5CSA0 - Tumor growth and the immune system - Project questions

Introduction

During this project a dynamical model is researched that describes tumor development. This model describes the interaction between malignant (tumor) cells and normal (immune or healthy) cells in an organic tissue. The immune system reacts on the presence of malignant cells by activating specific antibodies or 'hunting' cells that eliminate the malignant cells. In turn, the hunting cells belong to a population of resting cells that are latent in the tissue and that do not directly interfere with the malignant cells. The model has the following form:

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

Where

- M is the density of the tumor cells ($M \geq 0$)
- H is the density of active hunting cells in the immune system ($H \geq 0$)
- R is the density of resting cells in the immune system ($R \geq 0$)
- a_1 is the growth rate of tumor cells ($a_1 \geq 0$)
- a_2 is the rate of destruction of tumor cells by the hunting cells ($a_2 \geq 0$)
- a_3 is the conversion rate from resting cells to hunting cells ($a_3 \geq 0$)
- a_4 is the natural death rate of hunting cells ($a_4 \geq 0$)
- a_5 is the growth rate of resting cells ($a_5 \geq 0$)
- a_6 is the conversion rate from hunting cells to resting cells ($a_6 \geq 0$)
- a_7 is the natural death rate of resting cells ($a_7 \geq 0$)

Date:
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Names:	**Student number:**
Bob Clephas	1271431
Job Meijer	1268155

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1. Determine all fixed points of the system

First the nullclines are determined, then the fixed points of the system. To determine the nullclines, the following equations are solved:

$$\dot{M} = 0, \dot{H} = 0,\ \dot{R} = 0$$

resulting in the following nullclines:
The nullclines of $\dot{M}$ are:

$$\mathcal{N}_{M_1} = \frac{1}{2} - \frac{a_2}{2a_1}H + \sqrt{\frac{a_1^2 + a_2^2H^2 - 2a_1a_2H + 4a_1}{4a_1^2}}$$

$$\mathcal{N}_{M_2} = \frac{1}{2} - \frac{a_2}{2a_1}H - \sqrt{\frac{a_1^2 + a_2^2H^2 - 2a_1a_2H + 4a_1}{4a_1^2}}$$

The nullclines of $\dot{H}$ are:

$$\mathcal{N}_{H_1} = 0$$

$$\mathcal{N}_{H_2} = \frac{a_5(1-R) - a_7}{a_6}$$

$$\mathcal{N}_{H_3} = \frac{-a_1M(M-1) - 1}{a_2M}$$

The nullclines of $\dot{R}$ are:

$$\mathcal{N}_{R_1} = 0$$

$$\mathcal{N}_{R_2} = \frac{a_4}{a_3}$$

$$\mathcal{N}_{R_3} = \frac{-a_6H - a_7 + a_5}{a_5}$$

From the nullclines, the following fixed points can be derived by finding the intersections of the nullclines: $\mathcal{N}_{M_{1,2}} = \mathcal{N}_{H_{1,2,3}} = \mathcal{N}_{R_{1,2,3}}$. The fixed points for this system are shown in Table 1.

Table 1 – Fixed points of system

M	**H**	**R**
$\frac{1}{2}+\frac{1}{2}\sqrt{\frac{a_1+4}{a_1}}$	0	0
$\frac{1}{2}+\frac{1}{2}\sqrt{\frac{a_1+4}{a_1}}$	0	$\frac{a_5-a_7}{a_5}$
Equation 1	$\frac{-a_4\cdot a_5+a_3\cdot a_5-a_3\cdot a_7}{a_3\cdot a_6}$	$\frac{a_4}{a_3}$
$\frac{1}{2}-\frac{1}{2}\sqrt{\frac{a_1+4}{a_1}}$	0	0
$\frac{1}{2}-\frac{1}{2}\sqrt{\frac{a_1+4}{a_1}}$	0	$\frac{a_5-a_7}{a_5}$
Equation 2	$\frac{-a_4\cdot a_5+a_3\cdot a_5-a_3\cdot a_7}{a_3\cdot a_6}$	$\frac{a_4}{a_3}$

Equation 1

$$\frac{1}{2}-\frac{a_2}{2\cdot a_1}\cdot\left(\frac{-a_4\cdot a_5+a_3\cdot a_5-a_3\cdot a_7}{a_3\cdot a_6}\right)+\sqrt{\frac{a_1^2+a_2^2\cdot\left(\frac{-a_4\cdot a_5+a_3\cdot a_5-a_3\cdot a_7}{a_3\cdot a_6}\right)^2-2\cdot a_1\cdot a2\cdot\left(\frac{-a_4\cdot a_5+a_3\cdot a_5-a_3\cdot a_7}{a_3\cdot a_6}\right)+4\cdot a_1}{4\cdot a_1^2}}$$

