CHEME 7770: Advanced Biomolecular Engineering Prelim 1 Solution

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Problem 1

(a)

Mass of single cell, m_{cell} = 2.8 e-13 g
N_A = 6.02 e23
fraction_dry_cell, f_{dry} = 0.3
<n> = [19, 21, 41, 67, 86, 93, 93] mRNA/cell
mRNA = <n> * 1/(m_{cell} f_{dry} N_A) * 10^9 nmol/gDW
mRNA = [0.37, 0.41, 0.81, 1.32, 1.70, 1.84, 1.84] nmol/gDW

(b)

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

@ S.S, $\dot{m}_i = 0$

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

$$G_j + R_x \rightleftharpoons (G_j : R_x)_c$$
$$(G_j : R_x)_c \longrightarrow (G_j : R_x)_o$$
$$(G_j : R_x)_o \longrightarrow R_x + G_j$$
$$(G_j : R_x)_o \longrightarrow m_j + R_x + G_j$$

kinetic rate of TX $r_{x,j} = k^x_{E,j}(G_j : R_x)_o$ (RDS)

@ S.S.

$$k_+ G_j R_x = k_-(G_j : R_x)_c + k_I (G_j : R_x)_c$$
$$k_I (G_j : R_x)_c = k_A (G_j : R_x)_o + k^x_{E,j} (G_j : R_x)_o$$

$$(G_j : R_x)_c = \frac{k_+ G_j R_x}{k_- + k_I}$$

$$(G_j : R_x)_o = \frac{k_I}{k_A + k^x_{E,j}} (G_j : R_x)_c$$

RNAP abundance : $R_{x,T} = R_x + (G_j : R_x)_c + (G_j : R_x)_o$

$$\Rightarrow \quad (G_j : R_x)_0 = \frac{G_j \, R_x}{K_{x,j} \, \tau_{x,j}}$$

where $K_{x,j} = \dfrac{k_+}{k_- + k_I}$ and $\tau_{x,j} = \dfrac{k_I}{k_A + k_E^x}$

$$R_{x,T} = R_x \left[1 + \frac{G_j R_x}{K_{x,j}} + \frac{G_j R_x}{K_{x,j} \tau_{x,j}} \right]$$

or

$$R_x = \frac{R_{x,T} \, K_{x,j} \, \tau_{x,j}}{\left[K_{x,j} \tau_{x,j} + G_j \tau_{x,j} + G_j \right]}$$

$$r_{x,j} = \frac{K_{E,j}^x \, R_{x,T} (G_j)}{\tau_{x,j} K_{x,j} + G_j (1 + \tau_{x,j})}$$

$$m_j^* = \frac{r_{x,j} \, \bar{u}_j}{(\mu + \theta_{m,j})}$$

$$u(I) = \frac{w_1 + w_2 b_I}{1 + w_1 + w_2 b_I}$$

w_1 = due to RNAP bound to DNA

w_2 = due to inducer

where $b_I = \dfrac{I^n}{K^n + I^n}$ (Moon et al.)

$$m_j^* = \frac{K_{E,j}^x R_{x,T} G_j}{\tau_{x,j} K_{x,j} + G_j (1 + \tau_{x,j})} \cdot \frac{1}{(\theta_{m,j} + \mu)} \cdot \bar{u}_j$$

$$m^* \text{ (lacZ mRNA)} = \frac{K_{E,j}^x R_{x,T} G_j}{\tau_{x,j} K_{x,j} + G_j (1 + \tau_{x,j})}$$

$$m^* \text{ (lacZ mRNA)} = \underbrace{\frac{K_E^x R_{x,T} G}{\tau_x K_x + G(1 + \tau_x)} \cdot \frac{1}{(\theta + \mu)}}_{K_x(G, \theta)} \cdot \underbrace{\frac{w_1 + w_2 \cdot b_I}{1 + w_1 + w_2 b_I}}_{\bar{u}(I, K)}$$

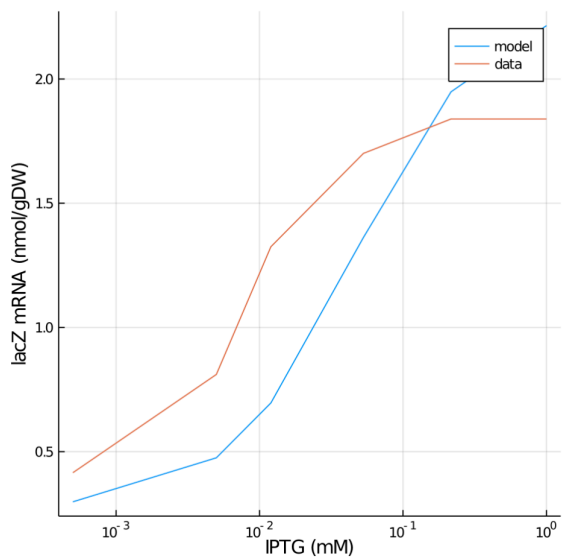
where $b = \dfrac{I^n}{I^n + K^n}$

(c)

