Problem 1

(a)

IPTG(mM)	<n> (mRNA/cell)	low (mRNA/cell)	high (mRNA/cell)	nmol/gDW	low (nmol/gDW)	high (nmol/gDW)
0	19	18	20	0.105204873	0.099667774	0.110741971
5.00E-04	21	17	26	0.11627907	0.094130676	0.143964563
0.005	41	37	44	0.227021041	0.204872647	0.243632337
0.012	67	65	69	0.370985604	0.359911406	0.382059801
0.053	86	84	88	0.476190476	0.465116279	0.487264673
0.216	93	91	95	0.514950166	0.503875969	0.526024363
1	93	92	94	0.514950166	0.509413068	0.520487265

(b)

$G + R_x \underset{k_-}{\overset{k_+}{\rightleftharpoons}} (G:R_x)_c$ binding

$(G:R_x)_c \xrightarrow{k_I} (G:R_x)_o$ initiation

$(G:R_x)_o \xrightarrow{k_A} R_x + G$ open complex can fall apart

$(G:R_x)_o \xrightarrow{k_E^x} m + R_x + G$ elongation

$\boxed{r_x = k_E^x (G:R_x)_o}$ Rate limiting step

$$\frac{d}{dt}(G:R_x)_c = k_+ G R_x - k_-(G:R_x)_c - k_I (G:R_x)_c$$

$$\frac{d}{dt}(G:R_x)_o = k_I (G:R_x)_c - k_A (G:R_x)_o - k_E^x (G:R_x)_o$$

$$R_{x,T} = R_x + (G:R_x)_c + (G:R_x)_o$$

Total RNAP = Free RNAP + Closed complex + Open complex

At steady state: $\frac{d}{dt}(G:R_x)_c = \frac{d}{dt}(G:R_x)_o = 0$

$\rightarrow \quad k_+ G R_x - k_-(G:R_x)_c - k_I (G:R_x)_c = 0$

$$(G:R_x)_c = \left(\frac{k_+}{k_- + k_I}\right) G R_x$$

→ Similarly $k_I \, (G:R_x)_c - k_A \, (G:R_x)_o - k_E^x (G:R_x)_o = 0$

$$(G:R_x)_o = \left(\frac{k_I}{k_A + k_E^x}\right) (G:R_x)_c$$

$$(G:R_x)_o = \underbrace{\left(\frac{k_I}{k_A + k_E^x}\right)}_{\tau_x^{-1}} \underbrace{\left(\frac{k_+}{k_- + k_I}\right)}_{K_x^{-1}} \; G \; R_x$$

$$\boxed{(G:R_x)_o = (K_x^{-1})(\tau_x^{-1}) \; G \; R_x}$$

$$R_{x,T} = R_x + (G:R_x)_c + (G:R_x)_o$$

$$R_{x,T} = R_x + K_x^{-1} G R_x + K_x^{-1} \tau_x^{-1} G R_x$$

$$R_{x,T} = R_x \left(1 + \frac{G}{K_x} + \frac{G}{K_x \tau_x} \right)$$

$$R_{x,T} = R_x \left(\frac{K_x \tau_x + \tau_x G + G}{K_x \tau_x} \right)$$

$$\boxed{R_x = \frac{K_x \tau_x \; R_{x,T}}{K_x \tau_x + (\tau_x + 1) G}}$$

So the final rate of transcription r_x can be written as $r_x = k_E^x (G:R_x)_0$

$$r_x = k_E^x \tau_x^{-1} K_x^{-1} G \frac{K_x \tau_x R_{x,T}}{K_x \tau_x + (\tau_x+1) G}$$

$$\boxed{r_x = k_E^x R_{x,T} \left(\frac{G}{\tau_x K_x + (\tau_x+1) G} \right)}$$

Now writing the material balance on mRNA

$$\dot{m} = \frac{dm}{dt} = r_x \bar{u} - (\mu + \theta_m) m$$

At pseudo steady state $\frac{dm}{dt} = 0$

$$\Rightarrow r_x \bar{u} = (\mu + \theta_m) m^*$$

$$\boxed{m^* = \frac{r_x \bar{u}}{\mu + \theta_m}}$$

$$m^* = \underbrace{\left(\frac{k_E^x R_{x,T}}{\mu + \theta_m} \right) \left(\frac{G}{\tau_x K_x + (\tau_x+1) G} \right)}_{K_x} \cdot \underbrace{\bar{u}}_{\bar{u}(I,K)}$$