Equation 2

$$\frac{1}{2}-\frac{a_2}{2\cdot a_1}\cdot\left(\frac{-a_4\cdot a_5+a_3\cdot a_5-a_3\cdot a_7}{a_3\cdot a_6}\right)-\sqrt{\frac{a_1^2+a_2^2\cdot\left(\frac{-a_4\cdot a_5+a_3\cdot a_5-a_3\cdot a_7}{a_3\cdot a_6}\right)^2-2\cdot a_1\cdot a2\cdot\left(\frac{-a_4\cdot a_5+a_3\cdot a_5-a_3\cdot a_7}{a_3\cdot a_6}\right)+4\cdot a_1}{4\cdot a_1^2}}$$

2. Positive invariant set

In this exercise is verified whether $\mathcal{P}$ is a positive invariant set for the system for specific or for all parameter values $a_i > 0$ (with i = 1 till 7).

The solutions (M, H, R) and fixed points (M^*, H^*, R^*) of the system are biologically feasible if they belong to the positive orthant. That is, if the triple $(M(t), H(t), R(t))$ belongs to the set

$$\mathcal{P} \coloneqq \{(M, H, R) \in \mathbb{R}^3 | M \geq 0, H \geq 0, R \geq 0\}$$

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

If the system is a positive invariant set, it means that

- Trajectories that enter- or start in $\mathcal{P}$ stay in $\mathcal{P}$
- Trajectories can cross into-, but never out of $\mathcal{P}$

To determine if it is possible for solutions to exit $\mathcal{P}$, the limits of the functions $(\dot{M}, \dot{H}, \dot{R})$ are investigated.

When M approaches 0 from a positive number, $\dot{M}$ becomes 1. This indicates that M is increasing again, meaning that M does not become negative. This is shown in the following formula.

$$\lim_{M \to 0^+} (\dot{M}) = 1 + a_1 \cdot 0 - a_2 \cdot 0 \cdot H = 1$$

When H approaches 0 from a positive number, $\dot{H}$ becomes also 0. This indicates that H does not decrease past 0.

$$\lim_{H \to 0^+} (\dot{H}) = a_3 \cdot 0 \cdot R - a_4 \cdot 0 = 0$$

When R approaches 0 from a positive number, $\dot{R}$ becomes also 0. This indicates that R does not decrease past 0.

$$\lim_{R \to 0^+} (\dot{R}) = a_5 \cdot 0 - a_6 H \cdot 0 - a_7 \cdot 0 = 0$$

The limits above show that once a solution enters $\mathcal{P}$, it stays in $\mathcal{P}$. Once a solution has positive values for M, H and R, these remain positive.

3. Biologically feasible fixed points

During this exercise is proven that ($a_4/a_3 + a_7/a_5$) < 1 is a sufficient condition to guarantee that the system has at least 3 biologically feasible fixed points. Under this condition it is assumed that these points have the following 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.

For a fixed point to be biologically feasible, it must lay in the positive octant of the state space, because a negative concentration does not exist in practice. When using this, the following fixed points can be found:

$$E_1^* = \left(\frac{1}{2} + \frac{1}{2}\sqrt{\frac{a_1 + 4}{a_1}}, 0{,}0\right)$$

$$E_2^* = \left(\frac{1}{2} + \frac{1}{2}\sqrt{\frac{a_1 + 4}{a_1}}, 0, \frac{a_5 - a_7}{a_5}\right)$$

$$E_3^* = \left(, \frac{-a_4 \cdot a_5 + a_3 \cdot a_5 - a_3 \cdot a_7}{a_3 \cdot a_6}, \frac{a_4}{a_3}\right)$$

Using that the parameters $a_1, \ldots, a_7$ are all strictly larger than 0, then E_1^* always exists. For E_2^* to exist, the following condition must be met: $a_7 < a_5$. For E_3^* to exist, the following term must be larger than 0:

$$\frac{-a_4 \cdot a_5 + a_3 \cdot a_5 - a_3 \cdot a_7}{a_3 \cdot a_6}$$

This can be rewritten to the following:

$$\frac{a_4 \cdot a_5 + a_3 \cdot a_7}{a_3 \cdot a_6} < \frac{a_3 \cdot a_5}{a_3 \cdot a_6}$$

$$\frac{a_4 \cdot a_5}{a_3} + a_7 < a_5$$

$$\frac{a_4}{a_3} + \frac{a_7}{a_5} < 1$$

If this condition is met, the condition for the existence of E_2^* is also met automatically, because a_5 must be larger than a_7.

4. Matlab implementation

The system is implemented in Matlab and simulated with the three parameter combinations of Table 2. The three conditions are simulated with different initial conditions M(0), H(0) and R(0) ranging between 0 and 2 with steps of 0.5. To solve the selution, an ode45 solver was used with a simulation time between 0 and 1000. The result of the simulations are shown in Figure 1, Figure 2 and Figure 3 where initial conditions are shown with cyan dots, trajectories with a black line, unstable fixed points with red and stable fixed points with green.

