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QBIO 482
Spring 2025
HW 2

Homework 2

1. Oscillations in biology

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a. Describe three examples of oscillations in biological systems. Do the oscillations in each case form a limit cycle? Explain your reasoning.

1. Circadian Rhythms: This cycle is a sleep-wake cycle observed in mammals. It is driven by feedback loops involving clock genes. Biological oscillations occur during the 24 hour period.

   Limit Cycle: Yes, the oscillations form a limit cycle as even when external stimuli, like

2. Cell Cycle Oscillations: The progression of a cell through the G1, S, G2, and M phases is controlled by oscillations in CDK activity and regulated by cyclins.

   Limit Cycle: Yes, the oscillations form a limit cycle, as one a cell enters a particular phase, it progresses through the cycle in a defined, repetitive pattern. While external perturbations may alter the duration of each phase, the cell continues to oscillate through the same cycle.

3. Calcium Signal Oscillations: Intracellular calcium levels oscillate in response to signals such as hormones or neurotransmitters.

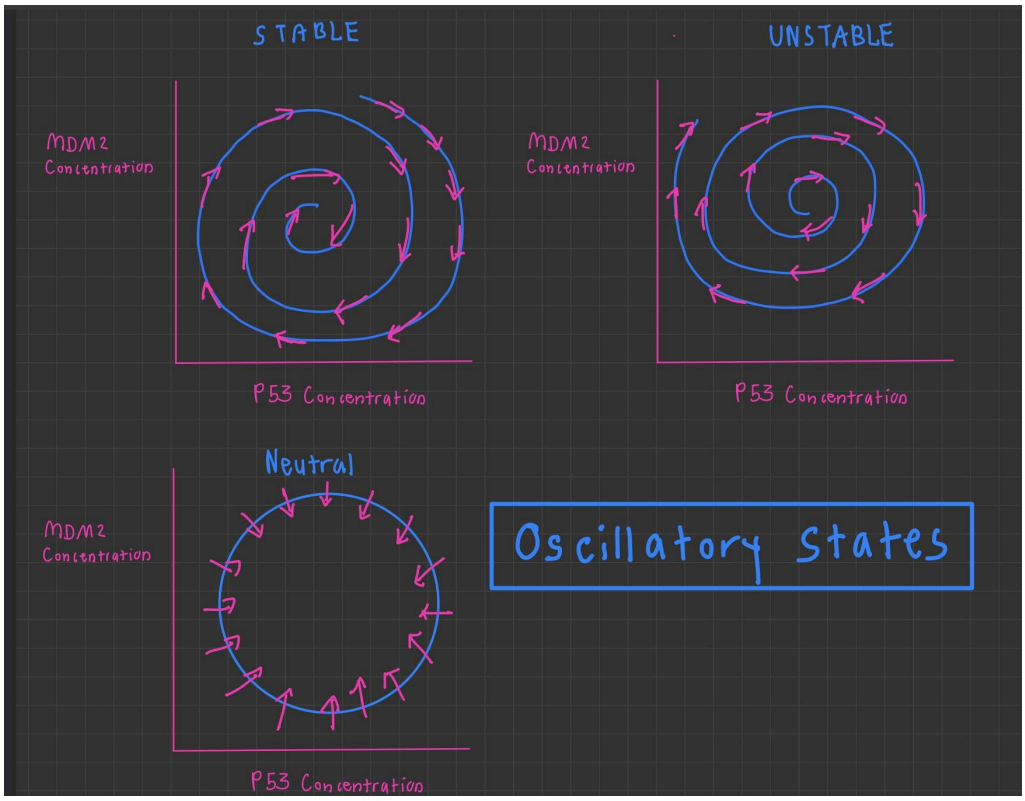
   Limit Cycle: They do not always form a limit cycle, as they may not form a sustained limit cycle if there is not continuous feedback. However, if there is continuous feedback, they can form a limit cycle.

b. Consider a gene regulatory model consisting of interactions between two proteins: P53 and MDM2. This model has an oscillatory steady state. Describe what it means for an oscillatory steady state to be (i) stable; (ii) unstable; (iii) neutral (a center). Draw phase plane portraits for each of these three cases. Label the axes.

(i) Stable: An oscillatory steady state is stable when small perturbations in protein levels (P53 and MDM2) eventually decay, returning the system back to its original oscillatory state.