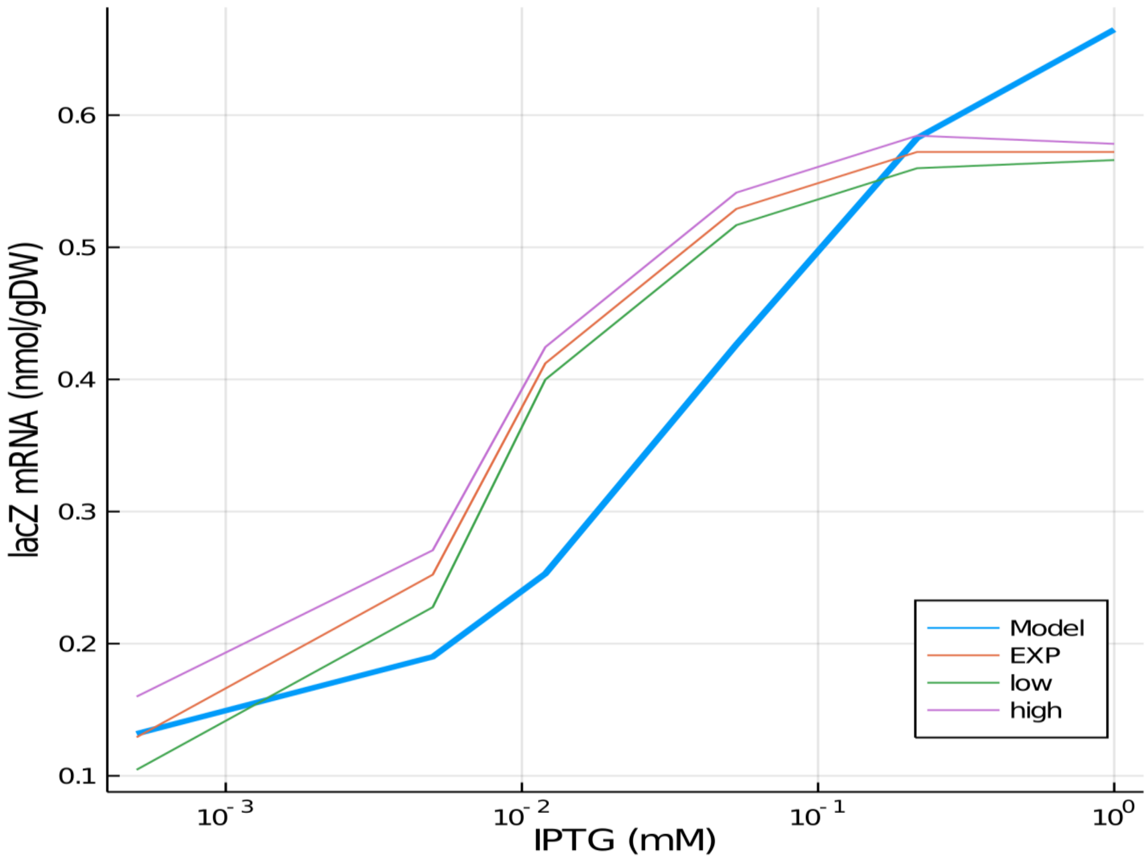
$$\boxed{\text{Gain function } K_x = \left(\frac{k_E^x R_{x,T}}{\mu + \theta_m} \right) \left(\frac{G}{\tau_x K_x + (\tau_x+1) G} \right)}$$

(c)

Parameter	Value	Units	Source
Mass of dry cell	1.00E-12	gram	Bionumbers : 101789
Fraction of dry cell	0.27	unitless	Bionumbers : 110086
RNAP copy number	4600	copies/cell	Bionumbers : 108601
Transcription elongation rate	50	nt/s	Bionumbers : 111871
Characteristic initiation time	42	s	https://github.com/varnerlab/JuGRN-Generator/blob/master/src/distribution/Default.json
Transcription saturation constant	0.24	nmol/gDW	https://github.com/varnerlab/JuGRN-Generator/blob/master/src/distribution/Default.json
Dissociation constant	4.96E-02	mM	Bionumbers : 101976
Guess parameters			
n	0.9	unitless	
W1	0.01	unitless	
W2	0.05	unitless	

The guess parameters determine the fit of the plot significantly.

(d)



Problem 2

(a)

Dimensional form

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

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

dimensional form

(b)

Non dimensional substitutions

$$X = \frac{\bar{X}\bar{\delta}_x}{\bar{\alpha}_z} \qquad Z = \frac{\bar{Z}\bar{\delta}_x}{\bar{\alpha}_z} \qquad t = \bar{t}\,\delta_x$$

$$\alpha_x = \frac{\bar{\alpha}_x}{\bar{\alpha}_z} \qquad \beta_x = \frac{\bar{\beta}_x}{\bar{\alpha}_z} \qquad z_x = \frac{\bar{z}_x\bar{\delta}_x}{\bar{\alpha}_z} \qquad \delta_z = \frac{\bar{\delta}_z}{\bar{\delta}_x}$$

