EXCELing with Mathematical Modeling
Prof. Sandip Banerjee
Department of Mathematics
Indian Institute of Technology Roorkee (IITR)
Week – 07
Lecture – 33 (Tumour Model II)

Hello, welcome to the course EXCELing with Mathematical Modelling.

Today we will be talking about a tumour model with immunotherapy.

Now what is this immunotherapy?

So it is a kind of cancer treatment and generally a component is made or our immune system that generally tackle this cancer and try to destroy the cancer cells.

So inside our body we have these T cells which is our second line of defence. So, whenever a virus or any cancer is formed inside our body, see the body sends these T cells to destroy and kill the foreign objects that gets inside our body.

So, there are many a kind of immunotherapies. First is, say, the monoclonal antibodies, then we have oncolytic virus therapy, we have cancer vaccines and T cell therapy. There are many more, I just named four of them.

In this model, we will be using this T cell therapy as our immunotherapy.

So, why we go for this immunotherapy?

Obviously, there are chemotherapy and other treatments.

So, it sometimes it boosts this immune system and without some side effects just as the chemotherapy has, it generally allows or stops the growth of this tumour cells.

So, what are these T cells? So, they are a kind group of white blood cells known as lymphocytes. And they play a central role in cell mediated immunity. The one which directly kills the cancer cells are called cytotoxic T lymphocyte or cytotoxic T cells. So they generally find these cancer cells and directly kill them.

There are another kind of immune cells. It is called T helper cells or TH cells. So, some sort of secretes some kind of protein that boosts this cytotoxic T cells or in short Tc cells and once they activate those, they find the cancer cells and kills them.

So, a little bit of biological background is needed while you form this tumour model. So, basically you have a T cell, it is classified into two parts, one is this T_c cell, one is this T_h cell. T_c cells or cytotoxic T lymphocyte, they directly kills the tumour cells or cancer cells whereas T_h cells, they secrete some kind of protein that actually boosts this cytotoxic T cells to kill more tumour cells. So the mechanism goes like this that you have this cytotoxic T lymphocyte or EC cells, they are the killer cells of the immune system.

They release some kind of protein which is called perforin and some enzymes which is called granzymes.

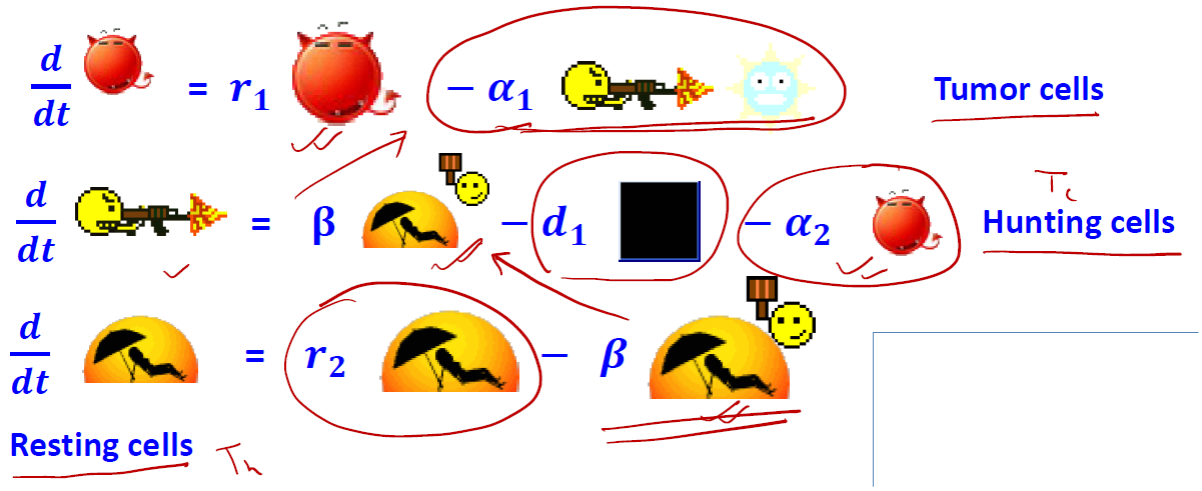
So what is the work of perforin? The perforin that creates a pore in the cell. And through that pore these granzymes they pass and activate certain enzymes that leads to apoptosis which is a programmed cell suicide program.