Table 2 – Matlab simulation conditions

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

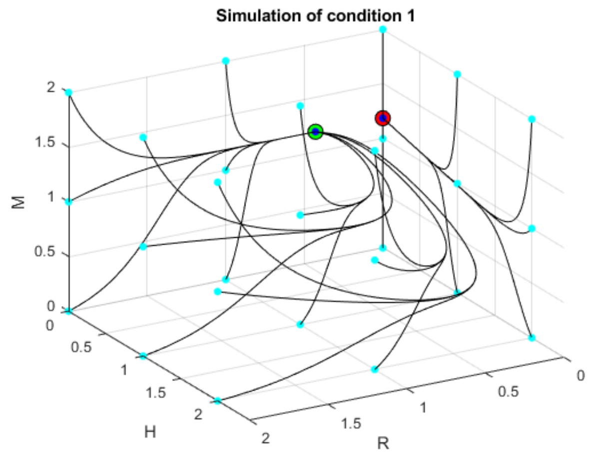

Figure 1 – Matlab simulation of condition 1

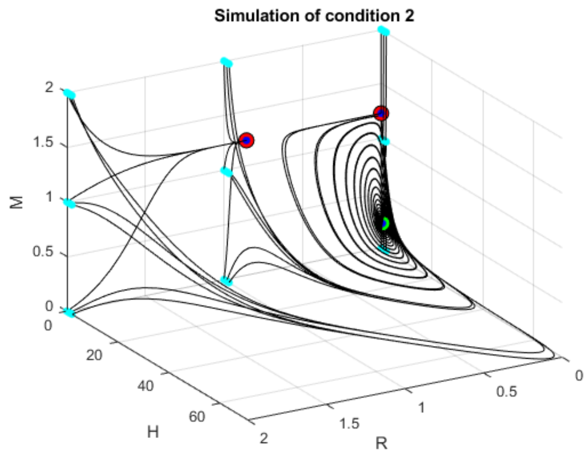

Figure 2 – Matlab simulation of condition 2

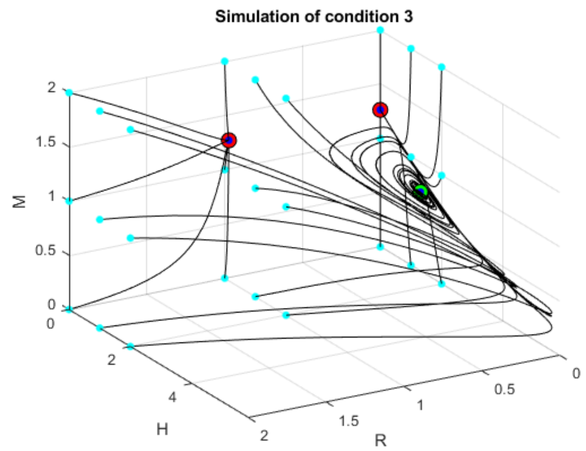

Figure 3 – Matlab simulation of condition 3

5. Stability of all biologically feasible fixed points

The stability of all biologically feasible fixed points (E_1^*, E_2^*, E_3^*) are addressed in this exercise. From Figure 1, using condition 1, it is visible that E_1^* is unstable, because all the initial conditions with $R > 0$ head for E_2^*, which makes this a stable fixed point. Condition 2 and 3 both have 3 fixed points. In both cases the fixed points E_1^* and E_2^* are unstable, because all initial conditions where $H > 0$ head for fixed point E_3^*. As can be seen in both Figure 2 and Figure 3.

To algebraically show the stability of the fixed points, the system is linearized by calculating the Jacobian matrix of the system as can be seen below:

$$A = \begin{bmatrix} \frac{\delta \dot{M}}{\delta M} & \frac{\delta \dot{M}}{\delta H} & \frac{\delta \dot{M}}{\delta R} \\ \frac{\delta \dot{H}}{\delta M} & \frac{\delta \dot{H}}{\delta H} & \frac{\delta \dot{H}}{\delta R} \\ \frac{\delta \dot{R}}{\delta M} & \frac{\delta \dot{R}}{\delta H} & \frac{\delta \dot{R}}{\delta R} \end{bmatrix}$$

$$A = \begin{bmatrix} a_1 - 2 \cdot a_2 \cdot M - a_2 \cdot H & -a_2 \cdot M & 0 \\ 0 & a_3 \cdot R - a_4 & a_3 \cdot H \\ 0 & -a_6 \cdot R & a_5 - 2 \cdot a_5 \cdot R - a_6 \cdot H - a_7 \end{bmatrix}$$

When substituting a certain fixed point in this matrix, the result is a linear system which approximates the behavior of the non-linear system close to the fixed point. To validate the stability of the fixed point, the eigenvalues of the matrix are used.
Table 3 shows the eigenvalues of the different conditions and fixed points. For a fixed point to be asymptotically stable, the real part of the eigenvalues must be negative. This concludes the stability of E_2^* for condition 1 and E_3^* for condition 2 and 3.

