BIO445: Quantitative Life Sciences: from Infectious Diseases to Ecosystems
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MODELLING CANCER
Exercise sheet

In this module we will learn about the usefulness of computational approaches to the understanding of tumor growth, evolution and the responses to clinical interventions. We will use both ordinary differential equations and an agent based model.

1 Using real clinical data to estimate brain tumor growth rate

We begin with using real clinical data to estimate brain tumor growth rate. The dataset (Nakamura et al 2003) contains 41 asymptomatic patients with meningioma that were examined in two time points and were not treated, hence a natural history and tumor growth rate could be investigated. Tumor volume is given in cm^3, follow-up time is given in months.

a. Load the data into R and explore it, `Nakamura_db_BT_start.csv`.

b. For each patient: calculate the absolute growth, absolute growth rate per year and the relative growth rate percent (per year). The latter can be obtained using:

$$(sqrt[t]{\frac{V_{latest}}{V_{initial}}} - 1) \cdot 100$$

c. Make a plot of the age of the patient versus absolute growth rate. Is there an apparent correlation?

d. Construct a linear regression using lm(), with age and absolute growth rate and plot the regression fit.

e. Calculate the tumor doubling time (in years) using:

$$(t_2 - t_1) \cdot (\frac{log(2)}{log(\frac{V_{latest}}{V_{initial}})})$$

1. Do tumors that were larger at the first screen also tend to have higher doubling time? How can you test this hypothesis?
2. Do calcified tumors have a higher doubling time? How can you test this hypothesis? Think of visualization as well.

2 Agent-based tumor development simulation

We proceed with a quick overview of an agent based simulation that demonstrates the development of a single healthy cell into a cancerous tumor. Install Netlogo version 5.3.1 from https://ccl.northwestern.edu/netlogo/5.3.1/. Download from OLAT and open the attached model file `"nlogo.cancer.nlogo"`, and click the “Setup” button, then click “Go”:

Model description:

- The model starts with one healthy (wild-type, WT) cell that has a given apoptosis, mutation, and division rate, as well as a neutral genotype (a string of 22 zeros, see Code):

- A cell divides and dies according to its rate (except that we do not allow any cells to die while under the carrying capacity, called “initial-max-population-size”).

- When a cell divides, it can get a new mutation.

- When a WT cell gets a new mutation, it can get a new mutation in any one of the 22 neutral locations or in the tumor suppressor gene p53.

- In cells that carry the mutated p53 gene, mutations have a higher probability to occur in general (P-53-mutation-rate-multiplier parameter), and they fall with an equal probability, in neutral sites or in genes controlling the division or the death (apoptosis) rates.

- The model stops when the total number of cells exceeds an arbitrarily set threshold (13,000), which typically corresponds to exponential growth and thus cancer as we define it in the model. In this simple model spatial placing of the cells is random but in general one of the benefits of agent based models is that space can be given a biological meaning.

a. Run the model with the default parameters and observe the behavior.
    - Inspect one cell (“turtle”) using right mouse click.
    - Explore what is happening in each plot and what are the meanings of the values represented in the parameter boxes.

b. Start the module with the switch “allow-p53-mutation” on: `"off"`, let the model run and then turn it on, turn it off again after a while. What do you observe?

c. Set the following parameters and run the model five times on the maximum speed: initial-division-rate: 0.018, initial-apoptosis-rate: 0.01, mutation-rate: 0.01, initial-max-population-size: 0
What do you observe in some of the runs? If you don’t get any output, what do you think has happened? This is a typical behavior of stochastic models which is absent in deterministic ODE models.

d. Set the default parameters again (or just re-load the file). Increase and decrease the mutation rate and observe the model behavior. Assume that the `"Ticks"` counter represents time in days, what is the relationship between the mutation rate and time to cancer?

e. What is the relationship between P-53-mutation-rate-multiplier and Median-number-of-neutral-mutations when cancer occurs? What is your interpretation?

f. ∗Go to the `Code` section and increase the number of zeros in the initial-neutral-genotype variable, hence increasing the pool of neutral (not cancer promoting) mutations. Run few simulations with a different added or subtracted number of neutral mutations. Notice the different times to cancer and make an R plot of the above-mentioned relationship. What is the conclusion?