And how it happens?

So, what you see is unhealthy cell and some sort of chain reaction will take place and this BCL2 protein will be inhibited. So, the idea is that there will happen some sort of chain reaction which will destroy the nucleus of this cell.

So, you see that this is the nucleus and this is called cytoskeleton which will be destroyed and this nucleus is going to split up into smaller nuclei that means they will be degraded and the cell will be split up into smaller cells and they will be eaten up by the neighbouring cells which are known as phagocytic cells. So this is how the cells get destroyed.

Now let us look into our model.



So this is the tumour cell.

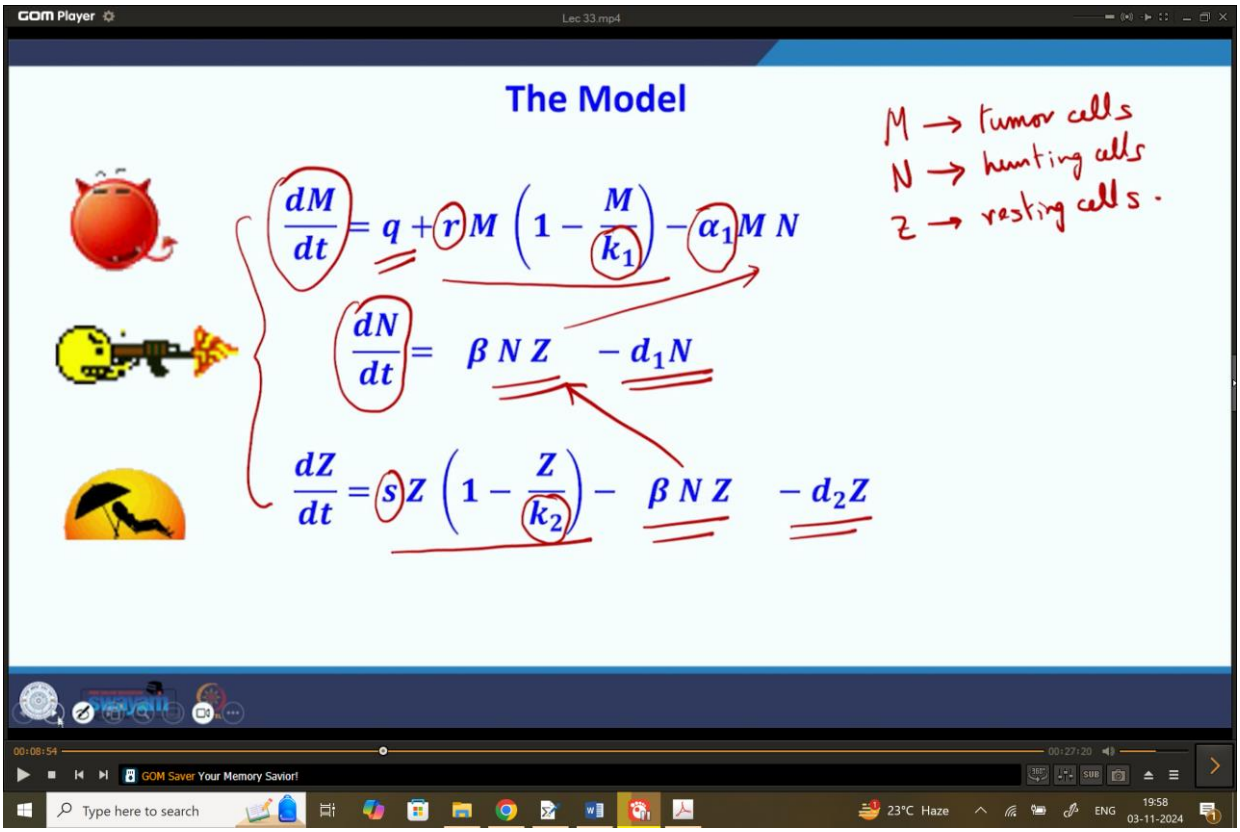
This is the T_C cell that is cytotoxic T lymphocyte which we call as the hunting cells and this is the resting cells, which is the T_h cell.

This is the growth of the tumour cell and this is where the cytotoxic T lymphocyte, that is, T_C cells they kill the tumour cells. Now, this is the T_C cells, this is the natural death of the T_C cells and this is where the tumour is harming the Tc cells.