Table 3:Eigenvalues Fixed points

	E_1^*	E_2^*	E_3^*
Condition 1	$\begin{pmatrix} -6.1847 \\ -0.4000 \\ 0.3000 \end{pmatrix}$	$\begin{pmatrix} -6.1847 \\ -0.3000 \\ -0.1857 \end{pmatrix}$	
Condition 2	$\begin{pmatrix} -5.1235 \\ -0.4000 \\ 0.6000 \end{pmatrix}$	$\begin{pmatrix} -5.1235 \\ -0.6000 \\ 3.8857 \end{pmatrix}$	$\begin{pmatrix} -4.2147 \\ -0.0280 + 0.4656i \\ -0.0280 - 0.4656i \end{pmatrix}$
Condition 3	$\begin{pmatrix} -4.5826 \\ -0.4000 \\ 3.6000 \end{pmatrix}$	$\begin{pmatrix} -4.5826 \\ -3.6000 \\ 4.2703 \end{pmatrix}$	$\begin{pmatrix} -3.6887 \\ -0.1542 + 1.1371i \\ -0.1542 - 1.1371i \end{pmatrix}$

6. Positive definite matrix P

In this exercise a suitable matrix $P = P^T > 0$ is found such that the quadratic function $V(M,H,R) = \begin{pmatrix} M - M_3^* \\ H - H_3^* \\ R - R_3^* \end{pmatrix}^T P \begin{pmatrix} M - M_3^* \\ H - H_3^* \\ R - R_3^* \end{pmatrix}$
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

$$\mathcal{V}_\gamma \coloneqq \{(M,H,R) \in \mathbb{R}^3 | V(M,H,R) \leq \gamma\}$$

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

The matrix P is determined using the Matlab function *"lyap(A',Q)"* where A is the linearized matrix and Q is a 3x3 identity matrix. This function returned the following matrix P which is symmetric and is positive definite:

$$P = \begin{bmatrix} 0.1355 & -0.0279 & -0.0580 \\ -0.0279 & 1.8439 & 3.3033 \\ -0.0580 & 3.3033 & 90.7114 \end{bmatrix}$$

To determine the constant γ, the distance between the fixed point and the closest point where $V(M,H,R) > 0$ and $V'(M,H,R) \leq 0$ needs to be determined.

$$V(M,H,R) = \begin{pmatrix} M - M_3^* \\ H - H_3^* \\ R - R_3^* \end{pmatrix}^{\mathrm{T}} \begin{bmatrix} p_{11} & p_{12} & p_{13} \\ p_{12} & p_{22} & p_{23} \\ p_{13} & p_{23} & p_{33} \end{bmatrix} \begin{pmatrix} M - M_3^* \\ H - H_3^* \\ R - R_3^* \end{pmatrix}$$

$$V(M,H,R) = p_{11} \cdot (M - M_3^*)^2 + p_{22} \cdot (H - H_3^*)^2 + p_{33} \cdot (R - R_3^*)^2 +$$
$$2 \cdot p_{12} \cdot \left((M - M_3^*) \cdot (H - H_3^*)\right) + 2 \cdot p_{13} \cdot \left((R - R_3^*) \cdot (M - M_3^*)\right) + 2 \cdot p_{23} \cdot \left((R - R_3^*) \cdot (H - H_3^*)\right)$$

$$V' = \langle \nabla \mathrm{V}(\mathrm{M}, \mathrm{H}, \mathrm{R}), f(M,H,R) \rangle$$

Results in

$$V'(M,H,R) = \dot{M} \cdot \left(2 \cdot p_{11} \cdot (M - M_3^*) + 2 \cdot p_{12} \cdot (H - H_3^*) + 2 \cdot p_{13} \cdot (R - R_3^*)\right) +$$
$$\dot{H} \cdot \left(2 \cdot p_{12} \cdot (M - M_3^*) + 2 \cdot p_{22} \cdot (H - H_3^*) + 2 \cdot p_{23} \cdot (R - R_3^*)\right) +$$
$$\dot{R} \cdot \left(2 \cdot p_{13} \cdot (M - M_3^*) + 2 \cdot p_{23} \cdot (H - H_3^*) + 2 \cdot p_{33} \cdot (R - R_3^*)\right)$$

