Here is my submission for Prelim 1.

Problem 1 has the attached written work, and corresponding excel spreadsheet with plots, and the converted data for Part A.

Problem 2 has the attached work and written explanations. For Parts C-D the corresponding files in the folders for each part can be run in MATLAB, the code to run is the specified above the plots for each part.

-Rachel Eichman

Rge32@cornell.edu

Problem 1

Part A

convert $\langle n \rangle$ values to $\beta = \langle m_c \rangle \hat{N}_c V$ where $\langle m_c \rangle$ is $\frac{gDW}{cell}$ gDW/culture

$\hat{N}_c = \frac{\#\ cells}{mL}$ V denotes Volume (mL)

$V = 1mL$ β[=] gDW

gDW in culture

#mRN/cell

$\langle n \rangle \rightarrow m^*$ ← nmol/gDW of total cell in the culture

According to Bionumbers

$\langle n \rangle$[=] $\frac{\#\ mRNA}{cell}$

$$\frac{\langle n \rangle}{\left(\frac{\#\ mRNA}{cell}\right)\left(\frac{1\ mol}{6.022\times10^{23}}\right)\left(\frac{10^9\ nmol}{1\ mol}\right)\left(\frac{cell}{avg\ gDW\ mass}\right)} \qquad \frac{1}{\langle m_c \rangle}$$

$\tau = 40$

$430 \times 10^{-15}\ \frac{gDW}{cell}$

[This conversion was used in excell to calculate Values given in the spread sheet.

BIO# 109836

* this calculation would be the same result as calculating the volume basis for total gDW of cell in the 1mL and dividing the total nmol of mRNA for the gene in the culture by this number.

$\frac{0.39\ gDW}{L} = 100600$ 100600

$0.100600 = 0.1 \times \frac{0.39\ gDW}{L} \times \frac{1L}{10^3 mL} \times \frac{1mL}{10^8\ cells}$

$\frac{gDW}{cell} = 3.9\times10^{-13}\ \frac{gDW}{cell}$

Part B

at steady state

$\dot{m}_i = r_{x,i}\,\bar{u}_i - (\mu + \theta_{m,i})\,m_i$ → 0

$$m_* = \frac{r_{x,i}\,\bar{u}_i}{\mu + \theta_{m,i}}$$

$$m_* = \frac{r_{x,i}}{(\mu + \theta_{m,i})}\,\bar{u}$$

$$\boxed{m_* = K_x(G,\theta)\;\bar{u}(I,k)} \quad \text{where} \quad \boxed{K_x = \frac{r_{x,i}}{(\mu + \theta_{m,i})}}$$

$r_{x,i}$ described by each TL in notes on transcription

Part C

Assume 2 copies of gene per cell half life for mRNA i, 5 minutes $n_T = 1000$

Assume P_{lac} is an indu promoter that responds to IPTG μ is dilution θ_m is related to half life.

Use Moon et al. promoter modeling approach.

determining $\bar{u}$

there is some expression when IPTG is not bound and this function saturates with IPTG.

K_x = max value of mRNA that can be present in a cell given max growth rate and and the degredation rate.

based on the moon et al. paper the positively indu promotr is described by some function of the approximate form

$$\frac{\alpha + \beta \bar{I}^n}{1 + \alpha + \beta I^n}$$

(this is the same as the moon et al result except I^n is used in place of f_{TL}, (I also test this and it also works to describe the data.

my first thought

The corresponding transfer function in the same form as this type of system we saw in N.A

eqn (4)

$$P_{TAC} = F_{TAC}^{max}\left(\frac{K_1 + K_2 f_{TL}}{1 + K_1 + K_2 f_{TL}}\right) \qquad \bar{u}$$

$$\text{where } f_{TL} = \frac{L^n}{K_D^n + L^n} \quad \text{where } L = [I]\ [=]\ \frac{mmol}{L}$$

