed at levels that are farther from the unstable oscillatory region - this means that the initial conditions won't be amplified over time and the cells won't oscillate out of sync like in the Hopf bifurcation example. Therefore, the change from S=40000, which is near but above the saddle bifurcation results in coherent oscillations. The authors state that the saddle-node bifurcation also allows the rapid establishment of constant amplitude oscillation after the signal is reduced, which is verified by the graph.

(f)

Using this same logic, I would make an educated guess that abruptly changing the signal from S=105 to S=100 would still be coherent, since decreasing the signal in the second example was coherent. When I tried to graph the change from S=105 to S=100, S=105 was still oscillatory so I'm not sure how to determine steady-state values to plug in. It is possible that they use different parameter values, but this would only affect the range of the oscillations or shift the oscillations on the x-axis for the most part. In conclusion, I trust that they used the values that they claimed.