Substituting for $\dot{M}, \dot{H}$ and $\dot{R}$:

$$V' = (1 + a_1 M(1 - M) - a_2 MH) \cdot \left(2 \cdot p_{11} \cdot (M - M_3^*) + 2 \cdot p_{12} \cdot (H - H_3^*) + 2 \cdot p_{13} \cdot (R - R_3^*)\right) +$$
$$(a_3 HR - a_4 H) \cdot \left(2 \cdot p_{12} \cdot (M - M_3^*) + 2 \cdot p_{22} \cdot (H - H_3^*) + 2 \cdot p_{23} \cdot (R - R_3^*)\right) +$$
$$(a_5 R(1 - R) - a_6 HR - a_7 R) \cdot \left(2 \cdot p_{13} \cdot (M - M_3^*) + 2 \cdot p_{23} \cdot (H - H_3^*) + 2 \cdot p_{33} \cdot (R - R_3^*)\right)$$

Now the formulas above are implemented in Matlab and for various points (M,H,R) is determined if $V(M,H,R) > 0$ and $V'(M,H,R) \leq 0$. This resulted in Figure 4 where the closest invalid Lyapunov point is at a distance of 0.001432 from the fixed point, resulting in $\gamma \leq 0.001432$.

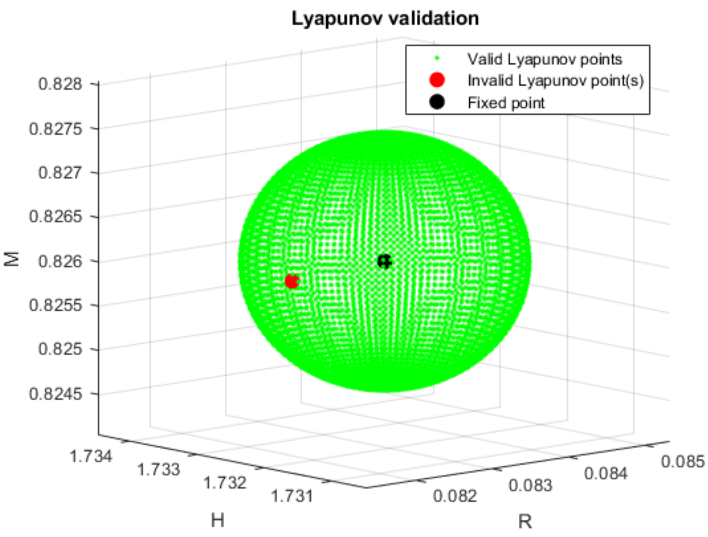

Figure 4 - Validation of Lyapunov points

7. Delay time influence on fixed points

To extend the model, a time delay τ is implemented in the growth rate of the hunting cells H as a response to the presence of the tumor cells. This results in the following model:

$$\dot{M} = 1 + a_1 M(t)\big(1 - M(t)\big) - a_2 M(t)H(t)$$
$$\dot{H} = a_3 H(t-\tau)R(t-\tau) - a_4 H(t)$$
$$\dot{R} = a_5 R(t)(1 - R(t)) - a_6 H(t)R(t) - a_7 R(t)$$

where $\tau > 0$ is a fixed delay in the response of the immune system. In the following exercises the effect of τ is investigated under the system parameters of condition 3.

When filling in the fixed points as initial condition and the parameters for condition 3, the resulting rates of change, $\dot{M}, \dot{H}, \dot{R}$, are still zero, which means that the fixed points are not affected by the added time delay. This is shown in Figure 5, where a delay time τ of 0.7 and a simulation time of 200 are used.

Fixed point E_1^*:

$$\dot{M} = 1 + 3 \cdot 1.2638 \cdot (1 - 1.2638) - 1 \cdot 1.2638 \cdot 0 = 0$$
$$\dot{H} = 4.8 \cdot 0 \cdot 0 - 0.4 \cdot 0$$
$$\dot{R} = 3.7 \cdot 0 \cdot (1 - 0) - 1.9 \cdot 0 \cdot 0 - 0.1 \cdot 0 = 0$$

Fixed point E_2^*:

$$\dot{M} = 1 + 3 \cdot 1.2638 \cdot (1 - 1.2638) - 1 \cdot 1.2638 \cdot 0 = 0$$
$$\dot{H} = 4.8 \cdot 0 \cdot 0.9730 - 0.4 \cdot 0$$
$$\dot{R} = 3.7 \cdot 0.9730 \cdot (1 - 0.9730) - 1.9 \cdot 0 \cdot 0.9730 - 0.1 \cdot 0.9730 = 0$$

Fixed point E_3^*:

$$\dot{M} = 1 + 3 \cdot 0.8260 \cdot (1 - 0.8260) - 1 \cdot 0.8260 \cdot 1.7325 = 0$$
$$\dot{H} = 4.8 \cdot 1.7325 \cdot 0.0833 - 0.4 \cdot 1.7325$$
$$\dot{R} = 3.7 \cdot 0.0833 \cdot (1 - 0.0833) - 1.9 \cdot 1.7325 \cdot 0.0833 - 0.1 \cdot 0.0833 = 0$$

