Technische Universiteit Eindhoven University of Technology

Tumor growth and the immune system - Questions

Project for the Course on Modeling Dynamics

Department of Electrical Engineering
Eindhoven University of Technology

Version: October 21, 2018

1 Purpose and problem formulation

As explained in the project description, we consider the dynamical model

$$\begin{aligned}\dot{M} &= 1 + a_1 M(1-M) - a_2 MH \\ \dot{H} &= a_3 HR - a_4 H \\ \dot{R} &= a_5 R(1-R) - a_6 HR - a_7 R\end{aligned} \tag{1}$$

where M, H and R represent the densities of tumor cells, active hunting cells and resting cells, respectively. All parameters $a_1, \ldots, a_7$ are non-negative real numbers. The aim of the project is to investigate the dynamics of the tumor-immune system and to understand the influence of parametric variations on the clinical conditions of organic tissue in which these densities of cells reside.

2 Questions

Fixed points and biological feasibility

Densities are non-negative. This means that solutions (M, H, R) and fixed points (M^*, H^*, R^*) of the system (1) will be *biologically feasible* if they belong to the positive orthant. That is, if the triple $(M(t), H(t), R(t))$ belongs to the set

$$\mathcal{P} := \{(M, H, R) \in \mathbb{R}^3 \mid M \geq 0,\ H \geq 0,\ R \geq 0\}.$$

for all time $t \geq 0$ once the initial condition $(M_0, H_0, R_0) \in \mathcal{P}$.

1. Determine all fixed points of the system (1).
2. Verify whether $\mathcal{P}$ is a positive invariant set for the system (1) for specific or for all parameter values $a_i > 0$, $i = 1, \ldots, 7$.
3. Prove that $\frac{a_4}{a_3} + \frac{a_7}{a_5} < 1$ is a sufficient condition to guarantee that the system (1) has at least 3 biologically feasible fixed points. Show that, under this condition, these points assume the form

   $$E_1^* = (M_1^*, 0, 0), \qquad E_2^* = (M_2^*, 0, R_2^*), \qquad E_3^* = (M_3^*, H_3^*, R_3^*)$$

   and give a biological interpretation of these fixed points.

Next, consider the model (1) with the parameter values as indicated in Table 1.

4. Implement the system in Matlab and compute numerical solutions (M, H, R) on a sufficiently large time interval for Conditions 1, 2 and 3. Simulate for a number of initial conditions in $\mathcal{P}$ and plot solutions $(M(t), H(t), R(t))$ both against time and/or in a 3-dimensional state space plot. Discuss the clinical implications of what you observe in these 3 conditions.

	a_1	a_2	a_3	a_4	a_5	a_6	a_7
Condition 1	4.5	1	0.5	0.4	0.7	0.2	0.4
Condition 2	3.5	1	5.0	0.4	0.7	0.1	0.1
Condition 3	3.0	1	4.8	0.4	3.7	1.9	0.1

Table 1: Parameter values for 3 clinical conditions

Stability and contractive properties

Only the fixed point E_3^* consists of positive densities of malignant, hunting and resting cells and is therefore of clinical relevance. When unstable, this fixed point implies a malignancy that spreads uncontrollably in density and may invade adjacent tissue cells. When stable, E_3^* represents a benign tumor which remains self contained and with self-limited growth. The stability properties of this fixed point is therefore of quite some interest.

5. Assess the stability of all biologically feasible fixed points of the system (1) with the parameter values of Condition 1, Condition 2 and Condition 3.

6. Find a suitable matrix $P = P^\top \succ 0$ such that the quadratic function

$$V(M,H,R) = \begin{pmatrix} M - M_3^* \\ H - H_3^* \\ R - R_3^* \end{pmatrix}^\top P \begin{pmatrix} M - M_3^* \\ H - H_3^* \\ R - R_3^* \end{pmatrix}$$

serves as a Lyapunov function to prove the stability of the fixed point E_3^* with the parameter values of Condition 3. Moreover, determine a (maximal) constant $\gamma > 0$ such that all trajectories initialized in the level set

$$\mathcal{V}_\gamma := \{(M,H,R) \in \mathbb{R}^3 \mid V(M,H,R) \leq \gamma\}$$

remain in this set and converge to the equilibrium point E_3^*.

Time delays

It is realistic to assume that the immune system reacts with a time delay in the growth rate of the hunting cells H as a response to the presence of the tumor cells. If we incorporate a delay τ in this response, the model equations are represented as

$$\begin{aligned} \dot{M}(t) &= 1 + a_1 M(t)(1 - M(t)) - a_2 M(t) H(t) \\ \dot{H}(t) &= a_3 H(t-\tau) R(t-\tau) - a_4 H(t) \\ \dot{R}(t) &= a_5 R(t)(1 - R(t)) - a_6 H(t) R(t) - a_7 R(t) \end{aligned} \tag{2}$$

where we assume that $\tau > 0$ is a fixed delay in the response of the immune system. In what follows we will investigate the effect of the delay time τ in the system. For this, consider the parameter values of Condition 3 in Table 1.

7. Are the fixed points of the delayed system (2) dependent or independent of the delay time $\tau > 0$?

8. Implement this system for a positive delay time $\tau > 0$ with the parameter values of Condition 3, and simulate solutions of (2) assuming that the initial condition (M_0, H_0, R_0) is constant on $[-\tau, 0]$. Make a number of plots of (2) as functions of time and/or in a 3D state space while varying the delay time $\tau > 0$.

   This requires some smart coding in Matlab. Consider using the routine `dde23` *to solve delay differential equations with constant delays in Matlab. See the demo* `ddex1.m` *for an example. As an alternative you might consider an implementation in Simulink.*

9. Investigate whether there are bifurcations of the delay parameter τ in which E_3^* changes its stability properties, or whether you observe different changes in the system response.

Stabilization

Typical treatments for cancer amount to influencing the immune system in such a way that a given range of initial cell densities belongs to the domain of attraction of a stable equilibrium in which either $M^* = 0$ or small. If we can directly activate the resting cells by a suitable medication, then this influence may become a protocol to actually control and bound the growth of malignant cells. To verify this idea, suppose that we have direct control on the concentration of the resting cells through appropriate medication. We model this by extending the model (1) with an input $u(t)$ as in

$$\begin{aligned} \dot{M} &= 1 + a_1 M(1 - M) - a_2 MH \\ \dot{H} &= a_3 HR - a_4 H \\ \dot{R} &= a_5 R(1 - R) - a_6 HR - a_7 R + u \end{aligned} \tag{3}$$

Consider the parameters of Condition 3 and let $E^* = (M^*, H^*, R^*)$ be a biologically desirable fixed point in which the malignant cell density is set to an acceptable level $M^* = 0.1$.

10. Determine a constant medication level u^* such that E^* becomes fixed point of (3) . Then find a static linear feedback of the form

$$u(t) = F \begin{pmatrix} M(t) - M^* \\ H(t) - H^* \\ R(t) - R^* \end{pmatrix} + u^*$$

with $F = \begin{pmatrix} F_1 & F_2 & F_3 \end{pmatrix} \in \mathbb{R}^{1\times 3}$ such that the fixed point E^* becomes asymptotically stable. Is it possible to choose F such that the positive orthant $\mathcal{P}$ remains positive invariant?