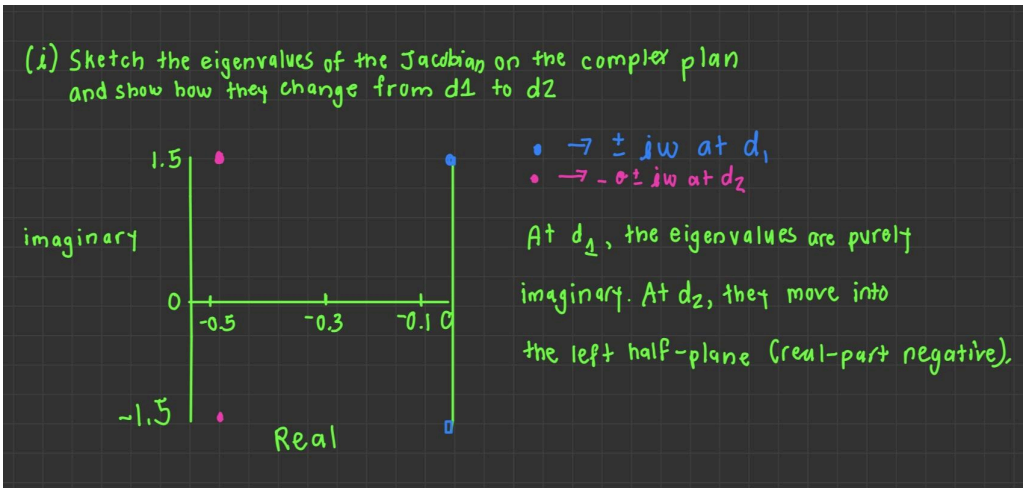
(ii) Unstable: An unstable oscillatory state is unstable when small deviations from the cycle grow over time, pushing the system away from oscillation.

(iii) Neutral (a center): A neutral oscillatory state occurs when the system oscillates around the steady state with a constant amplitude; it will neither decay to the steady state or move away from it.



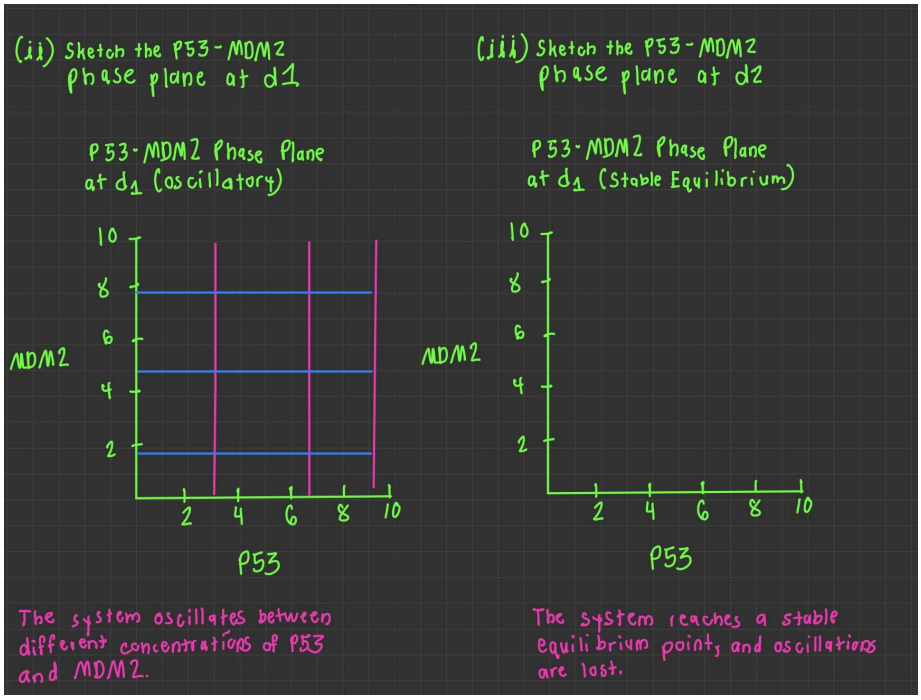
C. As the degradation rate of P53 increases from d1 to d2 the system undergoes a Hopf bifurcation and the oscillations are destroyed. (i) Sketch the eigenvalues of the Jacobian on the complex plan and show how they change from d1 to d2; (ii) sketch the P53-MDM2 phase plane at d1; (iii) sketch the P53-MDM2 phase plane at d2.

(i) Sketch the eigenvalues of the Jacobian on the complex plan and show how they change from d_1 to d_2;



(ii) sketch the P53-MDM2 phase plane at d1;

(iii) sketch the P53-MDM2 phase plane at d_2.