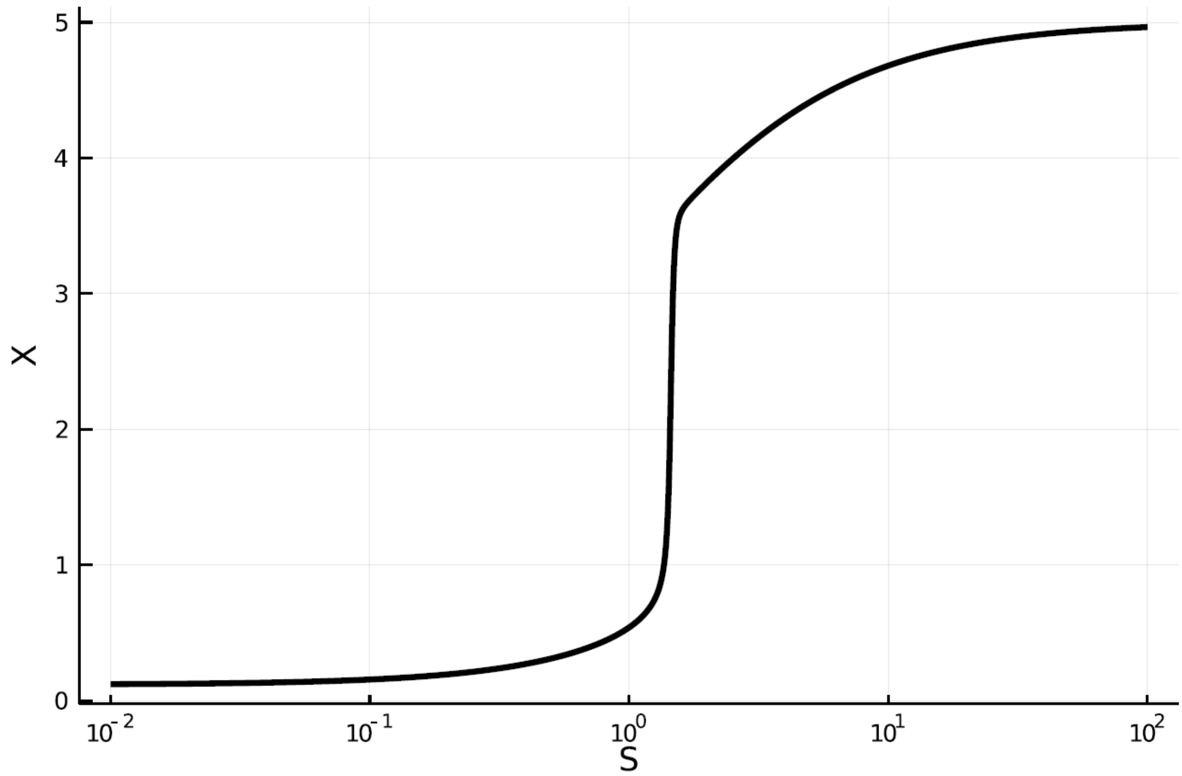
$$\frac{\bar{\delta}_x}{\bar{\alpha}_z}\left(\frac{d\bar{X}}{d\bar{t}}\right)\frac{1}{\delta_x} = \frac{1}{\bar{\alpha}_z}\frac{(\bar{\alpha}_x + \bar{\beta}_x S)}{1 + S + (\bar{Z}/\bar{z}_x)^{n_{zx}}} - \frac{\bar{X}\bar{\delta}_x}{\bar{\alpha}_z}$$

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

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

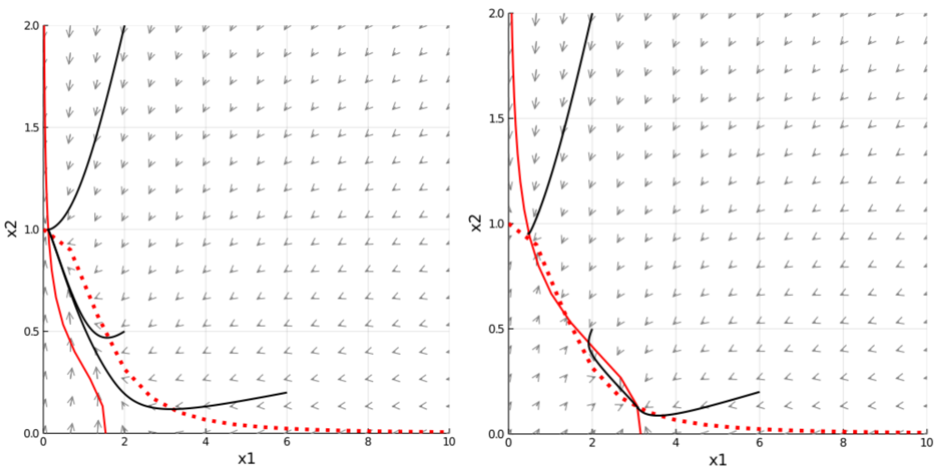
★ Since were left with $\left(\frac{\bar{\delta}_x}{\delta_x}\right)$ on the LHS of the equations
the error is in $t = \bar{t}\,\delta_x$. It should be $t = \bar{t}\,\bar{\delta}_x$ because there is no other instance of δ_x in equations.

(c)



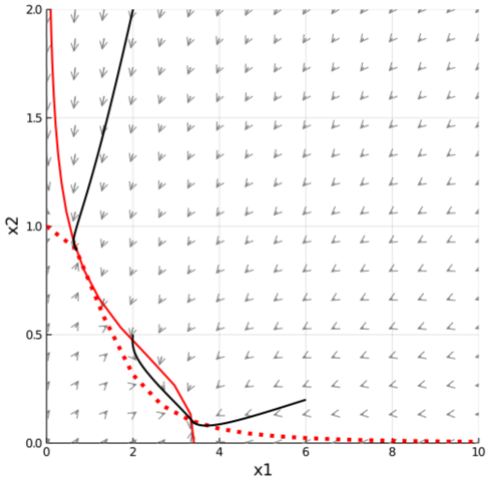
The solid black lines are **qualitatively** reproducible.

