# MATH3063 Assignment 1
# University of Sydney

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In the past decade or so, some cancer clinics have started trying to treat tumours using genetically-engineered anti-cancer viruses (called oncolytic virotherapy). Also, biomedical researchers are currently trying to develop experimental immunotherapies (i.e., immune-stimulating therapies) to combine with anti-cancer viruses to improve outcome. A simple differential equation model is

$$\frac{dC}{dT} = RC\left(1 - \frac{C}{K}\right) - VC^2 - IC \tag{1}$$

where $T$ is the time in days, $C$ is the cancer cell population, $R$ is the intrinsic reporduction rate per day of cancer cells, $K$ is the carrying capacity of the tumor, $V$ is the strength of the anti-cancer virus, and $I$ is the strength of the immune response indced by immunotherapy.

Assume that $R > 0$, $K > 0$, $V \geq 0$, and $I \geq 0$.

1. Show that the differential equation has the dimensionless form

$$\frac{dx}{dt} = g(x) - h(x)$$

where $g(x) = x(1-x)$ describes the tumor growth in the absence of treatment and $h(x) = vx^2 + wx$ descrbes the effect of combination virotherapy and immunotherapy treatment. Give appropriate expressions for dimensionless quantities $x$, $t$, $v$ and $w$.

Comparing the model in Equation 1 with the general spruce budworm model

$$\frac{dC}{dT} = RC\left(1 - \frac{C}{K}\right) + H(C)$$

it is evident that: $r = R$, $K = K$ and $H(C) = VC^2 + IC$. Thus, we choose $x = \alpha C$ and $t = \beta T$, where $\alpha$ and $\beta$ are constants. Equation 1 can be rewritten as

$$\begin{aligned} \frac{dx}{dt} &= \frac{\alpha}{\beta}\left(R\frac{x}{\alpha}\left(1 - \frac{x}{\alpha K}\right) - V\left(\frac{x}{\alpha}\right)^2 - I\frac{x}{\alpha}\right) \\ &= \frac{R}{\beta}\left(x\left(1 - \frac{x}{\alpha K}\right) - \frac{V}{\beta\alpha}x^2 - \frac{I}{\beta}x\right) \end{aligned}$$

Therefore, we can simplify towards $g(x)$ by letting $\beta = R$ and $\alpha = 1/K$ which gives

$$\frac{dx}{dt} = x\left(1-x\right) - \frac{VK}{R}x^2 - \frac{I}{R}x$$

and then simplify towards $h(x)$ by letting $v = VK/R$ and $w = I/R$ which gives

$$\begin{aligned} \frac{dx}{dt} &= x\left(1-x\right) - vx^2 - wx \\ &= g(x) - h(x) \end{aligned}$$

Therefore, the dimensionless quantities for $x$, $t$, $v$ and $w$ are:

$$x = \tfrac{C}{K}, \quad t = RT, \quad v = \tfrac{VK}{R}, \quad w = \tfrac{I}{R}$$

2. Assuming *only immunotherapy* is used, show that the minimum strength of the immune response required to eradicate the tumor corresponds to $w_{min} = 1$.

   In this case, $V = 0$ , so the term disapears and the dimensionless differential equation becomes

$$\frac{dx}{dt} = x\,(1-x) - wx$$

   where $g(x) = x\,(1-x)$ and $h(x) = wx$.

   We require the population to always go extinct, i.e. to always cause the tumor to get destroyed, $dx/dt < 0$. For this we need Case 2 of the models we have studied, $g(x) < h(x)$. This requires the gradient at 0 for the growth rate, $g(x)$ to be equal to the gradient of the immune response term.

$$g'(x) = 1 - 2x \Longrightarrow g'(0) = 1$$

   As the immune response in this case is determined by $h(x) = wx$, we can say the minimum value of $w$ must be

$$w_{min} = g'(0) = 1$$

   We can plot $g(x)$ and $h(x)$ and see the semi-stable point at $x = 0$ that it has, in non-dimensional form when $w = 1$.

