Name: _____

Roll No.: _____

BM2053 Mathematical Models & Systems Biology

Final Exam

Duration: 120mins **Total marks: 71**

1. Do not use a pencil to write answers or sketch the curves.
2. Use the following Hill's functions if required: $H_1(x) = \dfrac{x^2}{k^2 + x^2}$ and $H_2(x) = \dfrac{k^2}{k^2 + x^2}$.

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1. There is diffusion of a molecule in a one-dimensional domain $x \in [0, 2]$, and it is described by

$$\dot{\phi} = D\frac{\partial^2 \phi}{\partial x^2}.$$

The two boundaries of the domain have the following boundary conditions

$$D\frac{\partial \phi}{\partial x}\bigg|_{x=0} = 0.1, \qquad D\frac{\partial \phi}{\partial x}\bigg|_{x=2} = -0.2.$$

Assuming that you use the forward and central difference schemes in time and space, respectively, that is

$$\dot{\phi} = \frac{\phi(x, t + \Delta t) - \phi(x, t)}{\Delta t}$$

and

$$\frac{\partial^2 \phi}{\partial x^2} = \frac{\phi(x + \Delta x, t) - 2\phi(x, t) + \phi(x - \Delta x, t)}{(\Delta x)^2}$$

fill in the blanks in the following Python program to solve the diffusion equation **(5 × 3)**

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...
D = 1.0
deltax = 0.1
deltat = 0.1

% For interior nodes in the domain

phi[1:-1,i+1] =  phi[1:-1,i] + (D*deltat/(deltax**2))*(phi[2:,i] - 2*phi[1:-1,i] + phi[:-2,i])

% For left boundary

phi[0,i+1] = phi[0,i] + (D*deltat/(deltax**2))*(phi[1:,i] - 2*phi[0,i] + phi[1,i] - 0.2*deltax/D)

% For right boundary

phi[-1,i+1] = phi[-1,i]+ (D*deltat/(deltax**2))*(phi[-2:,i] - 2*phi[-1,i] + phi[-2,i] - 0.4*deltax/D)
...
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2. The following two-dimensional model describes the interaction between the membrane potential $v(t)$ and a slow recovery variable $w(t)$ (which represents the combined effect of sodium channel inactivation and potassium channel activation)

$$\dot{v} = -v - w + v^2$$
$$\dot{w} = v - \mu w.$$

(a) Find all the fixed points of the system. **(4)**
For fixed points, $\dot{v} = 0$, $\dot{w} = 0$, which gives

$$v^* = 0, 1 + 1/\mu$$
$$w^* = 0, 1/\mu + 1/\mu^2.$$

where the second FP exists only for $\mu \neq 0$.

(b) Identify the stability of the fixed points **(8)**
For stability analysis, we perturb the system about the FPs as $v = v^* + \tilde{v}$, $w = w^* + \tilde{w}$, and linearize to get

$$\dot{\tilde{v}} = -\tilde{v} - \tilde{w} + 2v^*\tilde{v}$$
$$\dot{\tilde{w}} = \tilde{v} - \mu\tilde{w}$$

This gives Jacobian to be

$$J = \begin{bmatrix} -1 + 2v^* & -1 \\ 1 & -\mu \end{bmatrix}$$ (2 marks)

i. For $(v^*, w^*) = (0, 0)$, we get eigenvalues $\lambda = \dfrac{-(1+\mu) \pm \sqrt{(1+\mu)^2 - 4(1+\mu)}}{2} = \dfrac{-(1+\mu) \pm \sqrt{(1+\mu)(\mu-3)}}{2}$.
For $\mu < -1$, we get real eigenvalues with one of them $> 0 \Rightarrow$ unstable.

For $-1 \leq \mu < 3$, we have $(1+\mu)(\mu-3) < 0$ and $1 + \mu > 0 \Rightarrow$ we get c.c. eigenvalues with negative real part $\Rightarrow$ stable.

For $\mu > 3$, we get real eigenvalues both of which $< 0 \Rightarrow$ stable (2 marks)

ii. For the second F.P., we get $\lambda^2 + \left(\mu - 1 - \dfrac{2}{\mu}\right)\lambda - (\mu + 1) = 0$.