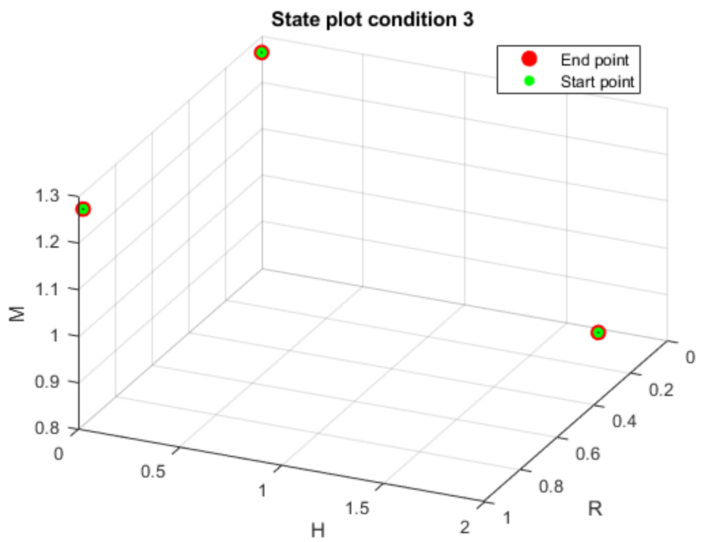

Figure 5 – Influence of delay time on fixed points with $\tau = 0.7$ and simulation time is 200

8. Matlab implementation of delayed system

To determine if the time delay has influence on the behavior of the system, the system with time delay is implemented in Matlab and simulated. This is done with various τ of 0, 0.2, 0.3 and 1. The results of this implementation are shown in Figure 6, Figure 7, Figure 8 and Figure 9.