By analysing the phase portrait we can clearly observe that for a certain range of parameters, there exist three solutions out of which two are stable and one is unstable.

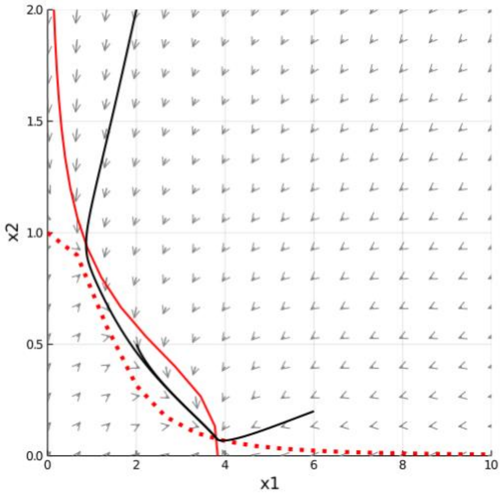


S = 0.01

S = 0.9

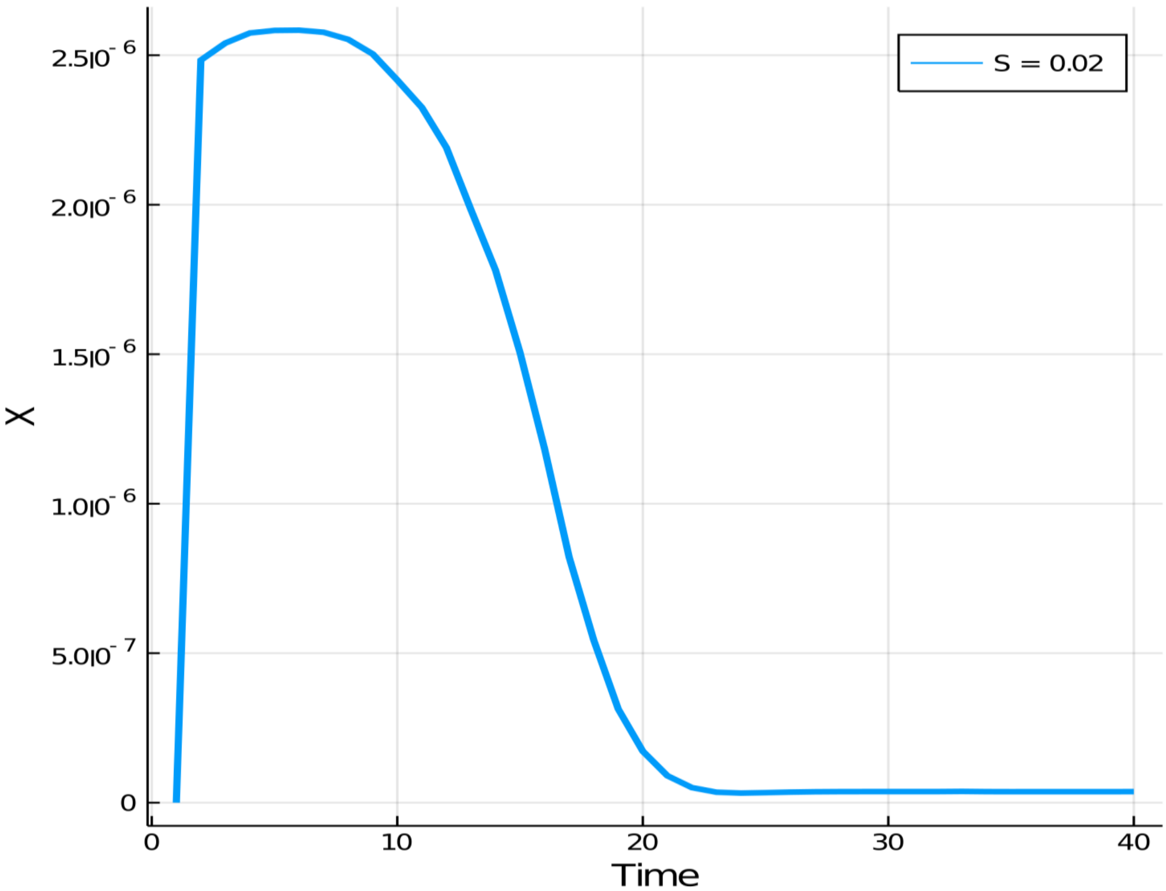


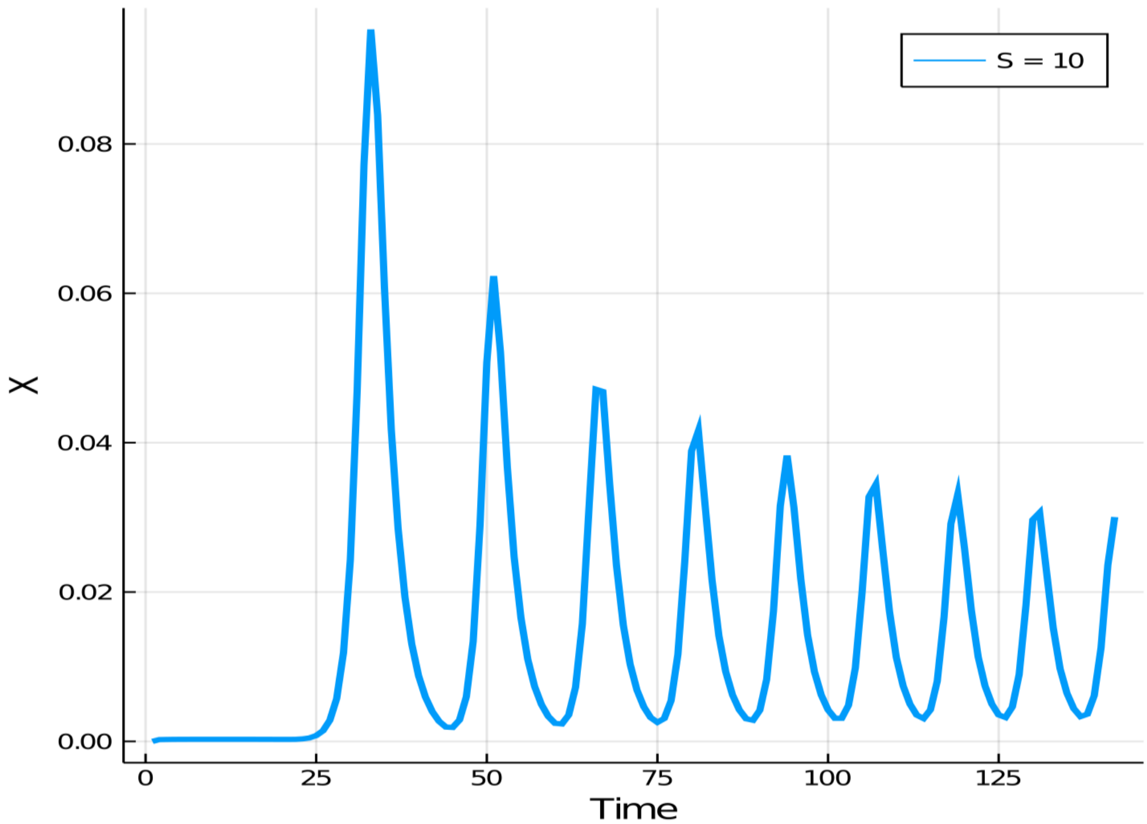