For $\mu < -1$, we have $\lambda_1\lambda_2 > 0$ and $\lambda_1 + \lambda_2 = 1 + \dfrac{2}{\mu} - \mu > 0 \Rightarrow$ both real and positive eigenvalues $\Rightarrow$ unstable

For $0 \neq \mu > -1$, we have $\lambda_1\lambda_2 < 0 \Rightarrow$ two real eigenvalues with opposite signs $\Rightarrow$ saddle point $\Rightarrow$ unstable (4 marks)

3. You are modeling the dynamics of a chronic viral infection, such as HIV or Hepatitis B. The variable V represents the viral load in the blood. The immune system (e.g., Cytotoxic T-cells) can clear the virus, but its efficacy saturates at high viral loads because the immune cells themselves become depleted or exhausted. A simple model for the rate of change of the viral load is

$$\dot{V} = rV - a\frac{V^2}{V_0^2 + V^2}.$$

For this system,

First, we non-dimensionalize the system to reduce the parameters (this is not necessary, but it reduces the complicated calculations in later parts) to get

$$\dot{v} = Rv - \frac{v^2}{1 + v^2}$$

where $V = vV_0$ and $R = V_0 r/a$. (No marks for this)

(a) identify the fixed points **(4)**,
For fixed point, $\dot{v} = 0$, which gives

$$v^* = 0 \text{ or } \frac{1 \pm \sqrt{1 - 4R^2}}{2R} := v_\pm$$

where the second one is real only for $-1/2 \leq R \leq 1/2$. (4 marks)

(b) their stability **(6)**,

Perturbing the system about the fixed point gives

$$\dot{\tilde{v}} = Rv^* + R\tilde{v} - \frac{v^{*^2} + 2v^*\tilde{v}}{1 + v^{*^2} + 2v^*\tilde{v}} = Rv^* + R\tilde{v} - \frac{v^{*^2}}{1 + v^{*^2}}\left(1 + \frac{2\tilde{v}}{v^*}\right)\left(1 - \frac{2v^*\tilde{v}}{1 + v^{*^2}}\right)$$

$$\approx R\tilde{v} - \frac{v^{*^2}}{1 + v^{*^2}}\left(\frac{2}{v^*} - \frac{2v^*}{1 + v^{*^2}}\right)\tilde{v} = \left(R - \frac{v^*}{1 + v^{*^2}}\left(2 - \frac{2v^{*^2}}{1 + v^{*^2}}\right)\right)\tilde{v}$$ (2 marks)

i. For $v^* = 0$, we have $\dot{\tilde{v}} = R\tilde{v} \Rightarrow$ the FP is stable only for $R < 0$. (1 marks)