So when there is an interaction between the tumour and the cytotoxic T lymphocytes, so either the tumour cell kills the immune cells or the immune cells kills the tumour cells. So that is why both the killing part will be here. Now this is the part which I will explain at the end. This is the growth of the resting cell. And this is the part where your resting cell is being boosted up and it is boosting the T_C cells so that its number is increased which in turn helps the tumour cells to get killed.

We now look into the model with the usual notations with a little modification.

So here, we take M to be the tumour cells, N to be the hunting cells whose job is to kill the tumours and Z to be the resting cells. So, the first equation we see that this is the rate of change of tumour that is how the tumour increases.



So, there is a constant input which is q and then it follows a logistic growth where r is the intrinsic growth rate of the tumour and k_1 is the carrying capacity and here there is a interaction between the tumour and the hunting cells and the hunting cells is killing the tumour at a rate α_1.

In the second equation this is the rate of change of the hunting cells and when they come in contact with the resting cells, so, they are converted to this hunting cells and which in turn helps in killing the tumour cells. So there is an increase and the resting cell is the source for this hunting cells. This d_1 is the rate which is at which there is a natural decay of this hunting cells.

Now the resting cells also follows a logistic growth of growth is s, which is the intrinsic growth rate and k_2 is the carrying capacity. And, here this β is the rate at which your resting cell is converted to the hunting cell and hence it has gone here and d_2 is the natural death of this resting cells.

So, this explains the model of the tumour and the immune system.

To find the equilibrium solution, we have to put

$$q + rM\left(1 - \frac{M}{k_1}\right) - \alpha_1 MN = 0,$$

$$\beta NZ - d_1 N = 0,$$

$$sZ\left(1 - \frac{Z}{k_1}\right) - \beta NZ - d_2 Z = 0.$$

So, you solve this and you get the corresponding equilibrium points. In this case, we will get 3 equilibrium points. The first one is

$$E_1 = \frac{k_1}{2}\left(1 + \sqrt{1 + \frac{4q}{rk_1}}, 0, 0\right)$$

The second equilibrium point is

$$E_2 = \frac{k_1}{2}\left(1 + \sqrt{1 + \frac{4q}{rk_1}}, 0, k_2\frac{(s - d_2)}{s}\right)$$

Now since these are the cells, they cannot be negative. So, $s - d_2 > 0 \Rightarrow s > d_2$. Hence, the existence of E_2 will imply that $s > d_2$.

And our final equilibrium point is

$$E_3 = \left(M^*, \frac{s}{\beta}\left(1 - \frac{d_1}{\beta k_2}\right) - \frac{d_2}{\beta}, \frac{d_1}{\beta}\right).$$

Again for the existence, $1 - \frac{d_1}{\beta k_2} > 0$, and this M^* can be obtained from the equation

$$\frac{r}{k_1}M^{*2} + \left[\frac{\alpha s}{\beta}\left(1 - \frac{d_1}{\beta k_2}\right) - \frac{\alpha d_2}{\beta} - r\right]M^* - q = 0.$$

So, this value of this M^* can be obtained from this equation and these two are other two values. So, once you get the equilibrium point, You can obviously solve this M^* by using the quadratic equation formula. So, next once you get the equilibrium points we go for the stability analysis.

So, Jacobian matrix say we call it

$$V_1 = \begin{pmatrix} -r\sqrt{1 + \frac{4q}{rk_1}} & -\alpha\frac{k_1}{2}\left(1 + \sqrt{1 + \frac{4q}{rk_1}}\right) & 0 \\ 0 & -d_1 & 0 \\ 0 & 0 & s - d_2 \end{pmatrix}$$

This is for the equilibrium point

$$E_1 = \frac{k_1}{2}\left(1 + \sqrt{1 + \frac{4q}{rk_1}}, 0, 0\right).$$

If you find the eigenvalue of this particular Jacobian matrix, you will get

$$\lambda_1 = -r\sqrt{1+\frac{4q}{rk_1}}$$

$$\lambda_2 = -d_1$$

$$\lambda_3 = s - d_2$$

Now, for this E_1 to be stable the first eigenvalue is less than zero, the second eigenvalue is less than zero and third will be less than zero, provided $s < d_2$. So, if $s < d_2$ then your E_1 this equilibrium point will be stable.