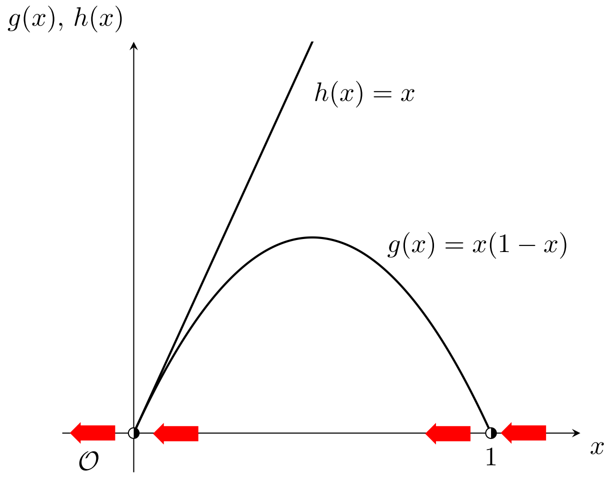


   Figure 1: Equilibrium solutions for tumor growth with immonetherapy

   For any value of $0 < w < 1$ the points of stability will look like Figure 2, with a straight line. For any value of $w > 1$, there will be another intersection point $N_{eq}$, along with $(0, 0)$, and therefore another semi-stable point. Then, the semi-stable point at the origin will become stable as $g(x) > h(x)$ for $N_{eq} < x < 0$ and the model will have two outer semi-stable points and a stable point at the origin. However, this is not necessary as the negative $x$-axis is not useful in this model, therefore $w_{min} = 1$ is sufficient.

3. Assume *only virotherapy* is used. Can the tumor be eliminated? If so, find the minimum amount of virotherapy $v_{min}$ required to eradicate the tumor.

   In this case, $I = 0$ , so the term dissapears and the dimensionless differential equation becomes

$$\frac{dx}{dt} = x\,(1 - x) - vx^2$$

   where $g(x) = x\,(1 - x)$ and $h(x) = vx^2$.

   We require the population to always go extinct, i.e. to always cause the tumor to get destroyed $dx/dt < 0$ for $x > 0$. We need the same situation as part 2., $g(x) < h(x)$, with an different function for $h(x)$. This requires the gradient at 0 for the growth rate, $g(x)$ to be equal to the gradient of the virotherapy response term.

$$g'(x) = 1 - 2x \Longrightarrow g'(0) = 1$$

   As $h'(x) = 2vx \Longrightarrow h'(0) \neq 1$ will never exists, there is no minimum value of $v$ such that $g(x) < h(x)$ for all $x$. The stable solution appears to be at $N_{eq}$, which will depend on $v$. Therefore, $v_{min}$ does not exist and the tumor will approach a stable, non-zero, size and not alter, so long as the virotherapy is continued at the same rate.

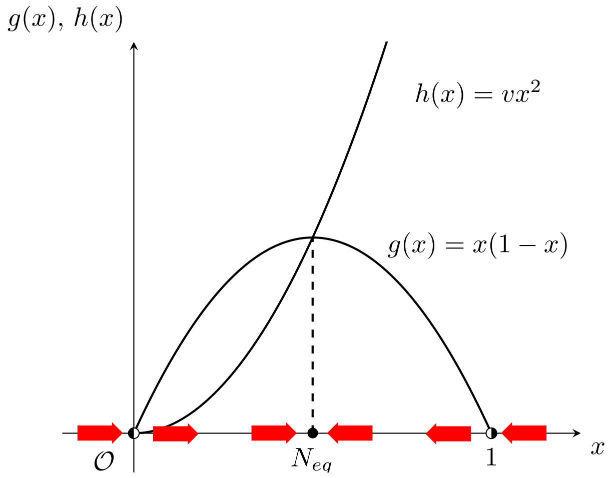


Figure 2: Equilibrium solutions for tumor growth with virotherapy