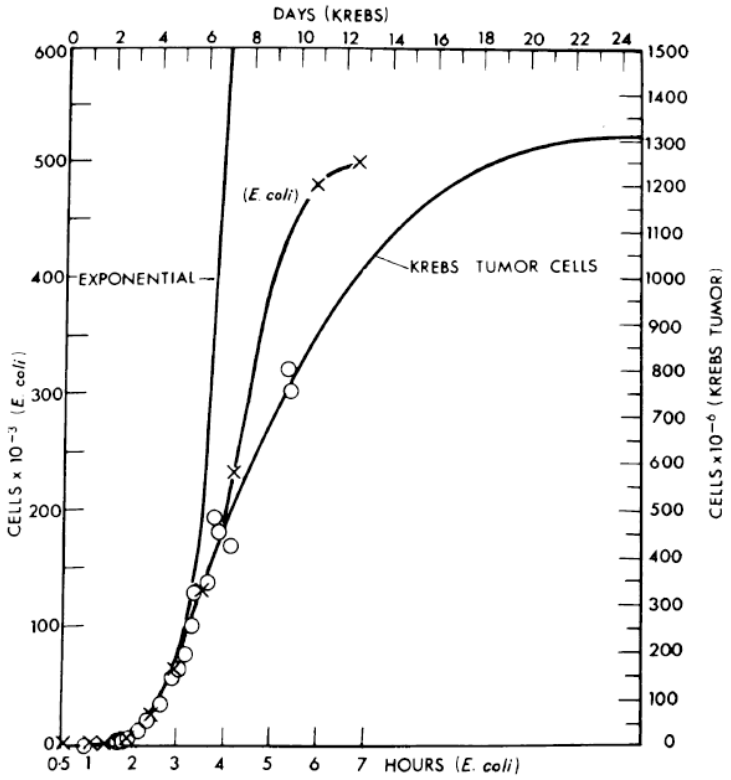
g. What are the benefits of agent based simulations in your view? How many compartments an ODE model with the same number of neutral mutations would have to have? Which tool (ODE vs. agent-based stochastic models) is more realistic?

3 Modeling the size of the tumor over time with ODEs

a. Let's assume that we are interested in the number of cancer cells in a tumor (N) over time. We begin with 1000 non-cancerous cells that proliferate with a rate α and die due to apoptosis with a rate β. Hence, we obtain the following ordinary differential equation (ODE):

$$\frac{dN}{dt} = \alpha \cdot N - \beta \cdot N$$

Without solving in R, what happens in the following three scenarios: $\alpha > \beta$, $\alpha < \beta$, $\alpha = \beta$? Quickly draw the solutions by hand.
We assumed that the tumor growth rate is constant over time (α) which leads (when $\alpha > \beta$) to exponential growth, ignoring carrying capacity. However, it was shown that solid tumors initially grow fast but the growth rate decelerates as tumors grow bigger. The so-called Gompertz growth was shown to reproduce biological growth that decelerate with population size:



A classical paper by Laird (1964), showing that tumors grow more slowly as the tumors get larger (the right-hand-side solid line demonstrates Gompertz fit).

$$\frac{dN}{dt} = r \cdot N(t) \cdot log(\frac{K}{N(t)})$$

b. Use the starting script "`Start_Cancer.R`" and plot the Gompertz growth. What happens to the growth rate when N(t) approaches K (carrying capacity)?

c. Now let's examine the effect of therapy (chemotherapy or immunotherapy) by adding a right hand side negative term (because now we deal with a growing tumor we can omit apoptosis):

$$\frac{dN}{dt} = r \cdot N(t) \cdot log(\frac{K}{N(t)}) - \alpha \cdot c(t) \cdot N(t)$$

α: a positive constant representing drug strength (0 to 1)
c(t): drug concentration at the tumor site at time (t), first we can assume that it is constant for all t.

1. Assume that treatment starts 3 years after the beginning of the simulation (the tumor has already reached carrying capacity). Plot the tumor dynamics. Use pars= c(r=0.015, K=40, alpha=0.7, c=0.3), yini= c(N=0.001), times =seq(0, 2000, by = 1). After how many days following treatment initiation will the tumor shrink by half?

2. When the tumor will be eliminated? (defined as N < 0.001 cm^3).
   It is more realistic to assume that drugs are cleared by the body and lose their activity with time, assume that the drug concentration is reduced with a rate of 0.25 per day. Modify the ODE accordingly.

3. With this 0.25 drug clearance rate, how many days after treatment initiation will the tumor shrink by half? Plot the dynamics. Was the therapy successful?

4. For the same clearance rate, will increasing the drug strength α lead to a different outcome?

4 Adding resistance to therapy

Now let's assume that 1% of the treated cells develop resistance to treatment. Modify the system accordingly (assume that c(t) is constant again).

a. What's the volume of the resistant cells one month after the first treatment?

b. Plot the dynamics of both cells types. When will the resistant cells predominate?

c. ∗Now assume that resistant cells can revert back and become susceptible again, with a certain rate "q", modify the system accordingly and explore.

Recommended
If time permits, explore different Netlogo models that came with the installation: After launching Netlogo you can find them at the top bar in `File :: Models Library`.

References

Laird, A. K. 1964. "Dynamics of Tumor Growth." *British Journal of Cancer* 18 (3): 490–502. https://doi.org/10.1038/bjc.1964.55.

Nakamura, M., F. Roser, J. Michel, C. Jacobs, M. Samii, N. De Tribolet, B. George, H. Brem, K. Weaver, and A. H. Kaye. 2003. "The Natural History of Incidental Meningiomas." *Neurosurgery* 53 (1): 62–71. https://doi.org/10.1227/01.NEU.0000068730.76856.58.