Part C take 2

we have

$$m^* = K_x(G, \Theta)\,\bar{u}(I, K)$$

$$\bar{u} = \frac{k_1 + k_2 f_{TL}}{1 + k_1 + k_2 f_{TL}} \quad \text{where } f_{TL} = \frac{I^n}{K_D^n + L^n}$$

$$\frac{r_{x,j}}{(\mu + \Theta_{m,i})}$$

where $I = [IPTG]$

we need to determine the associated biological parameters

we can calculate the parameter values for μ and Θ based on growth rate and half life and doubling time

$$-r_{deg} = \Theta_{m,i} \cdot m^*$$

for first order rxn: $t_{1/2} = \frac{\ln(2)}{\Theta_{m,i}}$ $\quad \Theta_{m,i} = \frac{\ln(2)}{t_{1/2}} = \frac{\ln(2)}{5\,min} = 0.139\ min^{-1}$

for the dilution term, the doubling time is the time it takes the cell to dilute by a factor of 2 so it can also be thought of like a half life and to calculate

$$\mu = \frac{\ln(2)}{\tau_D} = \frac{\ln(2)}{40\,min} = 0.0173\ min^{-1}$$

we know need to describe $r_{x,j}$ From the course notes on models of transcription eq (26) describes one such model for this term

$$r_{x,j} = k^x_{E,j} \underbrace{R_{x,T}}_{nmol/gDW} \left(\frac{G_j}{\tau_{x,j} K_{x,j} + (\tau_{x,j} + 1) G_j} \right)$$

where $k^x_{E,j}$ is elongation rate constant

R_{x_T} is total RNAP concentration/cell

G_j is the copy # of the gene $\Rightarrow$ Given as 2 in the problem

$\tau_{x,j}$ is the time constant for transcription

$$\hookrightarrow \simeq \frac{K_E{}^x_{,j}}{K_I}$$ $K_I \rightarrow$ rate of initiation

$\{ K_{x,j}$ saturation constant for transcription.

$$k^*_{E,j} = \langle k_E{}^x \rangle = \underbrace{e_x}_{\text{elongation rate nt/s}} \times \frac{1}{L}$$ length of gene (we will ballpark this #)

Based on the McClure paper

$K_I = \widetilde{K_2}^{\text{thats}} = 4\times10^{-2}\ s^{-1}$

$K_{x,j} = \frac{K_- + K_I}{K_+}$

in his notation

$K_{x,j} = \frac{K_{-1}}{K_1} + \frac{K_2}{K_1}$

$\frac{K_{-1}}{K_1} \sim \frac{K_{off}}{K_2}$

The value of ex the transcription elongation rate is $ex = 25\ nt/s$ BIO#: 112325

$L = 1000\ nt$

The avg total RNAP [] in a cell RXT is 1500 molecules/cell BIO#: 101440

(with BIO #s are ~1500 as well.)

~1400 we will use 1500

$$\frac{1500\ molec}{cell}\ \frac{1\ cell}{3.9\times10^{-13}\ GDW}\left(\frac{1\ mol}{6.022\times10^{23}\ molec}\right)\left(\frac{10^9\ nmol}{1\ mol}\right) = 6.38\ nmol/GDW$$

Based on the values we use in problem set 2

$K_{x,j} \approx 0.0136\ \mu M$

we need

$\mathcal{G}$ in units of μM to agree with the units of $K_{x,j}$

$$\frac{2\ gen}{cell}\ \frac{1\ cell}{1\ \mu m^3}\left(\frac{1\ \mu m^3}{1\times10^{-15}\ L}\right)\left(\frac{1\ mol}{6.022\times10^{23}\ molec}\right)\left(\frac{10^6\ \mu mol}{1\ mol}\right) = 0.0033\ \mu M$$

BID: 100014

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we can do calculations now with these parameters

$K^*_{E_j} = ex \times \frac{1}{L} = \frac{25\ nt}{s} \times \frac{1}{1000\ nt} = 0.025\ s^{-1}$

$\frac{0.025}{s} \times \frac{60\ s}{1\ min} = 1.5\ min^{-1}$

$\tau_{x_i} = \frac{k_e^{x_j}}{K_I} = \frac{0.025\ s^{-1}}{4\times10^{-2}\ s^{-1}} = 0.625$

$$\left(\frac{\mathcal{G}_j}{\tau_{x_i} K_{x_j} + (\tau_{x_i}+1)\mathcal{G}_j}\right) = \frac{0.0033\ \mu M}{0.625 \times 0.0136\ \mu M + (1.625)\ 0.0033\ \mu M} = 0.238$$

