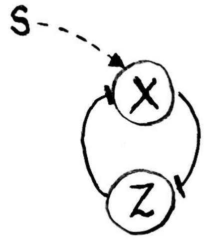
Problem 2

a) For the toogle switch network :-



$\Rightarrow$ Gene Y is not present, so eqn. 2 reduces to :-

$$\frac{d\tilde{X}}{d\tilde{t}} = \underbrace{\frac{\tilde{\alpha}_x + \tilde{\beta}_x S}{1 + S + \left(\tilde{Z}/\tilde{z}_x\right)^{n_{zx}}}}_{\text{production term for X}} - \underbrace{\tilde{\delta}_x \tilde{X}}_{\text{degradation term for X}} \qquad (1)$$

$$\frac{d\tilde{Z}}{d\tilde{t}} = \underbrace{\frac{\tilde{\alpha}_z}{1 + \left(\tilde{X}/\tilde{x}_z\right)^{n_{xz}}}}_{\text{production term for Z}} - \underbrace{\tilde{\delta}_z \tilde{Z}}_{\text{degradation term for Z}} \qquad (2)$$

Note :- This was erroneously written Z in the paper.

b) Non-dimensionalize the above ODE system with relevant non-dimensional quantaties.

from eqn 3 :- $\boxed{\delta_z = \frac{\tilde{\delta}_z}{\tilde{\delta}_x}}$

was erroneously δ_x in paper

$\boxed{t = \tilde{t}\,\tilde{\delta}_x}$

from eqn 4 :- $\boxed{\alpha_x = \frac{\tilde{\alpha}_x}{\tilde{\alpha}_z}}$ $\boxed{\beta_x = \frac{\tilde{\beta}_x}{\tilde{\alpha}_z}}$

from eqn 5 :- $\boxed{z_x = \frac{\tilde{z}_x \cdot \tilde{\delta}_x}{\tilde{\alpha}_z}}$ $\boxed{x_z = \frac{\tilde{x}_z \cdot \tilde{\delta}_x}{\tilde{\alpha}_z}}$

from eqn 6 :- $\boxed{X = \frac{\tilde{X}\tilde{\delta}_x}{\tilde{\alpha}_z}}$ $\boxed{Z = \frac{\tilde{Z}\tilde{\delta}_x}{\tilde{\alpha}_z}}$

Substituting the above variables in (1) yields :-

$$\frac{\cancel{\tilde{\delta}_x} \cdot \cancel{\tilde{\alpha}_z}}{\cancel{\tilde{\delta}_x}} \cdot \frac{dX}{dt} = \frac{\cancel{\tilde{\alpha}_z} \cdot \alpha_x + \cancel{\tilde{\alpha}_z}\,\beta_x S}{1 + S + \left(\frac{Z \cdot \cancel{\tilde{\alpha}_z}}{\cancel{\tilde{\delta}_x}} \cdot \frac{\cancel{\tilde{\delta}_x}}{z_x \cdot \cancel{\tilde{\alpha}_z}}\right)^{n_{zx}}} - \frac{\cancel{\tilde{\delta}_x} \cdot \tilde{\alpha}_z X}{\cancel{\tilde{\delta}_x}}$$

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

Similarly substituting parameters from eqns 3-6 in ②, yields,

$$\cancel{\tilde{\delta}_x}\cdot\frac{\cancel{\tilde{\alpha}_z}}{\cancel{\tilde{\delta}_x}}\cdot\frac{dZ}{dt} = \frac{\cancel{\tilde{\alpha}_z}}{1+\left(X\cdot\frac{\cancel{\tilde{\alpha}_z}}{\cancel{\tilde{\delta}_x}}\cdot\frac{\cancel{\tilde{\delta}_x}}{x_z\cdot\cancel{\tilde{\alpha}_z}}\right)^{n_{xz}}} - \cancel{\tilde{\delta}_x}\cdot\delta_z\cdot\frac{\cancel{\tilde{\alpha}_z}\cdot Z}{\cancel{\tilde{\delta}_x}}$$

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

⊛ Note:- For eqn. 3, t was incorrectly equated to $\tilde{t}\cdot\delta_x$, when it should have been $\boxed{t=\tilde{t}\cdot\tilde{\delta}_x}$ instead. Similarly in eqn. 2, $\tilde{Z}$ was mistakenly written as Z.

c) A plot for the steady state values of X vs. S is attached for the given parameter values. We are able to qualitatively produce the solid lines, representing the regions of S where stable steady states of X exist.
The region in between represents the unstable steady states of X and although this could not be reproduced in the code attached, we expect to see a similar pattern as described in Figure 1B.

d) For the AC-DC circuit, the system of ODEs becomes:-

$$\left.\begin{aligned}
\frac{dX}{dt} &= \frac{\alpha_x + \beta_x S}{1+S+(Z/z_x)^{n_{zx}}} - X \\
\frac{dY}{dt} &= \frac{\alpha_y + \beta_y S}{1+S+(X/x_y)^{n_{xy}}} - \delta_y Y \\
\frac{dZ}{dt} &= \frac{1}{1+(X/x_z)^{n_{xz}}+(Y/y_z)^{n_{yz}}} - \delta_z Z
\end{aligned}\right\}$$