Let us go to the second equilibrium point

$$E_2 = \frac{k_1}{2}\left(1+\sqrt{1+\frac{4q}{rk_1}}, 0, k_2\frac{(s-d_2)}{s}\right)$$

The corresponding Jacobian matrix will be given by V_2. So when I say Jacobian matrix it means that you will take this as some f_1, this as some f_2 and this as some f_3 these expressions and then find out the Jacobian matrix as $\frac{\partial f_1}{\partial M}$ $\frac{\partial f_2}{\partial N}$ $\frac{\partial f_3}{\partial z}$ and similarly for the other two functions at the equilibrium point (M^*, N^*, Z^*). So, your

$$V_2 = \begin{pmatrix} -r\sqrt{1+\frac{4q}{rk_1}} & -\alpha\frac{k_1}{2}\left(1+\sqrt{1+\frac{4q}{rk_1}}\right) & 0 \\ 0 & \frac{\beta k_2}{s}(s-d_2)-d_1 & 0 \\ 0 & -\frac{\beta k_2}{s}(s-d_2) & -(s-d_2) \end{pmatrix}$$

If you find the eigenvalues, they will be

$$\lambda_1 = -r\sqrt{1+\frac{4q}{rk_1}}$$

$$\lambda_2 = \frac{\beta k_2}{s}(s-d_2)-d_1, \quad \lambda_3 = -(s-d_2)$$

Now, if you notice for the existence of this E_2, we have already mentioned that $s - d_2 > 0$. So, λ_1 and λ_3 are always negative, and λ_2 can be simplified as So, this eigenvalue is always negative, this eigenvalue is always negative because of this and we can simplify this as

$$\lambda_2 = \frac{\beta k_2}{s}(s-d_2)-d_1 = \frac{k_2}{s}(s-d_2)\left\{\beta - \frac{sd_1}{k_2(s-d_2)}\right\}$$

So, if this particular equilibrium point E_2 has to be stable then we must have

$$\beta < \frac{sd_1}{k_2(s-d_2)}.$$

So, if this condition is satisfied then we get your equilibrium point E_2 to be stable.

And finally, the equilibrium point

$$E_3 = \left(M^*, \frac{s}{\beta}\left(1 - \frac{d_1}{\beta k_2}\right) - \frac{d_2}{\beta}, \frac{d_1}{\beta}\right)$$

The Jacobian matrix is

$$V_3 = \begin{pmatrix} -r\sqrt{1 + \frac{4q}{rk_1}} - \alpha M^* & -\alpha M^* & 0 \\ 0 & 0 & s\left(1 - \frac{d_1}{\beta k_2}\right) - d_2 \\ 0 & -d_1 & -\frac{sd_1}{\beta k_2} \end{pmatrix}$$

This part you can easily calculate but the point is that this part is negative.

If you calculate the eigenvalues, you will see that one of the eigenvalue is coming to be minus square root of a positive quantity and hence this will be less than zero and your other two will be solved from the equation of n star. So, your

$$\lambda_{2,3} = \frac{-p \pm \sqrt{p^2 - 4m}}{2} > 0 \quad \text{where } p = \frac{sd_1}{\beta k_2}.$$

So, if you see that both your λ_2 and λ_3 have a negative real part and this is also less than zero and so your equilibrium point E_3 is also stable.

So, in this particular model you have seen that we have three equilibrium points and we have separate conditions for each of them such that those equilibrium points are stable.

