Quantitative Life Sciences: from Infectious Diseases to Ecosystems
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Virus Dynamics
Exercise sheet

Objectives

By the end of this module, you should be able to:

1. understand and numerically solve ordinary differential equations for biological populations.
2. fit models to data
3. have a quantitative understanding of viral dynamics and insight into HIV replication
4. at a meta-level, "add layers of complexity" and move between simple/phenomenological models and more complex/mechanistic models.

Problem 1: The basic model of virus dynamcis

The simplest model of virus dynamics describes the dynamics of target cells T and infected cells I according to the following differential equation, corresponding to the following flow-diagram.

$$dT/dt = \Lambda - \delta_T T - \tilde{\beta} T I \quad (1)$$

$$dI/dt = \tilde{\beta} T I - \delta_I I \quad (2)$$

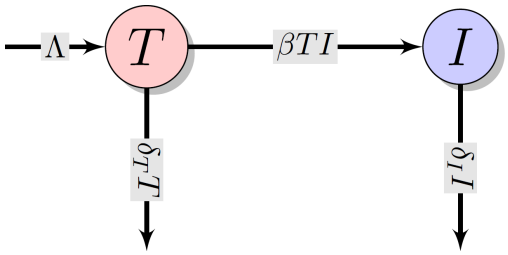

Figure 1: A flow chart of the basic model of virus dynamics with Target-Cells and Infected Cells.

a. Identify the terms in the differential equation with the arrows in the flow diagram and discuss their biological interpretation.

b. The numerical solution of these equations is implemented in the R-script $Problem1\_2\_start.R$. Analyze what the script is doing. Numerically solve these equations and describe the dynamical behavior of the system. Which aspects of viral dynamics are captured by the model which not? Explore the impact of model parameters on the dynamical behavior of the system.

c. Compute a numerical solution of the differential equation "by hand" as indicated in the R-script $Problem1\_3\_start.R$. Check the impact of the step length dt.

d. The above model assumes that new infected cells are produced at a rate βTI. This makes sense as the number of newly produced cells is expected to increase with both the number of target cells and the number of infected cells, but the model does not specify the mechanism by which this happens. This gap is (partly) filled by the more detailed TIV model:

$$dT/dt = \Lambda - \delta_T T - \beta TV \quad (3)$$
$$dI/dt = \beta TV - \delta_I I \quad (4)$$
$$dV/dt = pI - \delta_V V \quad (5)$$

1. Draw the flow-diagram for this model and interpret the difference between the two models.
2. Compare the dynamics of the two models for $\tilde{\beta} = \beta \frac{p}{\delta_V}$ and discuss the relative merits of using the more complex model or the simpler model.

e. The above models describe the dynamics of an HIV-1 infections in the absence of treatment. Assume that at day 100, antiretroviral treatment is started which reduces the infectivity of virus to 0. Simulate the dynamics of such a patient based on the T-I model.

Problem 2: Estimating the time-scales of HIV-dynamics

So far we have considered the dynamics of the above models using (more or less) invented parameters. In the next step, we want to use the model to estimate viral turnover rates (i.e. the half-life of infected cells and free viruses). This has been one of the earliest and most important applications of such models of virus dynamics. The biological question is whether the virus has a slow or a fast turnover – in the first case infected cells survive a long time and produce offspring (i.e. newly infected cells) at a low rate; in the second case they die quickly and produce offspring at a high rate.

a. Discuss with your partner the biological plausibility of the two scenarios and whether what we know from untreated chronic phase infections allows to distinguish between the two scenarios?
b. We will determine the turnover rate by fitting the decay of virus load in treated patients with the models discussed in exercise 1. As a simplification we assume that treatment is completely effective in reducing the infection-rate $\tilde{\beta}$ to 0 (i.e. it completely prevents infections of new cells). Write the equations of the basic T-I models under this assumption. Can you solve these equations?
c. Fit this solution to the data in virusLoadOnTreatment.csv under the assumption that virus load is proportional to the number of infected cells (this data is extracted from Perelson (2002) which in turn reproduced the data from Perelson et al. (1996)) and estimate the rate with which infected cells die. Should this fit be done on the orignial virus-load data or on the log-transformed data? (Tip: adapt the function *getSSQ()* and the subsequent procedures from the R introduction.)

1. Can you calculate from this the half-life of infected cells?
2. Could you obtain the same result by simply using lm()?

d. So far we have quantified the turnover of infected cells. Next we will determine the turnover of both free virus and infected cells by fitting the more detailed model 3-5 to the virus-load decay data on therapy. In order to do this, repeat steps (b) and (c) for model 3-5.

1. Could you obtain the same result by simply using lm()?

e. ∗ Read Box1 in (Perelson 2002) and discuss the difference between the model (4-7) discussed there and the model from (2d) and fit the model to virus load data. How do the conclusions between (2e) and (2d) differ?
f. ∗ So far we only obtained point estimates for the parameters; i.e. the parameters that can best explain the observed data. Discuss with your partner how you could obtain a measure for the uncertainty of these estimates and if possible implement this.
g. ∗ So far we have focused on data form one single patient from Perelson et al. (1996). Estimate viral dynamics from other patients included in this paper (use for this the data-extractraction approach sketched in Problem 3) and interpret the observed variability of the parameter estimates.

Problem 3: Estimating the long-term decay of HIV: The possibility of a cure?

The simple decay dynamics considered in exercise 2 holds only for the first days after therapy-initiation. We will next consider the longer-term dynamics and the possible implications for the cure of HIV.

a. Consider the long-term decay plot from Box1 in Perelson (2002) (right plot at the bottom of the box) and characterize the decay qualitatively.
b. Extract the data from this figure for example by using https://automeris.io/WebPlotDigitizer/index.html (you can use the online version of the app and do not have to install anything – just choose "Launch App" on the webpage). Tip: You can for example make a screenshot of the figure and then upload it as the image to be used by the app. If you know of any other method to extract quantitative data from a figure let us know.
c. We can capture the two-phase decay of the virus load (VL) shown in this figure if we extend the model 1-2 in the following way: We assume that upon infection, target cells can turn into two types of infected cells: with probability c a target cells turns upon infection into an infected cell with a high clearance rate ($\delta_{I,H}$) and high infectivity (β_H) and with a probability $1-c$ it turns into a infected cell with a slow clearance rate ($\delta_{I,L}$) and a low infectivity (β_L). Extend the Basic Model of Virus dynamics 1-2 in order to capture the distinction between high- and low-turnover infected cells (give the model equations of this extended model in the absence of treatment).
d. Fit this extended model to the extracted decay data and estimate the clearance rate $\delta_{I,L}$ and $\delta_{I,H}$ for the two types of cells. What is the half-live of the latently infected cells?
e. Extrapolate the behaviour of the fitted model under therapy. How long would it take according to this model until the virus is completely cured? Discuss whether this is in line with what we know about HIV biology.
f. Discuss with your partner alternative, qualitatively different models that could also fit this dynamics.

References

Perelson, A. S. 2002. "Modelling Viral and Immune System Dynamics." *Nature Reviews Immunology* 2 (1): 28–36. https://doi.org/10.1038/nri700.

Perelson, A. S., A. U. Neumann, M. Markowitz, J. M. Leonard, and D. D. Ho. 1996. "HIV-1 Dynamics in Vivo: Virion Clearance Rate, Infected Cell Life-Span, and Viral Generation Time." *Science* 271 (5255): 1582–6. https://doi.org/10.1126/science.271.5255.1582.