S = 1.2

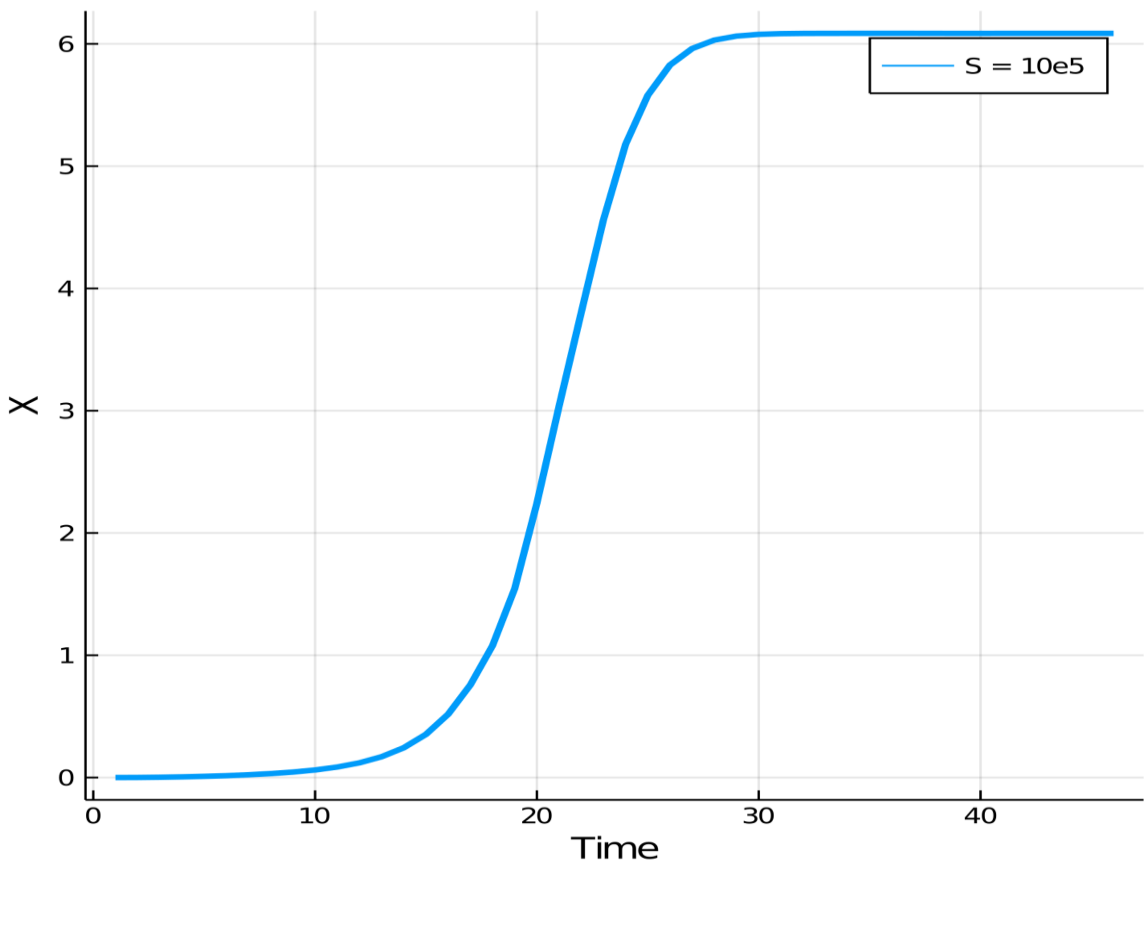


S = 2.0

(d)

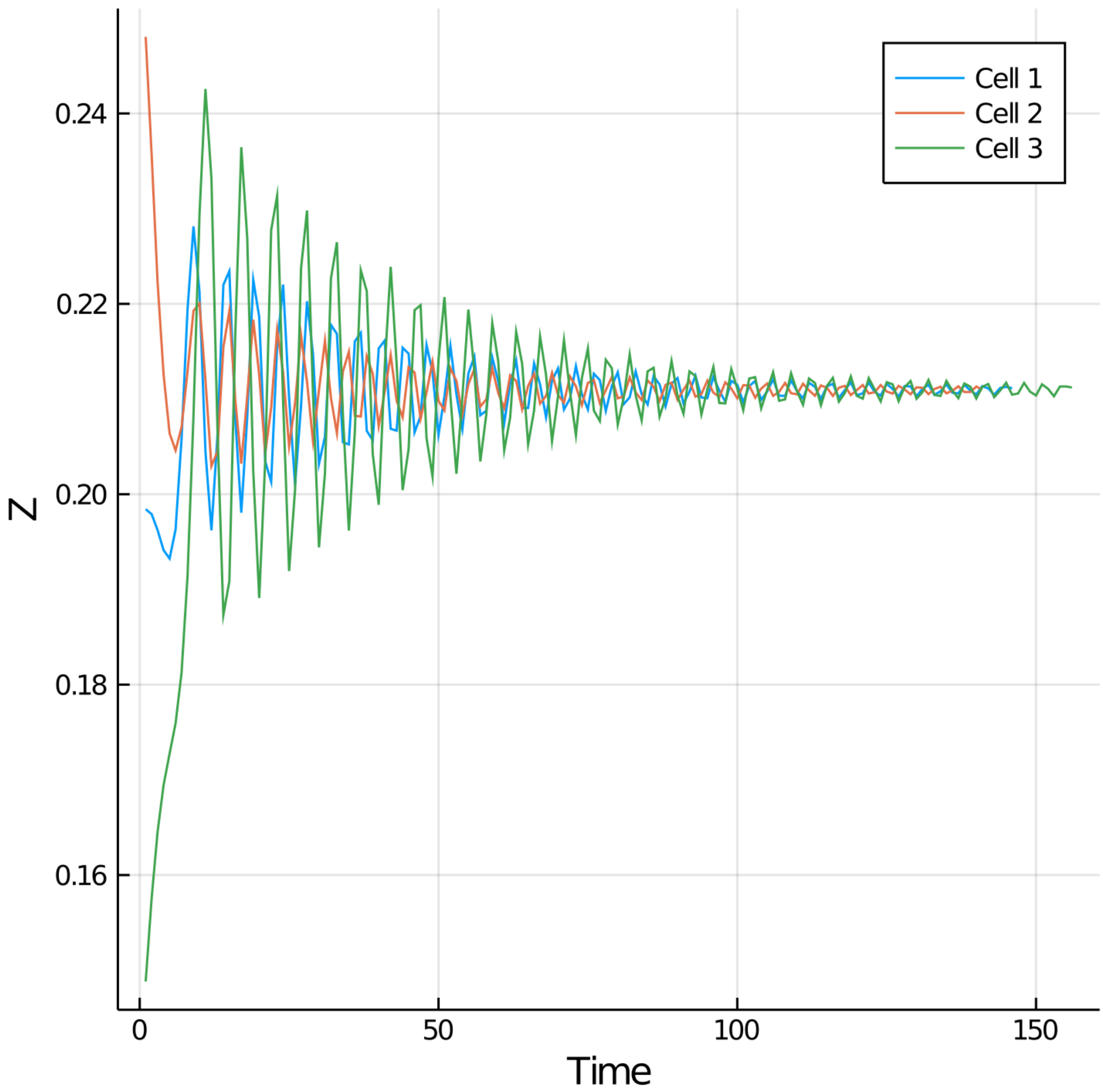



S = 10
0.08
0.06
0.04
0.02
0.00
X
0
25
50
75
100
125
Time


S = 10e5
6
5
4
3
2
1
0
X
0
10
20
30
40
Time

(e)

Point below the Hopf Bifurcation chosen as S= 80; Parameters chosen from Figure S1 (a)



As we increase the signal from the Hopf bifurcation point (S=80) to S=100, it induces asynchronous oscillations. The oscillations are incoherent which is in line with the observation made by the authors. This happens because the stable point turns from a spiral sink to spiral source which is unstable.