(non dimensional form)
eqn 1 from paper

⇒ Using the mode values of parameters listed in Table S.1 of the Supplementary information, initial conditions of $X_0 = Y_0 = Z_0 = 0$, X, Y and Z were solved & X was plotted with respect to time for $S = 0.02$, 10, and 10^5. The graphs have been attached along with this submission.

e) (*) A steady state (stable) value for S near but below the Hopf bifurcation point was found to be about $\boxed{S = 0.1}$

⇒ Solving the system of ODEs with this value of S, yielded the following steady state values of X, Y, and Z:-

$$X_{ss} = 0.0001383746\ldots \approx \underline{\underline{1.38 \times 10^{-4}}}$$

$$Y_{ss} = 0.483737446\ldots \approx \underline{\underline{0.484}}$$

$$Z_{ss} = 0.0004969447\ldots \approx \underline{\underline{4.97 \times 10^{-4}}}$$

⇒ We now consider the dynamics of 3 cells with their respective steady state values:-

$$\underbrace{\begin{array}{l} X_{ss_1} = 1.38 \times 10^{-4} \\ Y_{ss_1} = 0.484 \\ Z_{ss_1} = 4.97 \times 10^{-4} \end{array}}_{\text{CELL 1}}$$

(same as calc. S.S values)

$$\underbrace{\begin{array}{l} X_{ss_2} = 1.725 \times 10^{-4} \\ Y_{ss_2} = 0.605 \\ Z_{ss_2} = 6.2125 \times 10^{-4} \end{array}}_{\text{CELL 2}}$$

(25% higher than Calc. S.S. values)

$$\underbrace{\begin{array}{l} X_{ss_3} = 1.035 \times 10^{-4} \\ Y_{ss_3} = 0.363 \\ Z_{ss_3} = 3.7275 \times 10^{-4} \end{array}}_{\text{CELL 3}}$$

(25% lower than calc. S.S. values)

⇒ A plot of Z vs. time when the signal suddenly changes to a value of 100 was graphed for all three cells. (refer to attached plot)

(*) Similarly, a stable steady value for S near but above the saddle node bifurcation was found to be about $\boxed{S = 5 \times 10^4}$

⇒ Solving the system of ODEs with this value of S, yields the following steady state values of X, Y, and Z:-

$$X_{ss} = 5.73411474\ldots \approx \underline{\underline{5.734}}$$

$$Y_{ss} = 0.005147128\ldots \approx \underline{\underline{5.147 \times 10^{-3}}}$$

$$Z_{ss} = 0.00042088\ldots \approx \underline{\underline{4.209 \times 10^{-4}}}$$

⇒ We consider the dynamics of 3 cells with their respective steady state values:-

$$\underbrace{\begin{array}{l} X_{ss_1} = 5.734 \\ Y_{ss_1} = 5.147 \times 10^{-3} \\ Z_{ss_1} = 4.209 \times 10^{-4} \end{array}}_{\text{CELL 1}}$$

(same as calc. S.S. values)

$$\underbrace{\begin{array}{l} X_{ss_2} = 7.1675 \\ Y_{ss_2} = 6.43375 \times 10^{-3} \\ Z_{ss_2} = 5.26125 \times 10^{-4} \end{array}}_{\text{CELL 2}}$$

(25% higher than calc. SS values)

$$\underbrace{\begin{array}{l} X_{ss_3} = 4.3005 \\ Y_{ss_3} = 3.86025 \times 10^{-3} \\ Z_{ss_3} = 3.15675 \times 10^{-4} \end{array}}_{\text{CELL 3}}$$

(25% lower than the calc. SS values)

⇒ A plot of Z vs. time when the signal was changed to a value of a 100 was plotted for all 3 cells. (refer to attached plot)

DISCUSSION OF PLOTS

⊛ In line with what is described in the paper, we see from our plots that oscillations arising through the Hopf bifurcation are incoherent. After the signal was increased from 0.1 to 100 at $t=0$, the steady states become unstable and the observed oscillations for the 3 cells are seen to be out of phase (ie. incoherence) - small initial differences are amplified.

In contrast, from the plots for the oscillations through the saddle-node bifurcation, we observe coherent oscillations. After the signal was reduced from 50000 to 100 at $t=0$, the steady state disappears and stable in-phase (coherent) oscillations are observed for the 3 cells - expression levels are far from those associated with the attracting oscillatory regime.

f) No, this is not possible with the parameters provided in Table S.1, as with these parameters at $S=105$, the gene expression behavior is seen to be oscillating and not at steady state. This is counter to what is being described by the authors in Fig 3E, as the behavior suggest that we are no longer above the saddle point bifurcation, but instead we have already entered the oscillating regime.