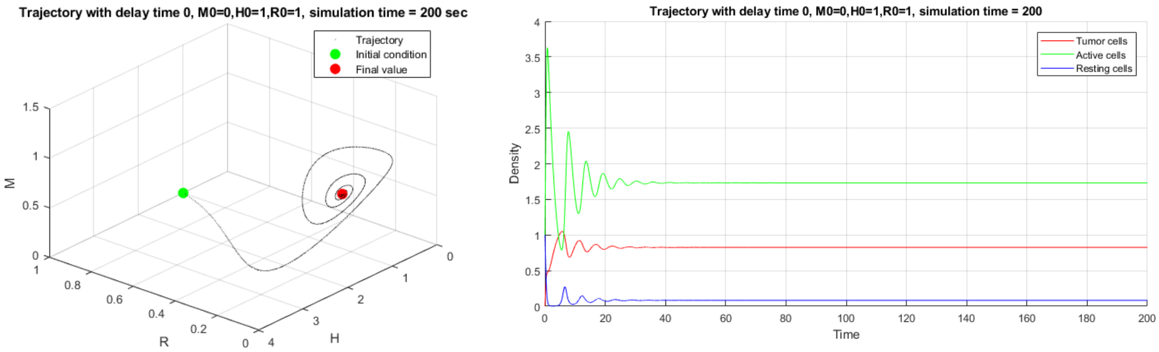

Figure 6 –System with time delay 0

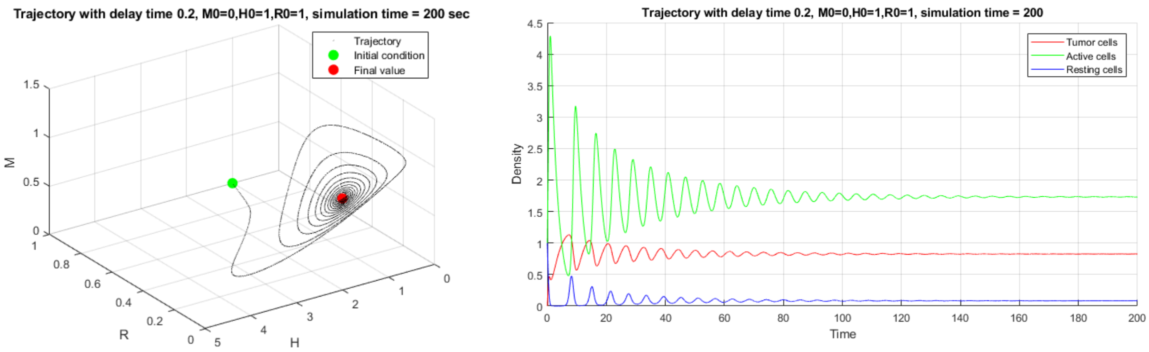

Figure 7 – System with time delay 0.2

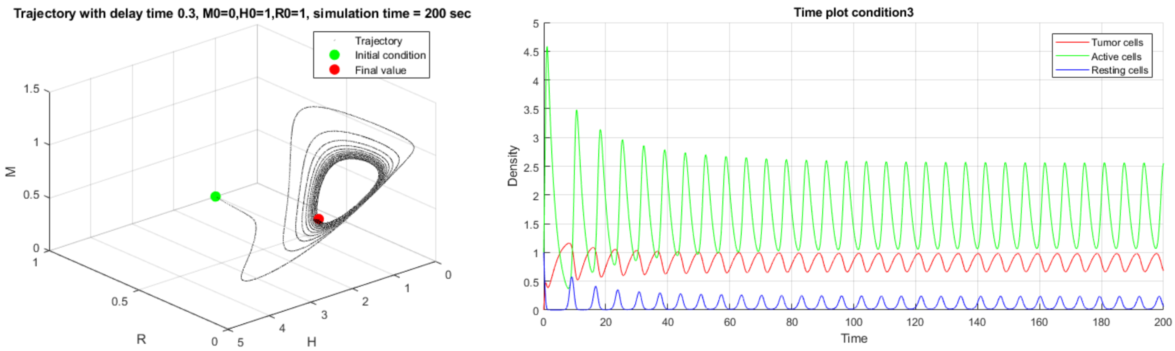

Figure 8 – System with time delay 0.3

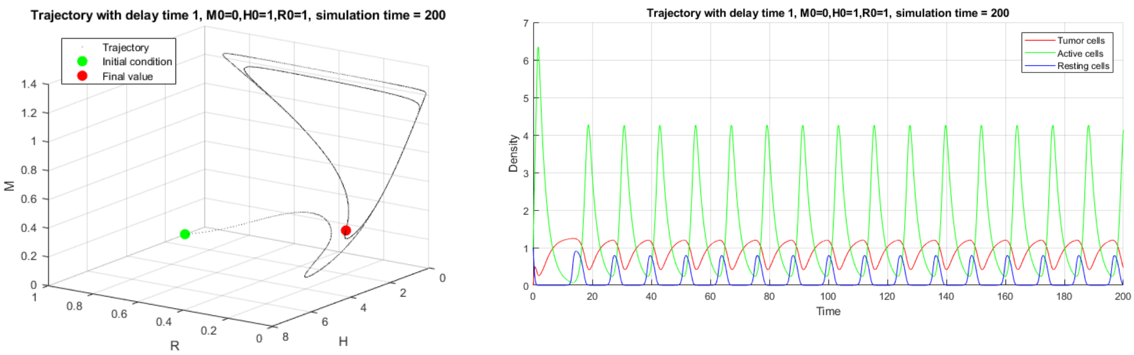

Figure 9 – System with time delay 1

9. Investigation of τ related bifurcations in E_3^*

From the figures of exercise 8 can be concluded that the delay time τ has influence on the stability of the fixed point E_3^*. In Figure 7 is a simulation shown with a delay time of 0.2, which still settles in the fixed point E_3^*. When the delay time is increased to 0.3, the fixed point becomes unstable and a limit cycle occurs as shown in Figure 8. If for a delay time of 0.3 and an initial condition is set at the fixed point with a slight perturbation, the solution moves towards the limit cycle meaning that it became unstable. Because the stability of this fixed point changes and a limit cycle branches from this point, it can be concluded that the bifurcation type is a Hopf bifurcation.

10. Determining medication level

To mitigate the Tumor amount, medication is applied which directly controls the concentration of the resting cells using input u(t) as is shown below:

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

With parameters of condition 3 and $E^* = (M^*, H^*, R^*)$ is a biologically desirable fixed point in which the malignant cell density M^* is set to an acceptable level of 0.1. Reaching this fixed point is done by determining a constant medication level u^* such that E^* becomes a fixed point with $M = 0.1$. Because the input u(t) is in R, this relation between the input and M is through H.

First the needed amount of H is determined by inserting $M = 0.1$ in the nullcline of $\dot{M}$ using parameters of condition 3.

$$\mathcal{N}_{M_1} := \frac{1}{2} - \frac{a_2}{2a_1} H + \sqrt{\frac{a_1^2 + a_2^2 H^2 - 2a_1 a_2 H + 4a_1}{4a_1^2}} = 0.1 \; results \; in \; H = 12.7$$

Next, the new nullcline of $\dot{H}$ is determined by:

$$\dot{R} := a_5 R(1 - R) - a_6 HR - a_7 R + u = 0 \rightarrow H = \frac{a_5(1 - R) - a_7 + \frac{u^*}{R}}{a_6}$$