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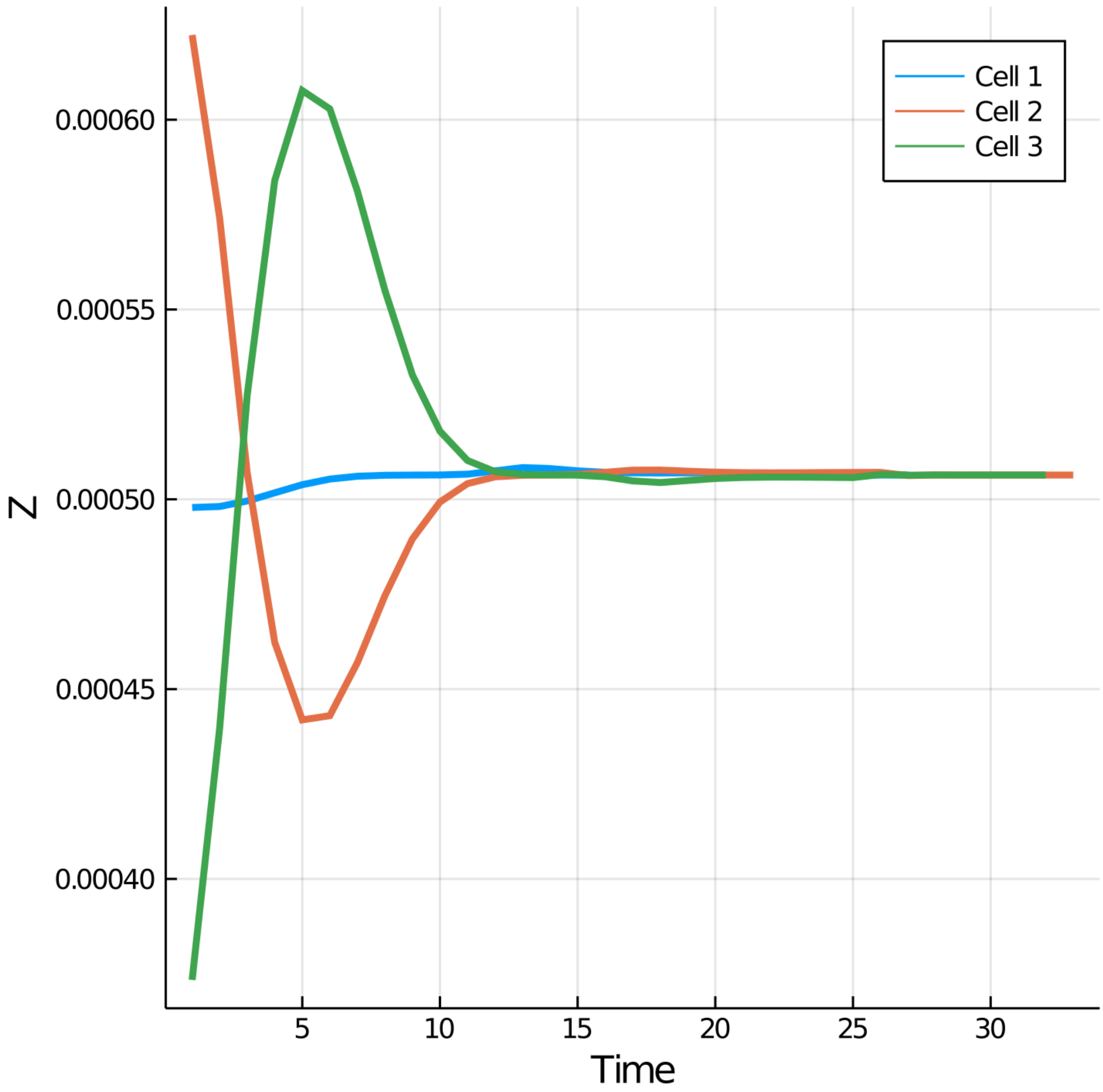
Point above the saddle node chosen as S = 5000; Parameters chosen from Figure S1 (a)



As we increase the signal from the saddle node bifurcation point (S=5000) to S=100, it induces synchronous oscillations. The oscillations are coherent which is in line with the observation made by the authors. In the figure above the oscillations dissipate after a few seconds. This means that the simulation might not be able to capture the oscillations after t=15s even though there might be some oscillations at a lower amplitude.