$r_{x_j} = K_E^{x_j} R_{x_T}\ (\quad)$

$1.5\ min^{-1}\ (6.38\ nmol/GDW)(0.238) = 2.28\ \frac{nmol}{GDW\ min}$

$K_x = \frac{r_{x_j}}{\Theta_{mix}} = \frac{2.28}{0.139\ min^{-1} + 0.0173\ min^{-1}} = 14.6\ nmol/GDW$

We can now fit to the parameters in the $\bar{u}$ function

→ K_1

we have $m^* = K_x \bar{u}$

at [IPTG] = 0 $I = 0$, $ftL = 0$

$$\bar{u} = \frac{k_1}{1 + k_1}$$

we have the data point @ [IPTG] = 0

$m^* = 0.0809$ nmol/60w from this we can solve for K_1 given the calculated K_x

$m^* = K_x \bar{u}$

$0.0809 = 14.6 \times \frac{K_1}{1 + K_1}$

$K_1 = 0.0056$

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C.J. Wilson et al. / Biophysical chemistry 26

A paper reports (in Table 1)

K_D for IPTG binding to LacI of 2.8×10^{-6} M

↳ which is 0.0028 mM

↳ we will use this for the value of K_D in the fTL function

See Excell Sheet pg1 for the requested table

We will assume n=1, the result of assuming only 1 molecule of IPTG binds the repressor, and there is only 1 site for the repressor to bind on the DNA

Based on all of these parameters I used a non-linear Least Squares fit to determine an appropriate value of K_2, and excell solver calculated a value of $0.0199 = K_2$