Solving for $H = 12.7$ results in $u^* = R(3.7R + 20.53)$. Now the new value of R has to be determined which is $\mathcal{N}_{R_2} = 0.083$, because $\mathcal{N}_{R_1} = 0$ yields $u^* = 0$ and $\mathcal{N}_{R_3} = -5.549$ is negative. The resulting constant medication level $u^* = 1.7365$ therefor has the following fixed point:

$$E^* = \begin{pmatrix} 0.1 \\ 12.7 \\ 0.083 \end{pmatrix}$$

Next, a static linear feedback is determined of the form

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

With $F = (F_1 \quad F_2 \quad F_3) \in \mathbb{R}^{1\times3}$ such that the fixed point E^* becomes asymptotically stable. To determine if the new fixed point is asymptotically stable, the Jacobian matrix of the new feedback system is calculated. The feedback terms are also present in this matrix as can be seen below:

$$A_{u(t)} = \begin{bmatrix} a_1 - 2 \cdot a_2 \cdot M - a_2 \cdot H & -a_2 \cdot M & 0 \\ 0 & a_3 \cdot R - a_4 & a_3 \cdot H \\ F_1 & -a_6 \cdot R + F_2 & a_5 - 2 \cdot a_5 \cdot R - a_6 \cdot H - a_7 + F_3 \end{bmatrix}$$

The final step is to determine if it possible to choose an F such that the positive orthant $\mathcal{P}$ remains positive invariant. It is already proven that the system without the added input remains positive invariant in $\mathcal{P}$. Therefor it is sufficient to prove that R remains positive when it starts with a positive initial condition.

To validate if R remains positive when it starts with a positive initial condition, $\dot{R}$ must be larger or equal to 0 when R approaches 0. This gives the following expression:

$$\dot{R} = a_5R(1-R) - a_6HR - a_7R + \mathrm{F}_1(M - M^*) + F_2(H - H^*) + F_3(R - R^*) + u^*$$

$$\lim_{R\to0^+}(\dot{R}) = a_5 0(1-0) - a_6H0 - a_7 0 + \mathrm{F}_1 \cdot (M - M^*) + F_2 \cdot (H - H^*) + F_3 \cdot (0 - R^*) + u^*$$

$$\lim_{R\to0^+}(\dot{R}) = F_1(M - M^*) + F_2(H - H^*) - F_3R^* + u^* \geq 0$$

It is already proven that M and H remain positive with a positive initial condition, therefor the smallest value they can be is 0. When F_1 or F_2 are negative, the total value can also become negative. Which means F_1 and F_2 must be larger or equal to zero to ensure positive invariance in $\mathcal{P}$. This simplifies down to the following inequality:

$$u^* \geq F_1M^* + F_2H^* + F_3R^*$$

When using a static linear feedback $F = (1\ 0 - 1)$, the positive orthant $\mathcal{P}$ remains positive invariant, because $1.7365 \geq 1 \cdot 0.1 + 0 \cdot 12.7 - 1 \cdot 0.0833$. and the fixed point is asymptotically stable, because the real parts from the eigenvalues of the filled in Jacobina matrix are all negative as can be seen below:

$$eig(A_{u(t)}) = \begin{pmatrix} -21.7262 \\ -10.2453 \\ -0.4740 \end{pmatrix}$$

The result of using this feedback can be seen in Figure 10.

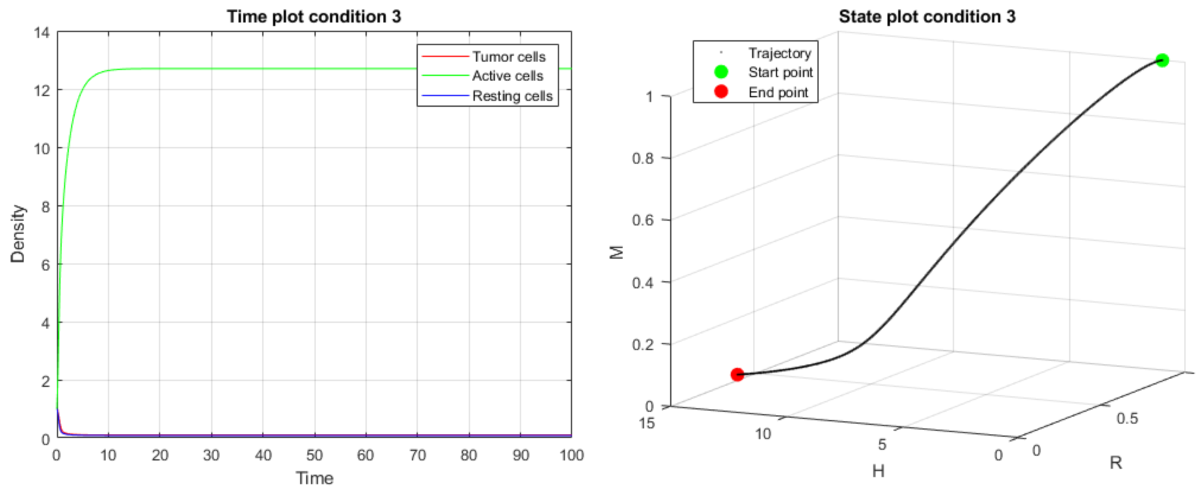

Figure 10 - System with linear feedback