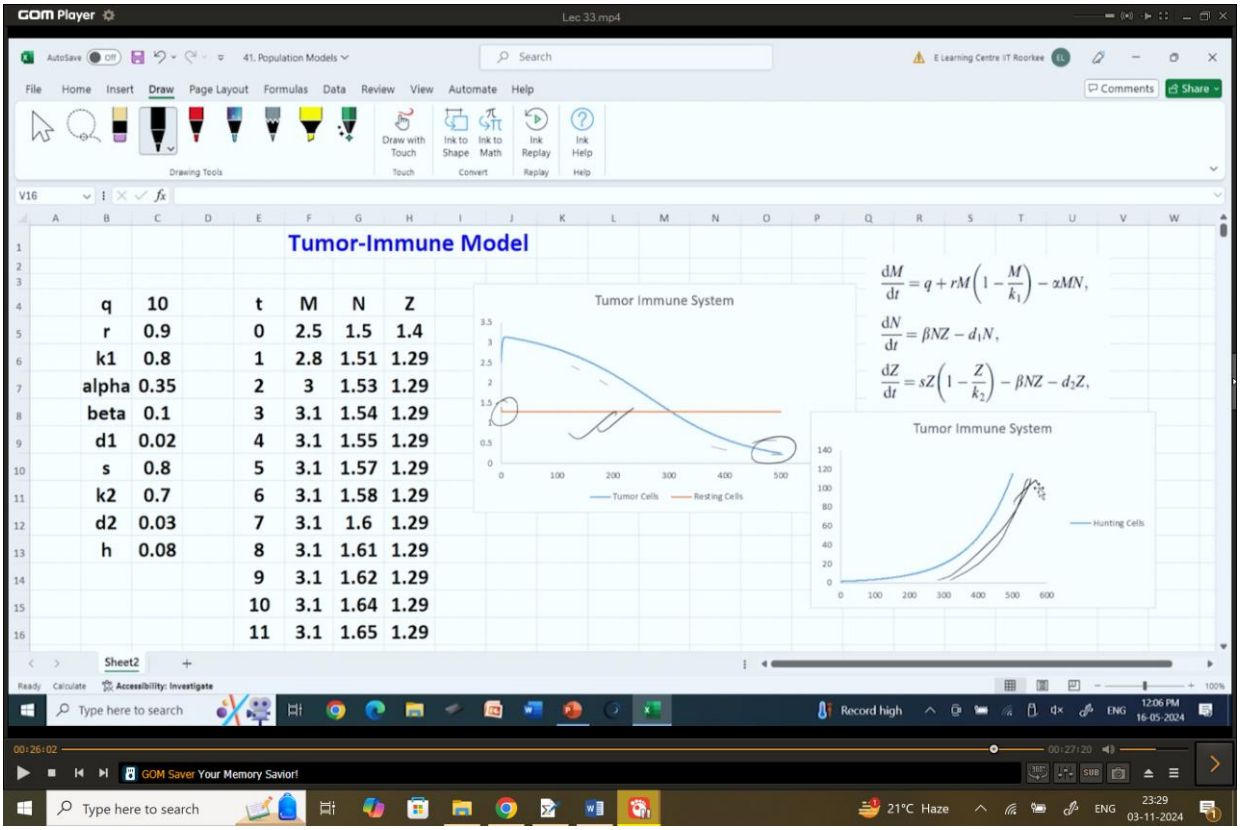
Let us now look into the numerical solution of this particular model using Microsoft Excel.

So, we already have the model here are the parameter values. I have already calculated these values of M, Z and N. So, let us just plot these values. So, first let me plot this.

So, first we will plot two of the graphs and then the third one and I will tell you why.

So, this graph along with the tumour graph and the resting cell. So if we plot this, go to insert, go to chart and this one. So the chart title is Tumour Immune System. Go to this data, chart design, select data, then series 1, edit. So this is tumour cells and this is resting cells.

And next we get the time and the hunting cells.



The reason we are doing the hunting cells separately is that you will see that the growth of the hunting cell is quite large and if we put them in the same graph, the dynamics of the other two graphs is lost.

So that is the reason why we are choosing the hunting cell separately. So go to insert tumour immune system, say I need a legend, go to data series one edit, Hunting cells.

Let me now explain this in the context of the model.

So, as you can see that here tumour cell is coming down. There is a small change here with our hunting cells sorry resting cells whereas the hunting cells are growing up.

This kind of makes sense because this is an interaction between the tumour and the immune system.

So, the immune system succeeded in bringing down the number of tumour cells to a minimum with the support of this resting cells and as the tumour is getting killed your hunting cells are also increase in numbers.

So, this model is kind of where your immune system is able to eradicate the tumour cells and that happens in very early stages of cancer or tumour.

So, summing up, we have taken a model showing the interaction between the tumour and the immune system. We have done the, find the equilibrium points, done the stability analysis and in the numerically, we have shown that with immunotherapy, the tumour cell goes down.

Now, in my next lecture, we will be talking about the vegetation model in a desert where we will be seeing the interaction between the water and the vegetation and we will see the dynamics between them.

Till then, bye-bye.