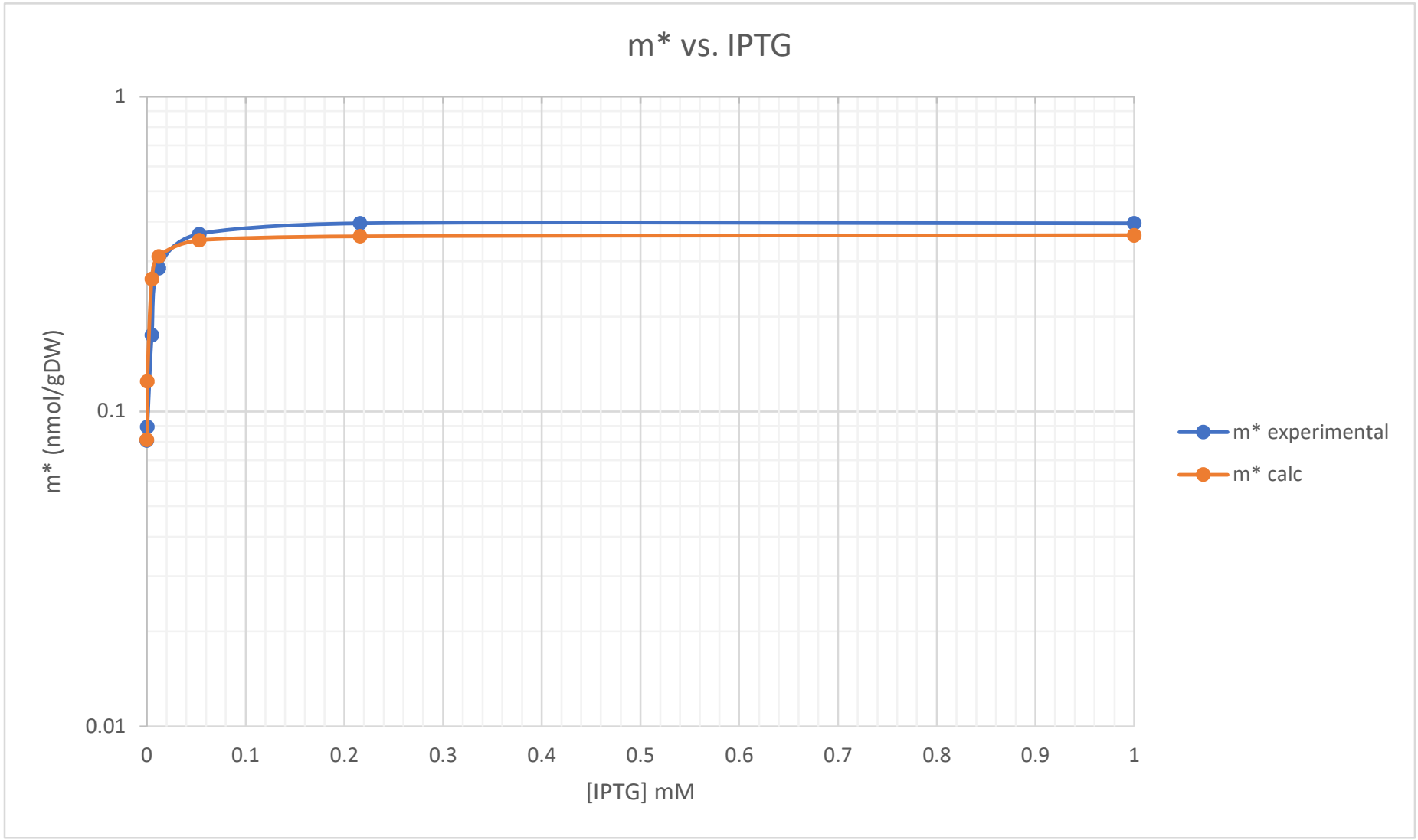
Part D

The model fits the data surprisingly well, it has the correct shape, the only predominate errors are in the value to which the calculated concentrations of m* saturate to.

All that is necessary to improve the fit is to fit both K_2 and K_D to the data, instead of just K_2, this result can be seen in the second figure, where both K_2 and K_D were fit to the data given all other parameters. This is enough to eliminate the offset.

Based on this I would say the value of K_D is the parameter that is controlling the fit of the data preventing a more exact fit of the model.

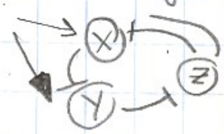
The graphs can all be recreated by entering these parameters into the equations for K_x and $\bar{u}$ and plotting in excell See the excell sheet.) (Problem 1 Excell Workbook)


m* vs. IPTG
m* (nmol/gDW)
1
0.1
0.01
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
[IPTG] mM
m* experimental
m* calc

Problem 2

$\Delta Z = 1.0$

AC-DC system



Oscillations and bi-stability!

coherence resonance

multifunctionality (w/ minimal param changes)

mapping is important

coh. reson.

look at gene knowns

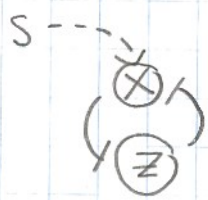
Bifurcation →

shown arms, stable oscillations

continuation

Part A

Figure 1B shows the following system



$$\frac{d\tilde{X}}{d\tilde{t}} = \text{generation of } X - \text{degradation of } X$$

generation: activated by S, inhibited by Z

degradation: $\tilde{\delta}_x \tilde{X}$ ← follow first order degradation

(I will follow the same pattern as the paper where the cooperativity for activation with S is 1, and repression cooperativity for z is n_{zx})

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

for z we have

$$\frac{d\tilde{Z}}{d\tilde{t}} = \text{generation of } z - \text{degradation of } z$$

$$\boxed{\frac{d\tilde{Z}}{d\tilde{t}} = \frac{\tilde{\alpha}_z}{1 + (\tilde{X}/\tilde{X}_z)^{n_{xz}}} - \tilde{\delta}_z \tilde{Z}}$$

Part B

This is the error!

we are now here to nondimensionalize the equations using the parameters given in equations (3) → (6).

first $t = \tilde{t}\,\delta x$ $\quad \tilde{t} = \frac{t}{\tilde{\delta x}}$ ⟶ t should be $\boxed{\tilde{t}\,\tilde{\delta x} = t}$

this is the error

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

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

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

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

when $\delta_z = \frac{\tilde{\delta}_z}{\delta x}$

now substitute for $X = \frac{\tilde{X}\,\tilde{\delta}_x}{\tilde{\alpha}_z}$ and $\frac{\tilde{z}\,\tilde{\delta}_x}{\tilde{\alpha}_z} = z$ into both expressions

