Modelling of Biological Systems

University of Hyderbad

Assignment

[Each question carry equal marks; Total Marks: 100]

Submit / Present as a Project Report following the Format: Introduction, Materials/Methods, Analysis/Results & Discussion.

1) Get the detail information about the **Lipoic acid metabolism** in ***Leishmania major*** from *KEGG* or any other database. Select major interactions involved in the Pathway and translate the interactions in terms of mathematical expressions (*Ordinary Differential Equation* or *Boolean formalism/Logical Models or Graph Theory or a combination of different approaches*). Study the system (structure/dynamics) and comment.

2) Find all the Equilibrium points (Steady States) and comment on the stability criteria only around the disease-free equilibrium (also discuss the biological importance of these criteria), for the following system of ODEs representing the disease transmission model with constant population and of two compartments, susceptible (S) & infected (I):

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \mu K - \beta SI - \mu S$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = (\beta S - \mu - \gamma)I$$

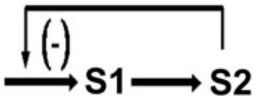
here $S > 0$, $I \geq 0$, $S + I \leq K$; K = Constant, μ = natural birth/death rate, β = disease transmission rate and γ = additional death rate due to infection.

3) Gliomas are the most common of the primary brain tumors and account for more than 40% of all central nervous system neoplasms. Gliomas include tumours that are composed predominantly of astrocytes (astrocytomas), oligodendrocytes (oligodendrogliomas), mixtures of various glial cells (for example,oligoastrocytomas) and ependymal cells (ependymomas). The most malignant form of infiltrating astrocytoma - glioblastoma multiforme (GBM) - is one of the most aggressive human cancers. GBM may develop de novo (primary glioblastoma) or by progression from low-grade or anaplastic astrocytoma (secondary glioblastoma). Primary glioblastomas develop in older patients and typically show genetic alterations (EGFR amplification, p16/INK4a deletion, and PTEN mutations) at frequencies of 24-34%. Secondary glioblastomas develop in younger patients and frequently show over expression of PDGF and CDK4 as well as p53 mutations (65%) and loss of Rb playing major roles in such transformations. Loss of PTEN has been implicated in both pathways, although it is much more common in the pathogenesis of primary GBM.

Get the detail information about the **Human Glioma signalling pathway** from *KEGG* or any other database. Re-plot the pathway map in *CellDesginer* or *CellNetAnalyzer*, using specific symbols and interactions for only the important (major) components of the map. Translate the interactions in terms of mathematical expression (*ordinary differential equation* or *boolean formalism*). **(Aman, Vikram, Sriram)**

4) Complex regulation of biochemical pathways in a cell is brought about by the interaction of simpler regulatory structures. Among the basic regulatory designs, feedback inhibition of gene expression is the most common motif in gene regulation and a ubiquitous control structure found in nature. A simple two-step reaction describing a negative auto-regulation is shown in the figure below (Figure 1a), where the substrate S1 being negatively regulated by the product S2. The corresponding gene circuit can be represented as a promoter-repressor gene transcriptional unit that on induction initiates transcription and

makes the messenger RNA, which is then translated to the repressor protein. The negative feedback is through the Repressor protein binding to its own operator-promoter complex and inhibiting transcription initiation, thereby repressing its own synthesis (Figure 1b).

(a) 

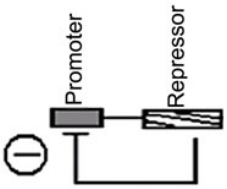
(b) 

Figure 1: (a) A simple negatively auto-regulated pathway; (b) The corresponding gene circuit

A mathematical model (Ordinary differential equation) of the circuit shown in Fig. 1(b) is given below:

$$\frac{dM}{dt} = \beta_1 G - \alpha_1 M$$

$$\frac{dP}{dt} = \beta_2 M - \alpha_2 P$$

$$\frac{dG}{dt} = k_2(G_t - G) - k_1 G P$$

Here, the transcription of the repressor gene (G) yields mRNA molecules (M), which are translated to produce the repressor protein (P). The repressor protein acts as a negative regulator of its own transcription by binding to the operator-promoter complex (shown as "promoter" here). k_1 and k_2 represent the rates of these forward and backward reactions, respectively. The amount of mRNA produced at any given instant is a function of the number of free promoters available for transcription. The parameters β_1 and β_2 represent the rates of transcription and translation, and α_1 and α_2 are the degradation rates of *M* and *P* that follow first order kinetics.

Write a programme in MATLAB or any other software/language to numerically simulate the model using the basal parameter values given in the table:

Parameters	Deterministic value
β_2	$4.3 \times 10^{-2}\ \text{sec}^{-1}$
β_1	$0.6 \times 10^{-9}\ \text{M sec}^{-1}$
α_1	$5.7 \times 10^{-3}\ \text{sec}^{-1}$
α_2	$1.15 \times 10^{-3}\ \text{sec}^{-1}$
$\mathbf{k_1}$	$1.2 \times 10^{+7}\text{M}^{-1}\ \text{sec}^{-1}$
k_2	$0.9\ \text{sec}^{-1}$
G_t	50

Show the time plot (for all variables) and M-P phase-portrait. From the simulation, comment on the stability of the system by varying different parameters one at a time. Comment on the changes observed in the dynamics of the system, when you increase or decrease 10 times, the parameters α_2 and k_2.

