Radiation treatment of cancer – Bertalanffys model

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The problem is inspired by Allan Baktoft Jakobsen: Supplement A om Strålebehandling i bogen Matematik i virkeligheden.

In 1960 von Bertalanffy[1] proposed a simple model for cancer growth. He assumed that only the cells on the surface of a globular cancer tumor, had access to enough nutrition to be able to divide. If the cancers volume is W, then the growth of new cancer cells volume per time is proportional to $W^{2/3}$, i.e. equal to $aW^{2/3}$, where a is a constant. Bertalanffy furthermore assumed that all cancer cells could die, i.e. that a certain fraction b of the cancer cells die per time. Thereby new cells are constantly born into the system, while cells are constantly dying. Thus the total growth of the cells volume over time is,

$$W'(t) \equiv \frac{dW(t)}{dt} = aW(t)^{2/3} - bW(t)$$

- Explain why the rate a has the unit 10^{-2} millimeters per day and b has the unit per day, if time units is in days and volume units is in 10^{-6} cubic millimeters.
- Explain the power 2/3 in Bertalanffy's model by calculating the surface area of a ball as a function of the balls volume. This type of argument is called 'Allometry' and was exactly the type of argument that Bertalanffy used when he constructed the model in 1960.
- If all cells are of equal size (lets say a cell has volume V), then n cells will have the size $W=nV$. Show that the differential equation for the amount of cancer cells n can be written as

$$n'(t) \equiv \frac{dn(t)}{dt} = \tilde{a}n(t)^{2/3} - \tilde{b}n(t),$$

  and show how $\tilde{a}$ and $\tilde{b}$ can be described in terms of the already introduced parameters and state their units.

The differential equation thereby describes how the growth in either volume or the amount of cancer cells depends on the amount of cancer cells (measured in either amount or volume) at any given time. Often it is written a bit sloppily with W for $W(t)$ and n for $n(t)$, and it is left for the reader to realize which terms are functions of the time t.

- Read the data from the figure below of Jurkat T-cell leukemia[2] and try to determine the parameter values of $\tilde{a}$ and $\tilde{b}$ so that Bertalanffy's model fits the data well. Can you quantify (establish a value for) what is meant by 'how well'?

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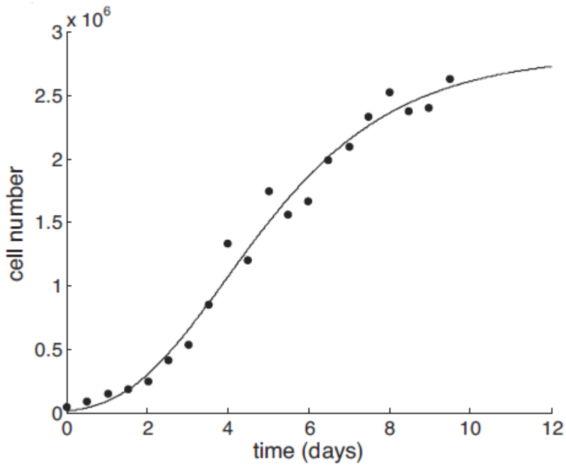
[1] L. von Bertalanffy (1960) *Principles and theory of growth In: W.W. Nowinski (Ed.), Fundamental Aspects of Normal and Malignant Growth*, Elsevier, Amsterdam, pp. 137-259

[2] Reuss et al (2004) *Intracellular delivery of carbohydrates into mammalian cells through swelling-activated pathways* Journal of Membrane Biology 200(2): 67-81



An effective treatment for some types of cancer is seen to be either by neutrons or x-rays. X-ray data from Barendsen and Broerse[3] is seen below,