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

$$\frac{\tilde{\alpha}_z}{\tilde{\delta}_x}\frac{\partial X}{\partial t} = \frac{1}{\tilde{\delta}_x}\left[\frac{\tilde{\alpha}_x + \tilde{\beta}_x S}{1 + S + (\tilde{z}/\tilde{z}_x)^{n_{zx}}}\right] - \frac{X\tilde{\alpha}_z}{\tilde{\delta}_x} \qquad \frac{\tilde{\alpha}_z}{\tilde{\delta}_x}\frac{\partial z}{\partial t} = \frac{1}{\tilde{\delta}_x}\left[\frac{\tilde{\alpha}_z}{1 + (\tilde{x}/\tilde{x}_z)^{n_{xz}}}\right] - \frac{\delta_z \tilde{\alpha}_z z}{\tilde{\delta}_x}$$

$$\frac{\partial X}{\partial t} = \frac{\frac{\tilde{\alpha}_x}{\tilde{\alpha}_z} + \frac{\tilde{\beta}_x}{\tilde{\alpha}_z} S}{1 + S + (\tilde{z}/\tilde{z}_x)^{n_{zx}}} - X \qquad \frac{\partial z}{\partial t} = \frac{1}{1 + (\tilde{x}/\tilde{x}_z)^{n_{xz}}} - \delta_z z$$

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

$$\frac{\partial X}{\partial t} = \frac{\alpha_x + \beta_x S}{1 + S + (\tilde{z}/\tilde{z}_x)^{n_{zx}}} - X$$

we now need to subsitute for $\tilde{x}/\tilde{x}_z$ and $\tilde{z}/\tilde{z}_x$

$$z_x = \frac{\tilde{z}_x\,\tilde{\delta}_x}{\tilde{\alpha}_z} \Rightarrow \tilde{z}_x = \frac{z_x\,\tilde{\alpha}_z}{\tilde{\delta}_x}$$

$$\frac{\tilde{z}}{\tilde{z}_x} = z/_{z_x}$$

$$x_z = \frac{\tilde{x}_z\,\tilde{\delta}_x}{\tilde{\alpha}_z} \qquad \tilde{x}_z = \frac{x_z\,\tilde{\alpha}_z}{\tilde{\delta}_x}$$

$$\frac{\tilde{X}}{\tilde{x}_z} = X/_{x_z}$$

$$\boxed{\frac{\partial X}{\partial t} = \frac{\alpha_x + \beta_x S}{1 + S + (z/z_x)^{n_{zx}}} - X} \quad (1)$$

$$\boxed{\frac{\partial z}{\partial t} = \frac{1}{1 + (X/x_z)^{n_{xz}}} - \delta_z z} \quad (2)$$

Part C

see plots in matlab.

@ s.s both eqn 1 and eqn 2 = 0

Yes the solid black lines are qualitatively reproducible.

