Treatment of leukemia with interferon therapy – competitive cell populations.

By Johnny T. Ottesen & Morten Andersen, Roskilde University.

A two species logistic grow model is presented in the book *Dynamics of Cancer* from 2004 by Wodarz and Komarova. The equations describe cell competition between cell type x and y,

$$x'(t) = r_x x(t)\left(1 - \frac{x(t) + \alpha_{yx} y(t)}{K_x}\right)$$

$$y'(t) = r_y y(t)\left(1 - \frac{y(t) + \alpha_{xy} x(t)}{K_y}\right)$$

For $\alpha_{yx} = \alpha_{xy} = 0$ the equations describes two independent logistic growths, one for species x ($x(t)$ denote the amount of cells) and one for species y (again does $y(t)$ denote the amount of cells). Whenever $\alpha_{yx} \neq 0 \neq \alpha_{xy}$ the spices take space from each other due to limited food/nutrition resources, pollution of the environment, etc.

Exercise 1. Give interpretations of all the involved parameters. What does it mean if 0<α_{yx} <1, α_{yx}=1, or α_{yx}>1 (0<α_{xy}<1, α_{xy}=1, or α_{xy}>1), respectively. Put K_x=K_y=12, r_x=1.3, and r_y=1.9 and plot the solutions versus time for, α_{yx}=1.3 and α_{xy}=1.5, for α_{yx}=0.7 and α_{xy}=1.5, for α_{yx}=1.3 and α_{xy}=0.8, and for α_{yx}=0.7 and α_{xy}=0.8. Do this for various initial conditions ($x(0)$, $y(0)$). Comment on what you see.

A constant solution (i.e. where both curves are constant in time) is denoted a steady state.

Exercise 2. Did exercise 1 suggest the existence of steady states? By putting $x'(t)$=0 and $y'(t)$=0 the above differential equations reduce to two algebraic equations, which can be solved, giving analytical expressions for the steady states. Do that for $\alpha_{yx} \cdot \alpha_{xy} \neq 1$ and show that there are three or four biologically relevant steady states (meaning that the coordinates do not become negative) depending on the values of α_{yx} and α_{xy}.

Instead of plotting the solutions versus time one may prefer to illustrate the solutions in a phase plane, where x is on the first axis and y on the second axis. The solutions normally denoted trajectories becomes curves ($x(t)$, $y(t)$) in such a phase plane. If the slope field is added and representative solutions having different initial conditions are plotted the phase plane is called a phase portrait. In the phase portrait steady states are points (why?). Hence, a phase plane of the general system of two coupled differential equations is a plot of selected solutions ($x(t)$, $y(t)$), for $t \geq 0$, to the differential equations for different initial conditions ($x(0)$, $y(0)$). The curves of selected solutions plotted in the phase portrait should give an expression of how solutions in general may look.

Exercise 3. Make phase portraits corresponding to each of the cases in exercise 1. Add the steady states to the phase portraitsWhat happens to trajectories in the vicinity of a steady state?

Treatments like radiation or chemo kills a certain fraction of cells per time but the cancerous cells are more affected by the treatment than the normal cells. Thus during treatment the right hand sides of the equations are modified accordingly,

$$x'(t) = r_x x(t)\left(1 - \frac{x(t) + \alpha_{yx} y(t)}{K}\right) - d_x x(t)$$

$$y'(t) = r_y y(t)\left(1 - \frac{y(t) + \alpha_{xy} x(t)}{K}\right) - d_y y(t)$$

Some drugs, e.g. interferone-2α, stimulate the natural immune system of the body to fight the cancer. For simplicity we may assume that normal cells do not die during the treatment, i.e. we put d_x=0 considering the y-cells as the cancerous cells.

The model stated above holds for a constant immune response killing cancerous cells, however the constant value increase with dose of the treatment.

Exercise 4. Can you tell (e.g. by help of simulations) if there is a threshold, which the dose needs to exceed to cure the patient simulated? (You may use parameter values from exercise 1).

Exercise 5. Below you find data for the fraction of cells in the blood which are malignant (cancerous cells) versus time measured in days. This fraction is of a specific mutation called JAK2 (or more precise JAK2*V617F*). The fraction is given as percentage. First the patient is observed without having treatment and thereafter the patient observed during treatment. Time is in days and may be converted into years. Try to put up a model and fit the data.

- Start by the untreated situation and then go to the treated situation. How will you determine the onset off treatment registered to be at Time=0?
- Which parameters should most likely be affected by treatment?
- After having merged the two scenarios could you predict a good treatment plan shifting between treatments and pauses?
- Describe criteria for a ‘good’ and realistic treatment plan. Can you quantify how well data are fitted by the model? Can you imagine why an (extremely) high treatment dose may be problematic?

Without treatment	
Time	JAK2
Days	%
0	0.7
196	4
224	0,9
294	1
426	2
552	6
993	3
1076	8
1133	8
1224	9
1259	7
1322	10
1420	12
1659	22
1784	19
1820	30
1890	31
1913	12
1941	32
1960	31
2094	22
2114	30
2136	31

With treatment		
Time	Time	JAK2
Years after	Days	%
0	2372.5	49
0.3258	2491.417	46
0.6516	2610.334	32
0.9911	2734.252	21
1.4949	2918.139	4
2.0315	3113.998	1
3.1431	3519.732	0.06
4.2738	3932.437	0.02
5.2704	4296.196	0.02

Want to know more?

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

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