2. *Cancer stem cell competition*. Recall the cancer stem cell competition model studied in class.

$$\frac{dC}{dt} = 3C - SC - C^2$$
$$\frac{dS}{dt} = 2S - \frac{1}{2}SC - S^2$$

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a. Calculate the stability of each of the model's fixed points using linear stability analysis and the Jacobian.

<u>Find fixed points:</u>

$$\frac{dC}{dt} = 0 \; = 3C - SC - C^2 = C(3 - S - C) \rightarrow C = 0, \; C = 3 - S$$

$$\frac{dS}{dt} = 0 \; = 2S - \frac{1}{2}SC - S^2 = S(2 - \frac{1}{2}C - S) \rightarrow S = 0, \; S = 2 - \frac{1}{2}C$$

Solve system: C = 3-S and S = 2 -0.5C

C = 3 - (2 - 0.5C) → C = 3 -2 + 0.5C = 1 + 0.5c → 0.5C = 1 → C = 2

Then, S = 2-0.5(2) = 2-1 = 1

The fixed points are (C, S): (0, 0) and (2, 1)

Compute the Jacobian:

f(C, S) $= 3C - SC - C^2$

g(C, S) = $2S - \frac{1}{2}SC - S^2$

$\frac{df}{dC} = \frac{d}{dC}(3C - SC - C^2) = 3 - S - 2C$

$\frac{df}{dS} = \frac{d}{dS}(3C - SC - C^2) = -C$

$\frac{dg}{dC} = \frac{d}{dC}(2S - \frac{1}{2}SC - S^2) = \frac{-1}{2}S$

$\frac{dg}{dS} = \frac{d}{ds}(2S - \frac{1}{2}SC - S^2) = 2 - \frac{1}{2}C - 2S$

$$J = \begin{bmatrix} \frac{df}{dC} & \frac{df}{dS} \\ \frac{dg}{dC} & \frac{dg}{dS} \end{bmatrix} = \begin{bmatrix} 3-S-2C & -C \\ \frac{-1}{2}S & 2-\frac{1}{2}C-2S \end{bmatrix}$$

Evaluate Jacobian at each fixed point:

At (0, 0):

$$J = \begin{bmatrix} 3 & 0 \\ 0 & 2 \end{bmatrix}, \; so\, \lambda_1 = 3, \; and\, \lambda_2 = 2$$

Thus, the point (0, 0) is an unstable fixed point because both eigenvalues are positive.

At (2, 1):

$$J = \begin{bmatrix} 3-1-2(2) & -2 \\ \frac{-1}{2} & 2-\frac{1}{2}(2)-2(1) \end{bmatrix} = \begin{bmatrix} -2 & -2 \\ \frac{-1}{2} & -1 \end{bmatrix}$$

$$\begin{bmatrix} -2-\lambda & -2 \\ \frac{-1}{2} & -1-\lambda \end{bmatrix} = 0$$

$$0 = (-2-\lambda)(-1-\lambda) - -(2)(-\tfrac{1}{2}) = 2 + 2\lambda + \lambda + \lambda^2 - 1$$

$$0 = 1 + 3\lambda + \lambda^2$$

$$\lambda = \frac{-b \pm \sqrt{b^2-4ac}}{2a} = \frac{-3 \pm \sqrt{3^2-4}}{2} = \frac{-3 \pm \sqrt{5}}{2}$$

Since both roots are negative, the point (2, 1) is a stable fixed point.

b. As the cancer evolves, the population of tumor cells gains a new mutation that increases its proliferation rate to 4. Analyze for this model the equilibria (i.e. calculate all of the model's steady states) and their stability. Has the point of coexistence changed in stability from the previous model?

Find fixed points with updated equations:

$$\frac{dC}{dt} = 0 = 4C - SC - C^2 = C(4 - S - C) \rightarrow C = 0,\ C = 4 - S$$

$$\frac{dS}{dt} = 0 = 2S - \tfrac{1}{2}SC - S^2 = S(2 - \tfrac{1}{2}C - S) \rightarrow S = 0,\ S = 2 - \tfrac{1}{2}C$$

Solve system: C = 34-S and S = 2 -0.5C

C = 4 - (2 - 0.5C) → C = 4 -2 + 0.5C = 2 + 0.5c → 0.5C = 2 → C = 4

Then, S = 2-0.5(4) = 2-2 = 0

The fixed points are (C, S): (0, 0) and (4, 0)