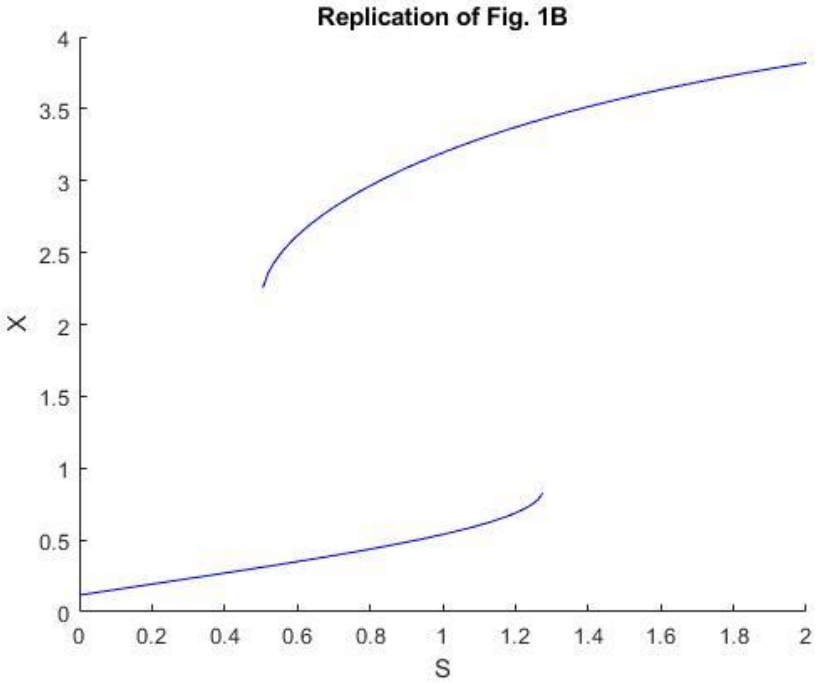
See the plot

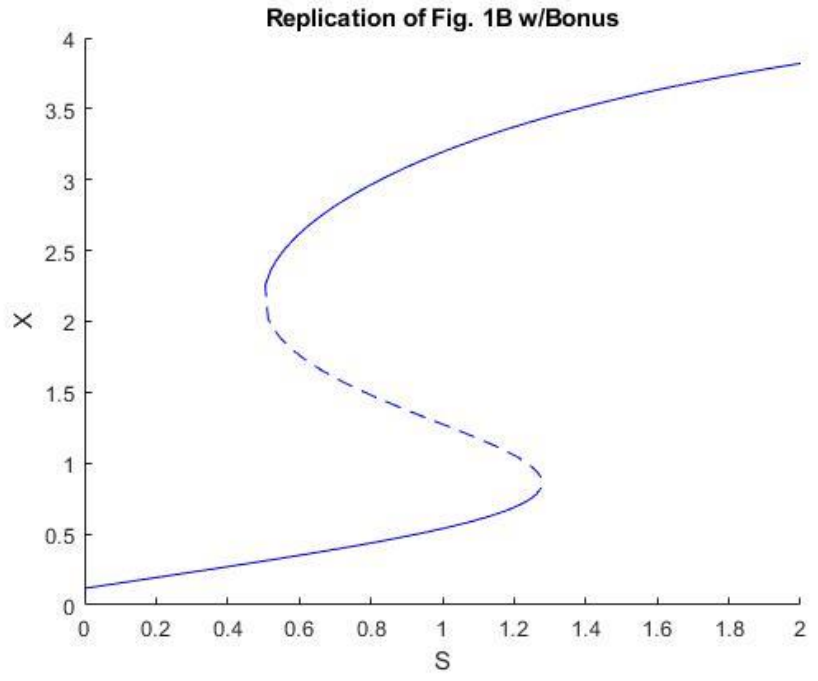
My plot has the same trends as that in the figure

See document for remaing parts, plots and analysis of the figures

Part C

The figures can be recreated by executing the code PartC.m in matlab. Which solves the equations using VPAsolve, the steady state regimes were calculated by using the previous value of X and Z, and the unsteady states were found by bounding the Z and X search space, where Z was arbitrarily bounded to successfully evaluate vpasolve, and X was bounded based on the X values two saddle node points from the steady state evaluations over the appropriate S space.