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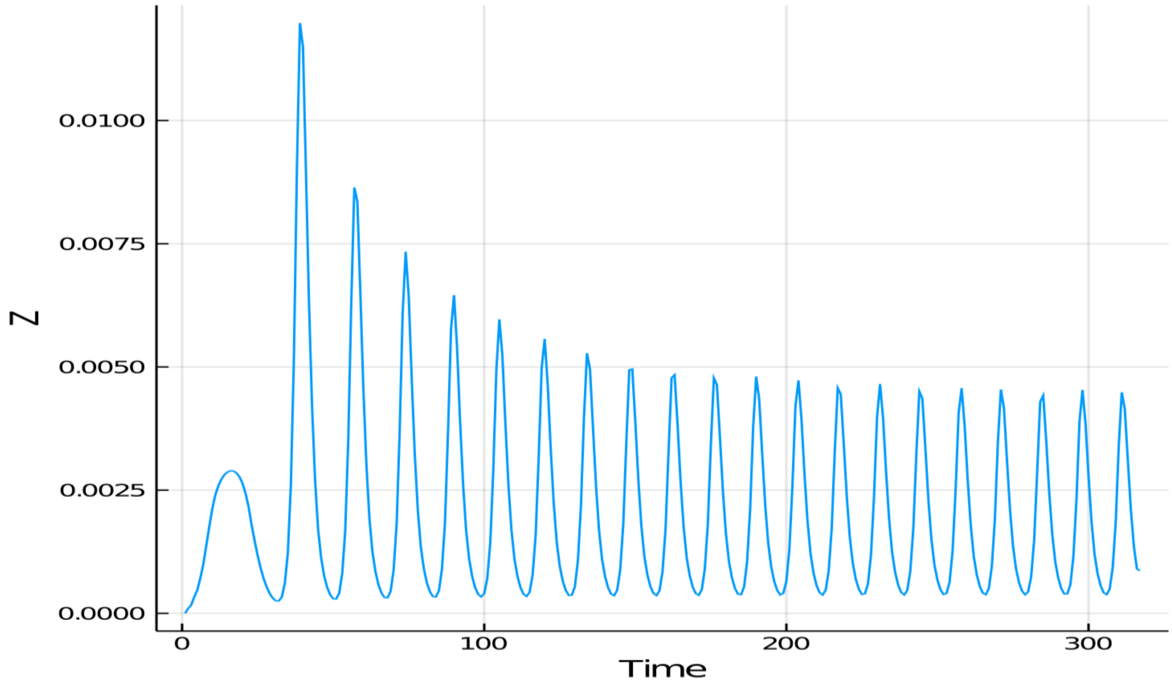
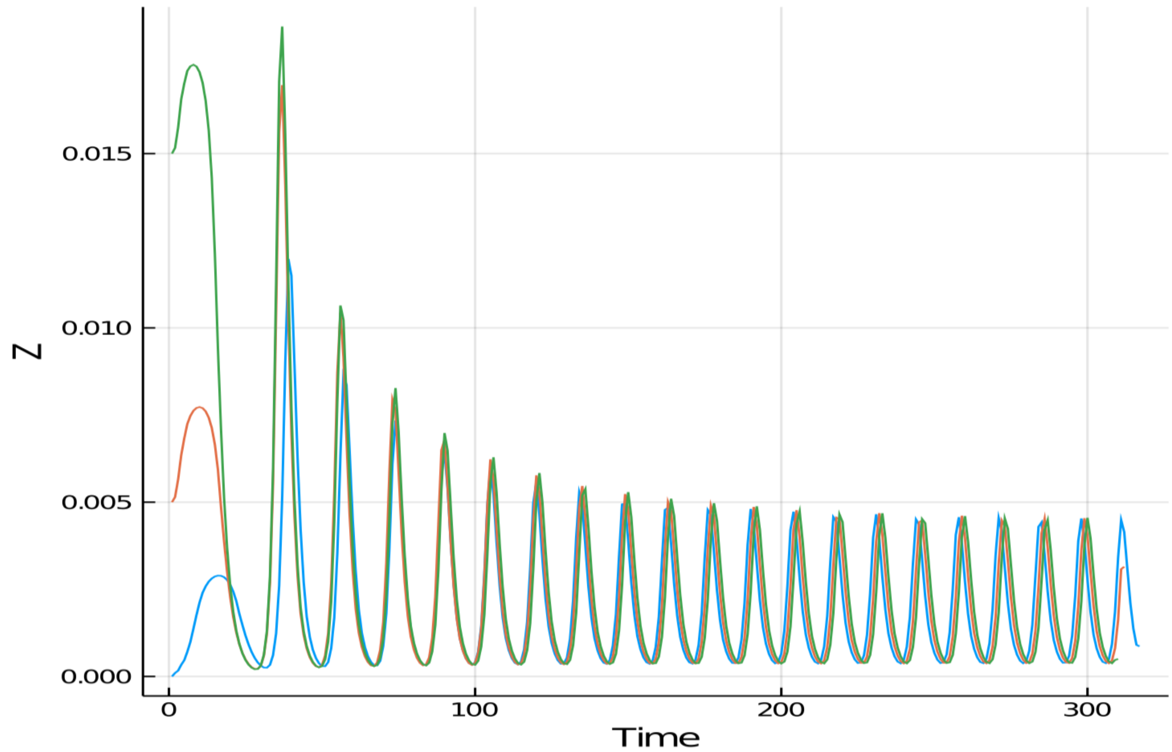
(f)





We do achieve coherent oscillations at S = 100, using the mean parameters in Table S1 and three different initial conditions. Note that the initial conditions have only been changed for Z. Changing the initial conditions for X and Y results in incoherent oscillations.