S.No	Parameter	Value	Unit	Reference
1	Doubling time	40	min	Given
2	mRNA half-life	5	min	Given
3	Characteristic transcript length	1000	nt	Given
4	LacZ copy number	2	copies/cell	Given
5	RNAPII copy number	1150	copies/cell	*
6	Transcription elongation rate	60	nt/s	*
7	Characteristic initiation time	42	s	*
8	Transcription saturation constant	0.24	nmol/gDW	*
9	Mass of single cell	2.8e-13	g	*
10	Fraction of dry cell	0.3	dimensionless	*
11	n_IPTG_RNAP	1.0		
12	W_IPTG_RNAP	0.01		
13	W_IPTG_LacZ	0.08		
14	K_IPTG_LacZ	49.6e-3		Bionumbers: 101976

* https://github.com/varnerlab/JuGRN-Generator/blob/master/src/distribution/Default.json

(d)



The model has a similar shape but is not a great fit. The fit and shape is mostly determined by the values of W and n in the control function.

Problem 2

(a)

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

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

(b)

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

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

$$\delta_y = \frac{\bar{\delta}_y}{\bar{\delta}_x} \qquad \delta_z = \frac{\bar{\delta}_z}{\bar{\delta}_x} \qquad t = \bar{t}\,\bar{\delta}_x$$

$$\alpha_x = \frac{\bar{\alpha}_x}{\bar{\alpha}_z} \qquad \alpha_y = \frac{\bar{\alpha}_y}{\bar{\alpha}_z} \qquad \beta_x = \frac{\bar{\beta}_x}{\bar{\alpha}_z} \qquad \beta_y = \frac{\bar{\beta}_y}{\bar{\alpha}_z}$$

$$Z_x = \frac{\bar{Z}_x \bar{\delta}_x}{\bar{\alpha}_z} \qquad X_y = \frac{\bar{X}_y \bar{\delta}_x}{\bar{\alpha}_z} \qquad X_z = \frac{\bar{X}_z \bar{\delta}_x}{\bar{\alpha}_z} \qquad Y_z = \frac{\bar{Y}_z \bar{\delta}}{\bar{\alpha}_z}$$

$$X = \frac{\bar{X}\bar{\delta}_x}{\bar{\alpha}_z} \qquad Y = \frac{\bar{Y}\bar{\delta}_x}{\bar{\alpha}_z} \qquad Z = \frac{\bar{Z}\bar{\delta}_x}{\bar{\alpha}_z}$$

$$\frac{d\left(\frac{\bar{X}\bar{\delta}_x}{\bar{\alpha}_z}\right)}{d(\bar{t}\,\bar{\delta}_x)} = \frac{\left(\frac{\bar{\alpha}_x}{\bar{\alpha}_z}\right) + \left(\frac{\bar{\beta}_x}{\bar{\alpha}_z}\right) S}{1 + S + \left[\left(\frac{\bar{Z}\bar{\delta}_x}{\bar{\alpha}_z}\right) \times \left(\frac{\bar{\alpha}_z}{\bar{Z}_x \bar{\delta}_x}\right)\right]^{n_{zx}}} - \frac{\bar{X}\bar{\delta}_x}{\bar{\alpha}_z}$$

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

$$\frac{d\left(\frac{\bar{Z}\bar{\delta}_x}{\bar{\alpha}_z}\right)}{d(\bar{t}\,\bar{\delta}_x)} = \frac{1}{1 + \left(\frac{\bar{X}\bar{\delta}_x}{\bar{\alpha}_z} \times \frac{\bar{\alpha}_z}{\bar{X}_z \bar{\delta}_x}\right)^{n_{xz}}} - \frac{\bar{\delta}_z}{\bar{\delta}_x} \frac{\bar{Z}\bar{\delta}_x}{\bar{\alpha}_z}$$

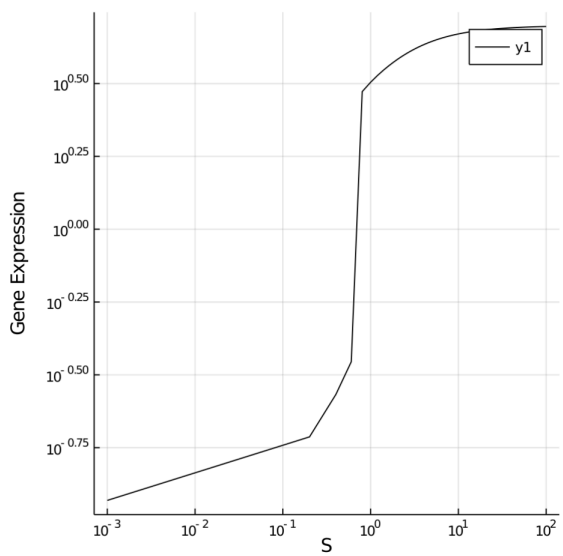
$$\frac{\bar{\delta}_y}{\bar{\delta}_x} \frac{d\bar{Z}}{d\bar{t}} = \frac{\bar{\alpha}_z}{1 + (\bar{Y}/\bar{X}_z)^{n_{xz}}} - \bar{\delta}_z \bar{Z}$$