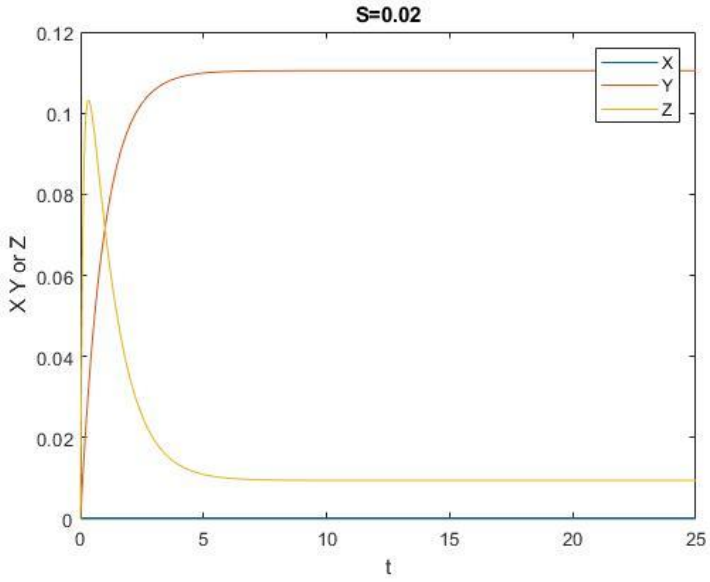


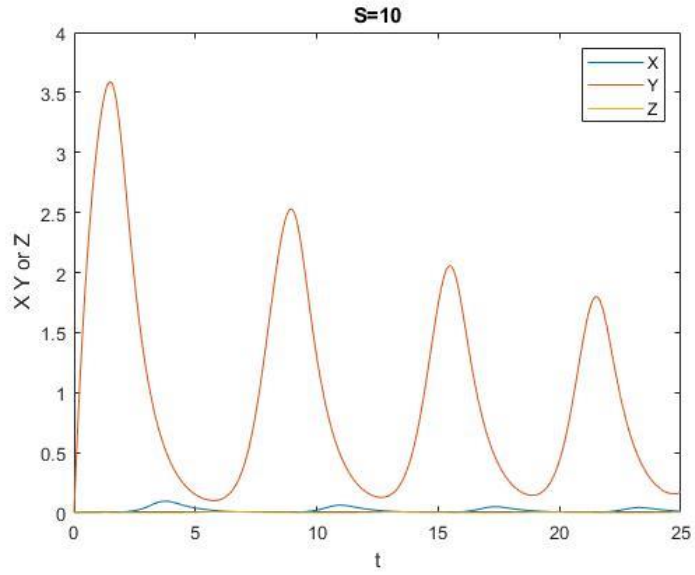


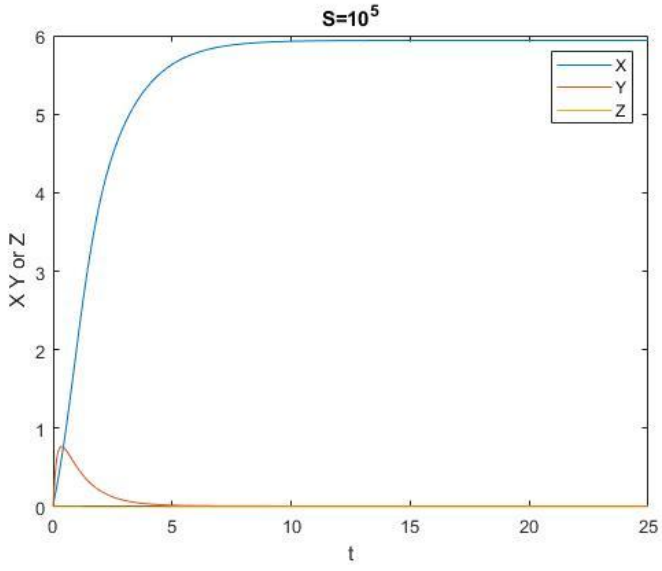
Part D

The figures can be recreated by executing the code PartD.m in matlab.

This uses the given mode parameters in the supplements, each system is solved by evaluating the set of ODEs with ODE 45 with the corresponding S, each of which is given in its own function. The initial state of the system is X=0, Y=0, Z=0