Effects of 15 MeV *Neutrons and* 300 kV *X-Rays on a Rat Rhabdomyosarcoma*

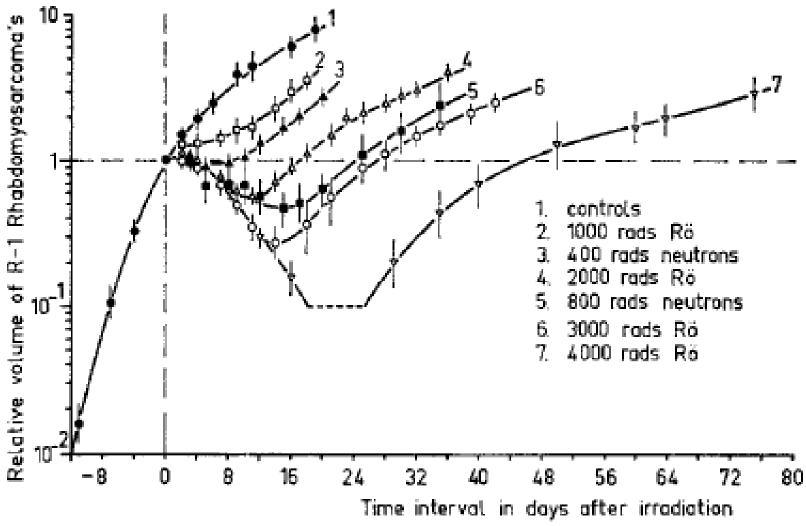


Fig. 3. Volume changes of R-1 *rhabdomyosarcomas as a function of the time interval after irradiation. The points indicate mean values of the ratios of the volume measured at a given time and the volume at the time of irradiation.*
Curve 1 *represents the growth of unirradiated tumours.*
Curves 2, 4, 6 *and* 7 *were obtained after irradiation with* 1000, 2000, 3000 and 4000 rad of 300 *kV X-rays respectively.*
Curves 3 *and* 5 *were obtained after irradiation with* 400 *and* 800 *rad of* 15 *MeV neutrons respectively.*

[3] Barendsen and Broerse (1969) *Experimental Radiotherapy of a Rat Rhabdomyosarcoma with 15 MeV neutroner and 300 kV røntgenstråler.* Europ. J. Cancer, 5:373-391

Data for the treatments effect, as well as for untreated are read from the figure to be:

Series 1.
t1 = [-11.01465233, -6.999089648, -4.011617826, 0.017058263, 1.976200798, 3.937966014, 5.899254378, 8.898409051, 10.97795648, 15.944837, 19.06296601];
V1 = [0.016237794, 0.108156895, 0.338477296, 1.030038134, 1.536251455, 1.958982818, 2.570218114, 4.002717997, 4.490327813, 6.245877509, 7.969033029];

Series 2.
t2 = [-11.01465233, -6.999089648, -4.011617826, 0.017058263, 2.094459858, 4.060039882, 6.949757239, 9.028827813, 10.99393099, 13.99570834, 15.95699671, 18.03559043];
V2 = [0.016237794, 0.108156895, 0.338477296, 1.030038134, 1.313548181, 1.333662867, 1.434112608, 1.655302385, 1.729212739, 2.30246351, 3.020870509, 3.587543948];

Series 3.
t3 = [-11.01465233, -6.999089648, -4.011617826, 0.017058263, 2.907967748, 5.107204786, 7.996922143, 10.1925828, 12.03895006, 14.92604474, 17.00440003, 20.12157534];
V3 = [0.016237794, 0.108156895, 0.338477296, 1.030038134, 1.031484993, 0.908357, 0.97677326, 1.065050416, 1.33883971, 1.683861873, 2.028416342, 2.739752499];

Series 4.
t4 = [-11.01465233, -6.999089648, -4.011617826, 0.017058263, 4.065285244, 6.960009537, 9.045279175, 11.01252818,14.01549766, 16.09266083, 18.0549029, 21.05668025, 23.01796861, 25.21362927, 28.10239293, 30.1814635, 31.91457864, 35.84168545];
V4 = [0.016237794, 0.108156895, 0.338477296, 1.030038134, 0.974910373, 0.777331083, 0.619550464, 0.569348422, 0.705984014, 0.913215109, 1.131801785, 1.507005039, 1.977215733, 2.155909182, 2.45419871, 2.832721054, 3.088038294, 4.05542679];