<u>Compute the Jacobian:</u>

f(C, S) $= 4C - SC - C^2$, g(C, S) = $2S - \tfrac{1}{2}SC - S^2$

$$\frac{df}{dC} = \frac{d}{dC}(4C - SC - C^2) = 4 - S - 2C$$

$$\frac{df}{ds} = \frac{d}{dS}(4C - SC - C^2) = -C$$

$$\frac{dg}{dC} = \frac{d}{dC}(2S - \tfrac{1}{2}SC - S^2) = \frac{-1}{2}S$$

$$\frac{dg}{dS} = \frac{d}{ds}(2S - \tfrac{1}{2}SC - S^2) = 2 - \tfrac{1}{2}C - 2S$$

$$J = \begin{bmatrix} \frac{df}{dC} & \frac{df}{dS} \\ \frac{dg}{dC} & \frac{dg}{dS} \end{bmatrix} = \begin{bmatrix} 4-S-2C & -C \\ \frac{-1}{2}S & 2-\frac{1}{2}C-2S \end{bmatrix}$$

Evaluate Jacobian at each fixed point:

At (0, 0):

$$J = \begin{bmatrix} 4 & 0 \\ 0 & 2 \end{bmatrix}, \; so\, \lambda_1 = 4, \; and\, \lambda_2 = 2$$

Thus, the point (0, 0) is an unstable fixed point because both eigenvalues are positive.

At (4, 0):

$$J = \begin{bmatrix} 4-S-2C & -C \\ \frac{-1}{2}S & 2-\frac{1}{2}C-2S \end{bmatrix} = \begin{bmatrix} -4 & -4 \\ 0 & 0 \end{bmatrix}, \; so\, \lambda_1 = -4, \; and\, \lambda_2 = 0$$

Since one eigenvalue is negative and the other is 0, the system might be marginally stable.

Conclusion:

In the new model, the point of coexistence (previously (2, 1) no longer exists. The system now only has two fixed points (0, 0) and (4, 0). The first is unstable and the second is marginally stable.

3. ***Numerical integration of ODE models.***

Different hormones in our bodies are under the joint control of two central nervous glands: the hypothalamus (H) and the pituitary (P). [NB for further reading on these feedback systems refer to examples in GSG or Alon Sys Med). Here we will study a model for the control of the hormone estradiol (E) by the hypothalamus and pituitary glands. The model is defined by the following equations.

$$\frac{dH}{dt} = \frac{1}{1+E^n} - k_1 \mathrm{H}$$

$$\frac{dP}{dt} = H - k_2 \mathrm{P}$$

$$\frac{dE}{dt} = P - k_3 \mathrm{E}$$

a. Find the equilibria of this model by hand when n=1. How many solutions are there, and which are biologically meaningful?

Set all derivatives to 0:

$$\frac{dH}{dt} = \frac{1}{1+E} - k_1 H = 0 \rightarrow \frac{1}{1+E} = k_1 H \rightarrow H = \frac{1}{k_1(1+E)}$$

$$\frac{dP}{dt} = H - k_2 P = 0 \rightarrow H = k_2 P \rightarrow P = \frac{H}{k_2} = \frac{1}{k_1 k_2 (1+E)}$$

$$\frac{dE}{dt} = P - k_3 E = 0 \rightarrow P = k_3 E \rightarrow E = \frac{P}{k_3} = \frac{\frac{1}{k_1 k_2 (1+E)}}{k_3} \rightarrow E = \frac{1}{k_1 k_2 k_3 (1+E)}$$

$$\rightarrow E(1+E) = \frac{1}{k_1 k_2 k_3} \rightarrow E^2 + E - \frac{1}{k_1 k_2 k_3} = 0$$

$$E = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} = \frac{-1 \pm \sqrt{1^2 - 4(1)(\frac{-1}{k_1 k_2 k_3})}}{2(1)} = \frac{-1 \pm \sqrt{1 + \frac{4}{k_1 k_2 k_3}}}{2}$$

Find H and P at equilibrium:

$$P = \frac{1}{k_1 k_2 (1 + \frac{-1 \pm \sqrt{1 + \frac{4}{k_1 k_2 k_3}}}{2})}$$

$$H = \frac{1}{k_1 (1 + \frac{-1 \pm \sqrt{1 + \frac{4}{k_1 k_2 k_3}}}{2})}$$

For E to be biologically meaningful, it must be non-negative, so we only take the positive root. Thus, there are two solutions for E, but only one is biologically meaningful (the one with the positive root).

QUESTION 3B-3E AND QUESTION 4 (all parts) ARE ANSWERED IN THE ATTACHED .IPYNB FILE.

Both **qbio-478-hw2-part2.ipynb** and **qbio-478-hw2-part2.pdf** included in submission (pdf file may be easier to view).