The error is with $t = \bar{t}\,\delta_x$ which should be $t = \bar{t}\,\bar{\delta}_x$ to get their nondimensional equations and z must be $\bar{z}$ in the equation for $\dot{z}$.
The nondimensional equations for 1B are:

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

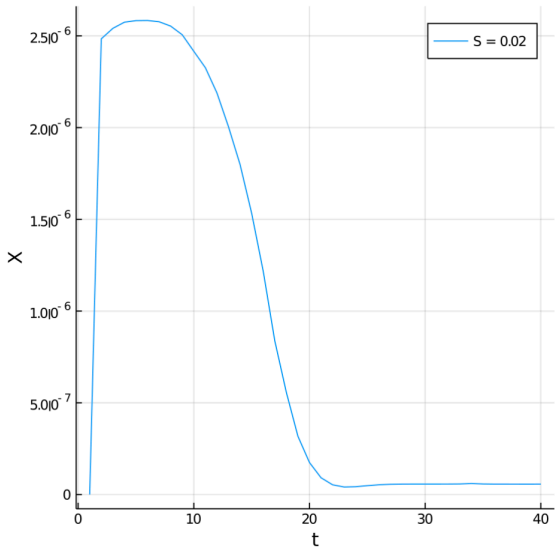
$$\frac{d\bar{z}}{d\bar{t}} = \frac{\bar{\alpha}_z}{1 + (\bar{x}/\bar{x}_z)^{n_{xz}}} - \bar{\delta}_z \bar{z}$$

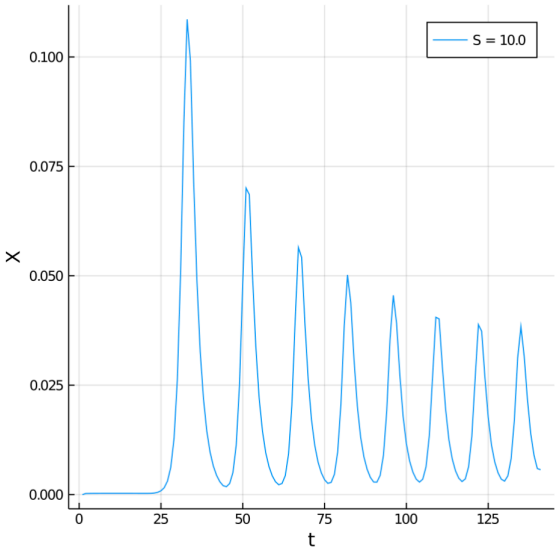
(c)

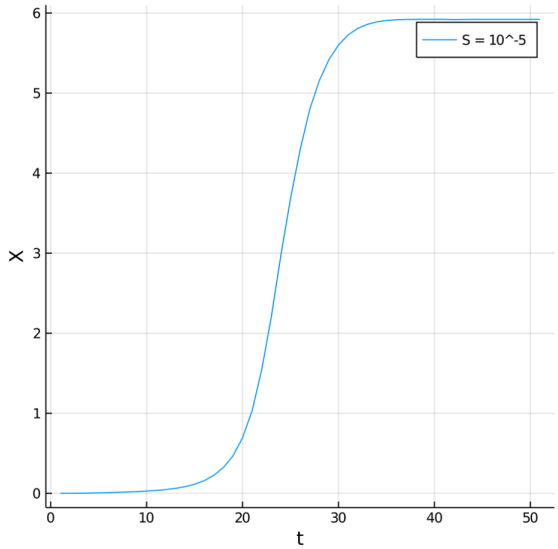


The black lines are indeed qualitatively reproducible. However, while using 'ODEProblem' in Julia, only a single steady state solution could be found which resulted in the above figure. To quantitively reproduce the author's figure, all steady state solutions (stable and unstable) would have to be found and plotted. Between the two saddle nodes shown in figure 2B, three steady state solutions exist: 2 stable and 1 unstable. We could capture all steady states by changing the initial conditions so that it would lead us to other solutions but doing this over a range of values for S seemed challenging.

