Treatment of cancer with immuno-therapy – Kuznetsovs model.

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The immune response is the body's response to defeat bacteria, viruses and other 'foreign' cells. It is not a constant response but depends on the amount of 'foreign' cells, e.g. most cancer cells. In 2001 Kuznetsov and Knott[1] proposed a model allowing the immune system to be stimulated by cancer cells. For simplicity we ignore the normal cells and consider a logistic growth of the cancer cells with an additional death term being proportional to the product of the amount of immune cells (effector T-cells) and the amount of cancer cells, $y = y(t)$. Hence the cancer equation becomes,

$$\frac{dy}{dt} = r_y y\left(1 - \frac{y}{K}\right) - d_y z y, \tag{1}$$

where $z = z(t)$ denote the amount of immune cells. Notice, if z was constant we obtain the usual differential equation for logistic growth.

Exercise 1. Give an interpretation of equation (1) and the parameters r_y, K, and d_y involved.

The equation for the immune cells is a bit more complicated. The rate of change, $\frac{dz}{dt}$, is given by the difference in a constant baseline production rate r_z and the natural death of immune cells per time, which is a fraction of the number immune cells at a given time t in the absence of cancer cells, i.e.

$$\frac{dz}{dt} = r_z - d_z z,$$

where d_z is the death rate of the immune cells, z. The present of cancer cells stimulate the production of immune cells additionally. Naively, one may take such term to be proportional to the product of the amounts of cancer cells and immune cells (i.e. equal to pyz), however, it turns out that the effect of the number of cancer cells saturates (e.g. as $p(y/(n+y))z$, where n is a constant, denoted the half-saturation constant (why?) . Thus the equation becomes,

$$\frac{dz}{dt} = r_z - d_z z + p\frac{y}{n+y} z, \tag{2}$$

. Notice, the factor $y/(n+y)$ as a function of y is approximately linear ($\approx y/n$) for small amount of cancer y (i.e. for $y \ll n$) while it tends to a constant (≈1) for large amount of cancer y (i.e. for $y \gg n$).

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[1] Kuznetsov and Knott (2001) *Modeling Tumor Regrowth and Immunotherapy* in Mathematical and Computer Modelling, 33:1275-1287

The factor p is set to zero until a given time $t = v$ and to a positive value afterwards. Kuznetsov and Knott argue that this is because it takes a short period of time (v =28 days) before the additional immune cells are produced when cancer cells are present. Hence, $p = 0$, for $t < v$, and $p > 0$, for $t \geq v$. In the description of how the immune cells grow, we have ignored the rare possibility that sometime it is the immune cell which dies when a cancer cell meets an immune cell. This was included in Kuznetsov and Knott's original work.

Four experiments on rats have been performed:

1) where 0.5 million cancer cells have been injected into otherwise healthy rats at time $t = 0$ but where their immune system has been knocked out (i.e. $z(t) = 0$, for all t),

2) where 0.5 million cancer cells have been injected into otherwise healthy rats at time $t = 0$ with a normal functioning immune system,

3) where 5 million cancer cells have been injected into otherwise healthy rats at time $t = 0$ with a normal functioning immune system, and

4) where 50 million cancer cells have been injected into otherwise healthy rats at time $t = 0$ with a normal functioning immune system. The number of cancer cells has been measured over time,

For group 1 time of measurements are [0, 20, 30, 50, 60, 70, 95] in days and the corresponding number cancerous cells in millions are [0.5, 16, 135, 405, 440, 468, 513].

For group 2 time of measurements are [0, 20, 35, 40, 50, 70, 90, 110] in days and the corresponding number cancerous cells in millions are [0.5, 6.31, 63.1, 35.48, 28.18, 2.82, 0.89, 0.89].

For group 3 time of measurements are [0, 20, 30, 70] in days and the corresponding number cancerous cells in millions are [5, 100, 177.8, 11.22].

For group 3 time of measurements are [0, 10, 20, 40, 60, 70, 90, 110] in days and the corresponding number cancerous cells in millions are [50, 251.2, 398.2, 281.84, 63.1, 50, 3.16, 1.26].

Exercise 2. Adopt the parameter values r_y = 0.188, K=526, d_y =0.14, r_z =0.177, d_z =0.59, n = 0.16; and let the time of onset v = 28 after which p=0.525. Since we expect the immune system to be dormant at a constant low level before injecting the cancer, the equation 0=$r_z - d_z z$ need to be fulfilled initially (why?) except for knocked out rats. Thus, $z(0) = 0$, for the knockout case and $z(0) = 0.3$, for the other three cases. Implement the model in a CAS tool and simulate the solutions.

- Make plots of data for all four cases and the corresponding model predictions. Can you improve the result by adjusting the parameter values? Can you suggest a measure quantifying how well the model fits data?

- What happens if at day 200 the effect of the immune system is reduced (i.e. decrease the value of d_y)?
- What if r_z or r_y are changed at time 200?
- Treatment with interferone-2α is believed to increase d_y, p, r_z or a combination of these.
- How does the solution curve $(y(t), z(t))$ look in a (y, z)-plane for $t \geq 0$? Such curve is denoted a trajectory and the figure is called a phase plane. A solution where both $y(t)$ and $z(t)$ are constant in time is called a steady state. Such solution becomes a point in the phase space (why?)
- Try to find steady states for the system of differential equations (1) and (2).
- What happens with the trajectories if you start at different initial conditions $(y(0), z(0))$ in the neighborhood of the steady state?

Want to know more?

Mathematics at RUC: ruc.dk/en/bachelor/mathematics-int

The Cancitis Research-group: dirac.ruc.dk/cancitis