5) A mathematical model of tumor-immune interaction is developed to understand the effect of cytokine (IL2) and to explore the possibilities of immunotherapy treatment. There are three populations. These include: E(t), the activated immune-system cells (commonly called effector cells) such as cytotoxic T-cells, macrophages, and natural killer cells that are cytotoxic to the tumor cells; T(t), the tumor cells; and $I_L(t)$, the concentration of IL-2 in the single tumor-site compartment of the model. The model that describes the interaction between the effector cells, tumor cells, and the cytokine (IL-2) is:

$$\frac{dE}{dt} = cT - \mu_2 E + \frac{p_1 E I_L}{g_1 + I_L} + s_1, \quad (1)$$

$$\frac{dT}{dt} = r_2(T)T - \frac{aET}{g_2 + T}, \quad (2)$$

$$\frac{dI_L}{dt} = \frac{p_2 ET}{g_3 + T} - \mu_3 I_L + s_2, \quad (3)$$

with initial conditions:

$$E(0) = E_0, \qquad T(0) = T_0, \qquad I_L(0) = I_{L_0}, \quad (4)$$

$$r_2(T) = r_2(1 - bT). \quad (5)$$

The model terms are described as follows. The first equation describes the rate of change for the effector-cell population. Effector cells are stimulated to grow based on two terms. One is a recruitment term (term 1) due to the direct presence of the tumor, where the parameter *c* models the *antigenicity* of the tumor. Antigenicity can be thought of as a measure of how different the tumor is from *self*. The other growth/source term (term 3) is a proliferation term whereby effector cells are stimulated by IL-2 that is produced by effector cells in both an autocrine and paracrine manner. This term is of Michaelis-Menten form to indicate the saturated effects of the immune response. Effector cells have a natural lifespan of an average $1/\mu_2$ days. Lastly, s_1 is a treatment term that represents an external source of effector cells such as LAK or TIL cells. The loss of tumor cells is represented by an immune-effector cell interaction at rate *a*. This rate constant, *a* represents the strength of the immune response and is modeled by Michaelis-Menten kinetics to indicate the limited immune response to the tumor. (This form could also account for the effects of a solid tumor, i.e. only a portion of the tumor mass comes in contact with the immune system cells.) Equation (3) gives the rate of change for the concentration of IL-2. Its source is the effector cells that are stimulated by interaction with the tumor and also has Michaelis-Menten kinetics to account for the self-limiting production of IL-2. The next term (k3) represents loss/degraded rate of IL-2. Finally, s_2 is a treatment term that represents an external input of IL-2 into the system.

Find all the steady states of the system. Study the stability of the system around each of these steady states and find out the analytical conditions.

The parameters in the model are given in the following table:

Table 1. Parameter values

Eq. (1)	$0 \leqq c \leqq 0.05$	$\mu_2 = 0.03$	$p_1 = 0.1245$	$g_1 = 2 \times 10^7$
Eq. (2)	$g_2 = 1 \times 10^5$	$r_2 = 0.18$	$b = 1 \times 10^{-9}$	$a = 1$
Eq. (3)	$\mu_3 = 10$	$p_2 = 5$	$g_3 = 1 \times 10^3$	

Performing suitable numerical simulations, study the dynamics of the system around the interior steady states (positive equilibrium point). Plot the bifurcation diagram with respect to the variation of the parameter *c*.

6) The prey-predator interactions can be modelled using a set of ODE, called Lotka-Volterra equations, which is given below as:

$$\frac{dx(t)}{dt} = a\,x(t) - b\,x(t)\,y(t)$$

$$\frac{dy(t)}{dt} = b\,x(t)\,y(t) - c\,y(t)$$

Here, *x* is the prey and *y* is the predator population. The parameters used in the model are, **a**, growth rate of prey; **b**, interaction between prey and predator (hunting/searching efficiency); and **c**, natural death rate of predator. Study this system of equations both theoretically and numerically. Find the steady states and conditions for stability from theoretical analysis. Consider the numerical values of the parameters as, *a* = 10, b = 0.01 and c = 10; Initial values: x(0) = 1000; y(0) = 100. Simulate the model using these parameter values by writing small programme in MATLAB or any other language and study

the dynamics. What type of dynamics you observe? Can you get a different kind of dynamics by changing any of these parameters? Are your numerical and theoretical results comparable?

7) The Notch signaling pathway is an evolutionarily conserved, intercellular signaling mechanism essential for proper embryonic development in all metazoan organisms in the Animal kingdom. The Notch proteins (Notch1-Notch4 in vertebrates) are single-pass receptors that are activated by the Delta (or Delta-like) and Jagged/Serrate families of membrane-bound ligands. They are transported to the plasma membrane as cleaved, but otherwise intact polypeptides. Interaction with ligand leads to two additional proteolytic cleavages that liberate the Notch intracellular domain (NICD) from the plasma membrane. The NICD translocates to the nucleus, where it forms a complex with the DNA binding protein CSL, displacing a histone deacetylase (HDAc)-co-repressor (CoR) complex from CSL. Components of an activation complex, such as MAML1 and histone acetyltransferases (HATs), are recruited to the NICD-CSL complex, leading to the transcriptional activation of Notch target genes.

Get the detail information about the **Human Notch signaling pathway** from *KEGG* or any other database. Re-plot the pathway map in *CellDesginer* or *CellNetAnalyzer*, using specific symbols and interactions for only the important (major) components of the map. Translate the interactions in terms of mathematical expression (*ordinary differential equation* or *boolean formalism*).