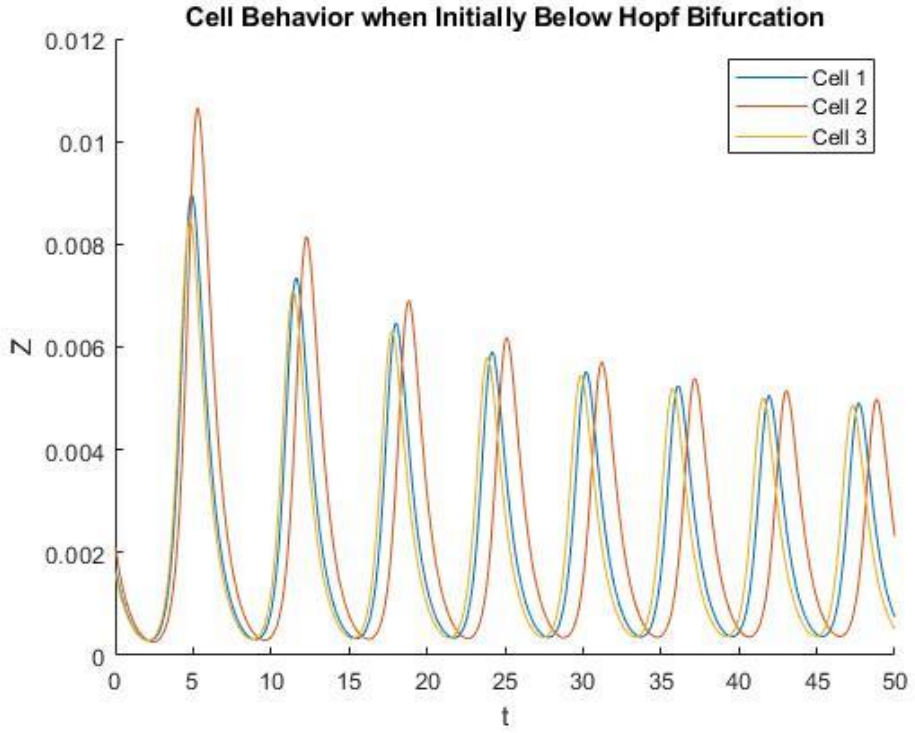




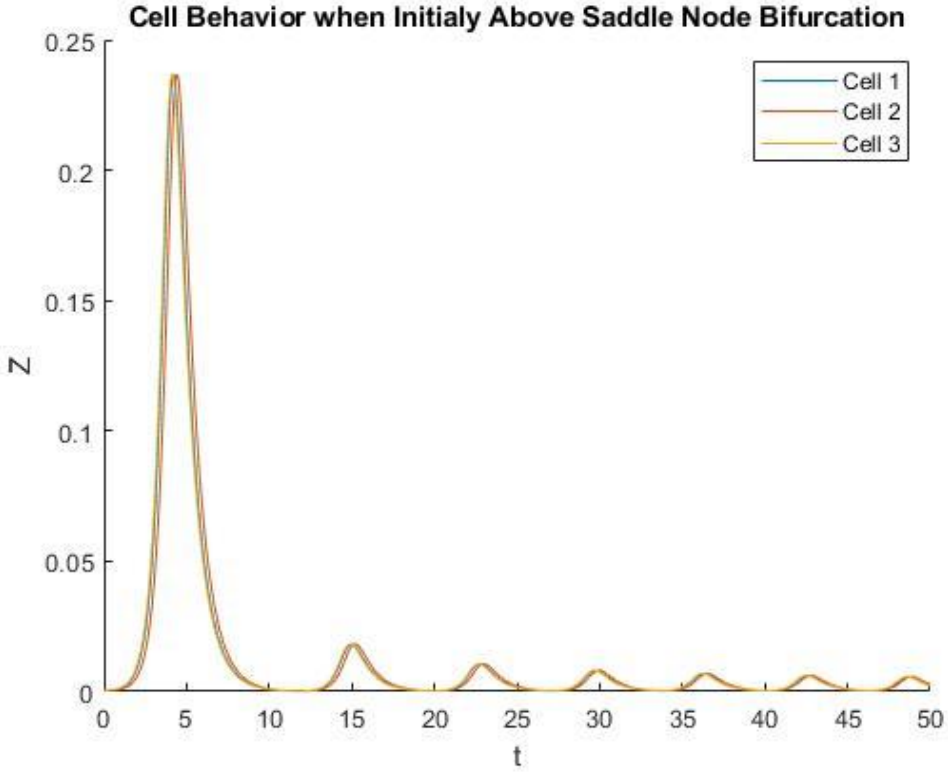
The time behavior of these three plots with different S values agrees at least qualitatively with the behavior shown in Figure 2. Where at low S there is low X in the middle range there are oscillations and above the saddle node bifurcation high constant X concentration for long time.

Part E

The figures can be recreated by executing the code ParE.m in matlab. Where the steady state values for a given S were calculated using vpasolve and then used to determine the time domain behavior of three cells with varying initial conditions from that steady state when S is now set to 100. The time domain behavior was calculated using ODE45 and the system of ODES in the included function.



The oscillations when switching from an S below the Hopf bifurcation (S read off Fig 3) to S=100, the oscillations are incoherent. The three cells oscillate slightly out of phase with one another and this is maginified over time.



When switching from an S value above the Saddle node Bifurcation to S=100, the three cells all oscillate with very similar behavior, in magnitude and period. Their behavior is also not phase shifted from one another; therefore, the oscillations are coherent.

Based on the explanation in the paper this difference in behavior as a result of increasing or decreasing S to the same value are the result of limiting behavior and trajectory toward the oscillating regime. In the case of decreasing S the initial value for expression is far from the attraction spiral so they settle into the oscillations with the same phase from the beginning allowing for coherent behavior. On the other hand, increasing S from below the Hopf bifurcation leads to instabilities because attracting spiral states shift to unstable behavior, and this means that variation in the exact initial state of the species leads different phase behavior and therefore incoherence. The plotted data in this problem agree with their discussion where slight variation initially leads to incoherence when increasing S across the Hopf bifurcation and coherence when decreasing from above the saddle node bifurcation

Part F

Given that decreasing the value of S in the system I part D was able to achieve coherent oscillations, I would expect decreasing S from 105 to 100 to also lead to a coherent behavior. I believe the authors statement about achieving coherent behavior with the given the parameter values we used when decreasing S from 105 to 100.