Series 5.
t5 = [-11.01465233, -6.999089648, -4.011617826, 0.017058263, 3.023604127, 5.227609676, 8.11804231, 10.08433761, 12.05301717, 15.06242414, 17.14268684, 20.03001994, 25.10919889, 30.07512572, 34.80977978];
V5 = [0.016237794, 0.108156895, 0.338477296, 1.030038134, 1.03154291, 0.683235805, 0.703965315, 0.684848901, 0.577807398, 0.487742828, 0.524272883, 0.650054482, 1.103790854, 1.625340187, 2.39305669];

Series 6.
t6 = [-11.01465233, -6.999089648, -4.011617826, 0.017058263, 2.098751517, 4.066477371, 6.961916941, 8.119949714, 9.048855557, 11.1360326, 14.03099532, 17.95786371, 21.07289319, 25.11253685, 27.99963152, 32.04237472, 34.93018467, 38.97435842, 42.09391798];
V6 = [0.016237794, 0.108156895, 0.338477296, 1.030038134, 1.016498416, 0.907898101, 0.693620468, 0.628155443, 0.500373078, 0.355861048, 0.279728219, 0.372628171, 0.572136384, 0.904252164, 1.137280088, 1.493639218, 1.799977335, 2.170362161, 2.542326198];

Series 7.
t7 = [-11.01465233, -6.999089648, -4.011617826, 0.017058263, 2.445183804, 7.770894746, 12.06326946, 16.00587394, 29.06873158, 34.95331195, 39.80241027, 49.7368866, 59.79272152, 63.60609936, 74.93202705];
V7 = [0.016237794, 0.108156895, 0.338477296, 1.030038134, 1.046046265, 0.71394314, 0.313188552, 0.162967566, 0.208934618, 0.452138942, 0.714879091, 1.325277654, 1.745633785, 2.045495407, 3.021322845];

- Describe with words the effect of x-rays and the neutron radiation, respectively, for varying doses using the graphs.

It turns out, that Bertalanffy's model only poorly can describe these data, if the treatment is built into the model. Therefore, we expand Bertalanffy's model by imagining that the cancer cells probably follow Bertalanffy's model equation in absence of radiation treatment, but by radiation treatment additional things happen. The expansion consists of an extra portion of cells beginning a death process by radiation, i.e. that an extra state of elimination should be included in the equation, which describes that an additional fraction (*d=d(t)*) of the cancer cells enter into a dying state by radiation. This fraction depends on the intensity of the radiation (dose) and is zero in absence of radiation. Thus Bertalanffy's equation is temporary changed to,

$$W' = aW^{2/3} - bW - dW$$

Notice that we consider *d* to be a constant for a given radiation intensity. Apart from the amount of cancer cells we must keep track of the amount of cancer cells in the dying state,

$$U' = dW - cU,$$

Where *U=U(t)* denotes the amount of dying cancer cells.

- Explain why this differential equation is formulated the way it is and give an interpretation of the parameter *c*.

We aren't completely done yet, as the radiated cancer cells excrete cytotoxic cytokines at their non-natural death process, i.e. *U* affects the nearest cancer cells by killing some of these. We assume that the amount of cancer cells additionally dying due to this cytotoxic effect is proportional to the product of the amount of cancer cells *W* and the amount of dying cancer cells *U*. Let us denote this proportionality constant by *h*. The full model thereby becomes,

$$\begin{aligned} W' &= aW^{2/3} - bW - dW - hWU \\ U' &= dW - cU \end{aligned}$$

The observed amount of cancer cells is *V=W+U*. The scenario without radiation can be described by the model with *c=d=h=0*.

- Construct a differential equation which describes the number of dead cells and explain why the two other differential equations can be solved numerically without regarding the third differential equation.
- Implement firstly the model in your preferred CAS tool without radiation (*U=0*) and determine the two parameters such that data for untreated patients are fitted as well as possible (Hint: *a* has to be between 0 and 1 and *b* may be between 0 and 0.1 per day)
- Implement the entire model with radiation for each radiation intensity. Maintain the parameter values of *a* and *b,* as these aren't thought to vary between the different scenarios (why?)

- Present you results in a graphical form, give an evaluation of the model and interpret the found parameter values.
- Try to find extra data which the model can reproduce. Consider how large an intensity of radiation is needed to eradicate the cancer completely?
- Can you quantify how well the model fits the data?

Want to know more?

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

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