(d)

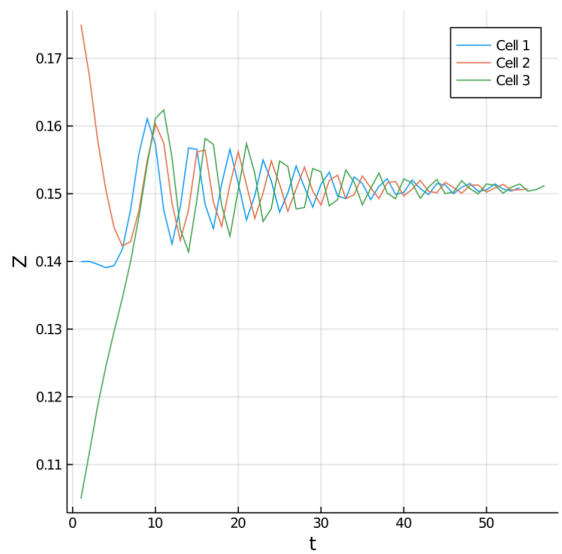

S = 0.02
X
t
2.5|0^-6
2.0|0^-6
1.5|0^-6
1.0|0^-6
5.0|0^-7
0
0
10
20
30
40


S = 10.0
X
t
0.100
0.075
0.050
0.025
0.000
0
25
50
75
100
125

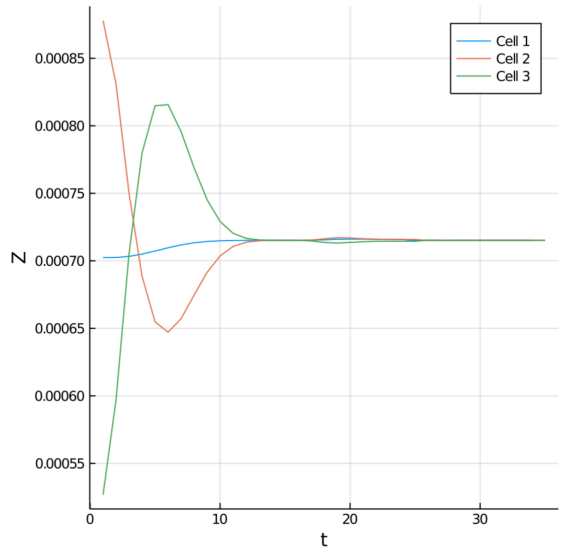

S = 10^-5
X
t
6
5
4
3
2
1
0
0
10
20
30
40
50

(e)

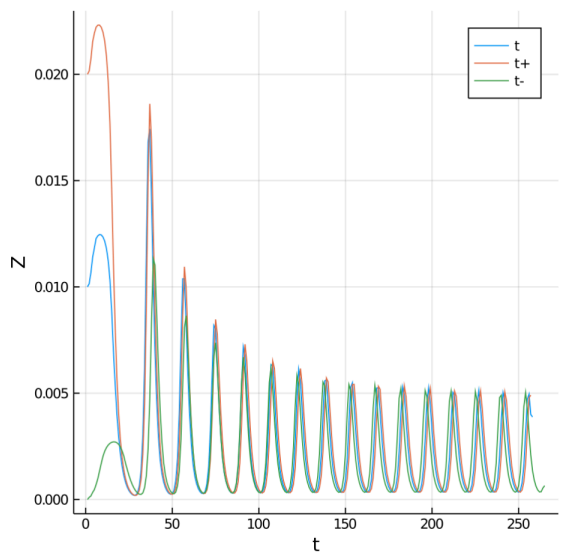
S = 90 is chosen as a point below the Hopf bifurcation point (ref. figure S.1.a). Parameters are taken from Figure S.1.a. At S = 90, a stable steady state solution is (0.086, 0.313, 0.140). When S is increased to 100 suddenly, the oscillations are incoherent. This is because oscillations arise through an attracting spiral which turns into a repulsing spiral by losing its stability. Since the oscillations start their transient close to the unstable spiral center, even small variations in the initial conditions can lead to a significant difference in the final oscillation phase. The initial differences in the three cells considered here (at steady state, 1.25* steady state and 0.75* steady state) are amplified, resulting in incoherence.



S = 2000 is chosen as a point below the Saddle node bifurcation point (ref. figure S.1.a). Parameters are taken from Figure S.1.a. At S = 2000, the stable steady state solution is (7.166, 0.001, 0.001). When S is decreased from 2000 to 100, it results in coherent oscillations. This is because when moving toward the limit cycle, the expression levels are far from those levels associated with those in the attracting oscillatory regime. Thus, there is a fast expression transient towards stable oscillations. In this way, we can make possible coherent or incoherent oscillations by choosing the appropriate signal values for a specific set of parameters.



(f)



Using the parameters in Table S.1, I was able to qualitatively reproduce the figure in 3 E by reducing S from 150 to 100. The oscillations are coherent, and this makes sense as these are oscillations through the saddle node bifurcation.