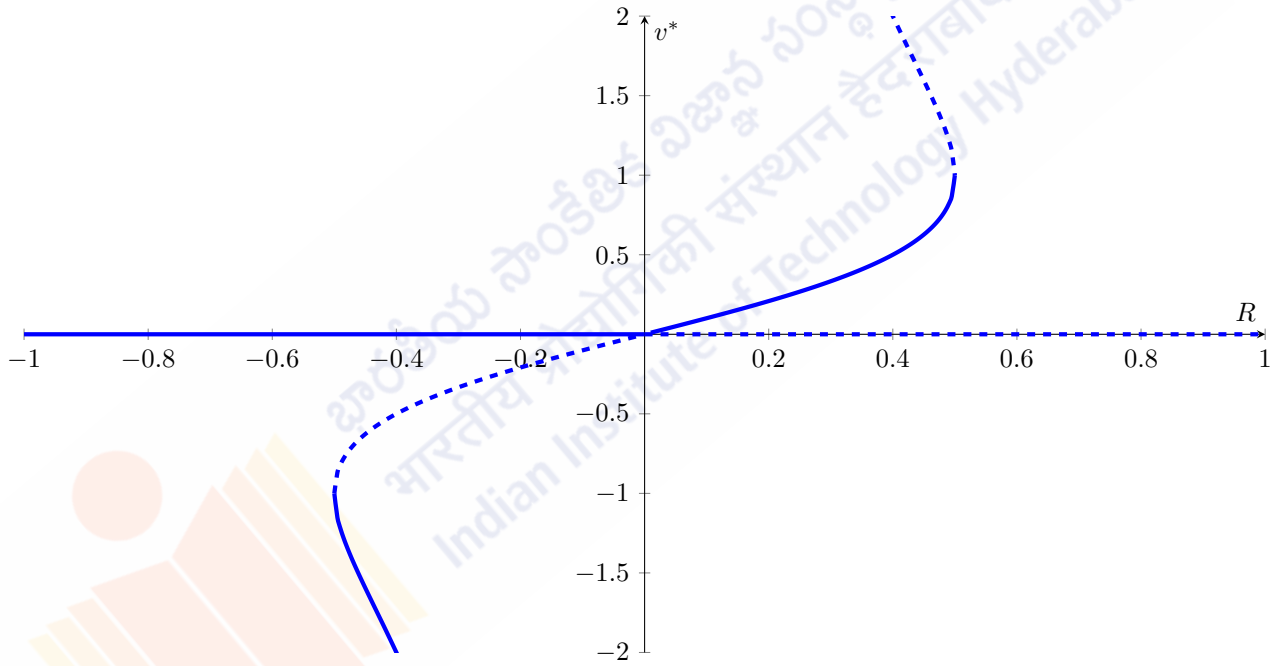
ii. For $v_\pm$, we have

$$\Rightarrow \dot{\tilde{v}} = \left(R - R\left(2 - \frac{2v^{*^2}}{1 + v^{*^2}}\right)\right)\tilde{v} = \left(-R + 2Rv^*\frac{v^*}{1 + v^{*^2}}\right)\tilde{v} = R\left(-1 + 2Rv^*\right)\tilde{v} = \pm\left(R\sqrt{1 - 4R^2}\right)\tilde{v}$$

we see that v_+, it is stable only for $-1/2 < R < 0$.

iii. For v_-, we see that it is stable only for $0 < R < 1/2$. (3 marks)

(c) sketch the bifurcation diagram as a function of r **(8)**, and (No partial makrs)

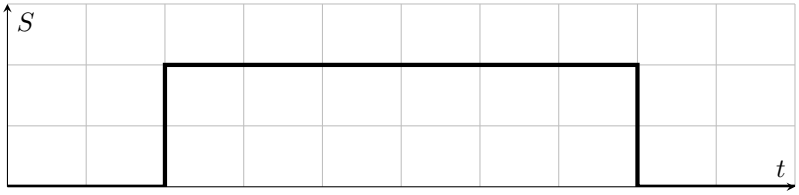


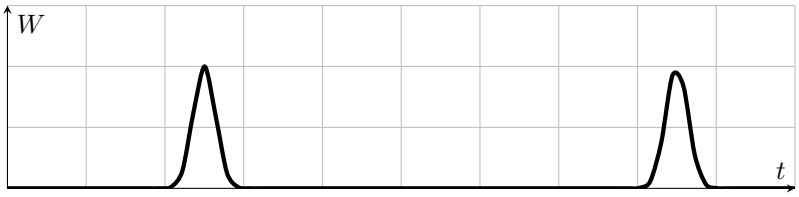
(d) identify the bifurcation type. **(6)**

At $R = \pm 1/2 \Rightarrow r = \pm a/2V_0$ the system undergoes saddle-node bifurcation. (4 marks)

At $R = 0 \Rightarrow r = 0$, the system shows transcritical bifurcation (*There is slightly more to it than just transcritical bifurcation here, but for this exam we will consider this as an acceptable answer.*) (2 marks)

4. In class, we looked at a gene regulatory motif using a feed-forward loop that detects a sudden increase in the external stimulus and gives out a pulsed response. Design a gene regulatory network that gives out a pulse when the external stimulus is switched on, and another pulse when it is switched off. The requirements are summarized in the sketch below





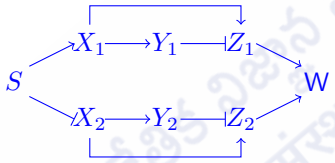
where S is the external stimulus, and W is the system output. **(20)**

Please note

- *that the W plot above is just a sketch and need not be considered in all its details for solving this problem, and*
- *you have to provide a coherent and succinct argument in 5 (or less) sentences for the design, and must not write several pages of text.*

We know that an incoherent FFL with strong repression gives out a pulse as an output when the external stimulus is switched on- the first pulse in the figure above. (4 marks)

We have to work out a regulatory network for the second pulse in the figure above. There are several ways to do it, and among them, the easiest to see is to use another incoherent FFL (of the same type) but with the top node repressed by the external stimulus. (10 marks)



The top half gives the first pulse in Z_1 (as seen in class), and the bottom half gives out the second pulse in Z_2. The two signals at W are combined in an OR manner. (6 marks)