Within-host HIV dynamics: the emergence of drug resistance

Level 1 module in "Modelling course in population and evolutionary biology"

(701-1418-00)

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1 Introduction

Modern medicine is not as defenseless against the deadly virus of AIDS as it used to be at the beginning of the epidemic. Combination antiretroviral therapy (cART), composed of several drugs that target key enzymes of the virus, can suppress virus replication to undetectable levels and keep treated patients free of disease. Unfortunately, hidden reservoirs of the virus persist in spite of long-term treatment and can "re-ignite" infection when treatment is stopped. In this sense, HIV infection is still incurable and may well require lifelong treatment. The greatest problem of long-term therapy is the emergence of drug resistance. Mutations in the targeted viral enzymes (or viral structures, in general) can abolish the effect of drugs. For many drugs, a single mutation suffices for complete resistance; for others, resistance requires the presence of several mutations. Given the enormous initial population size of HIV in chronic infection and its high mutation rate, monotherapy (i.e. treatment with a single drug) invariably results in the appearance of resistant virus and the loss of drug effect in a few weeks. Combination therapy can suppress HIV for many years or even decades in most patients. However, over the years of treatment an increasing fraction of patients develop drug resistance, which results in rising virus levels and can eventually lead to disease and death. Understanding the emergence of drug resistance is therefore vital for the management of HIV infection.

2 Developing the model

2.1 The basic model of drug treatment

Let us first implement the effect of treatment in the absence of drug resistance. We will use a simple variant of the basic model of HIV infection:

$$dT/dt = \lambda - \delta T - (1-\epsilon)bIT \quad (1)$$
$$dI/dt = (1-\epsilon)bIT - aI \ . \quad (2)$$

In this model, T is the level of infectable target cells that arise at a rate λ and have an intrinsic (per capita) death rate δ. I denotes the level of infected cells that die at a per capita rate a and are produced by the infection of target cells at a rate proportional to the current level of both target cells and infected cells[a]; the parameter b describes infectivity per cell. Drugs decrease the rate of new infections: the parameter ϵ characterises the degree of reduction in the infection term, i.e. the efficacy of the treatment[b]. Figure 1 shows the scheme of the model.

This model has been implemented in the R script `hivstart.R` that can be downloaded from the website of the course. Download and run the script. Experiment with setting different values for the efficacy of the treatment. Can you find the critical value, above which treatment results in the eradication of the virus in the long run[c]? Will the virus ever be eradicated completely in the ODE system? Set a low threshold level (e.g. $thr = 10^{-5}$) and plot the time to reach this threshold from the start of treatment as a function of the efficacy. Look at the shape of this curve: does it allow us to predict the long term outcome of therapy (i.e. whether the virus will be eradicated eventually) from the observed short term effect?

2.2 Implementing drug resistance

To approach the problem of drug resistance, we need to implement both the drug sensitive "wild type" virus and the drug resistant variant(s). This can be done by duplicating the equation for infected cells in Eq 2:

$$dT/dt = \lambda - \delta T - ((1-\epsilon)b_s I_s + b_r I_r)T \quad (3)$$
$$dI_s/dt = (1-\epsilon)(1-\mu)b_s I_s T - aI_s \quad (4)$$
$$dI_r/dt = b_r T I_r - aI_r + (1-\epsilon)\mu b_s I_s T \ . \quad (5)$$

[a] In the full model of HIV dynamics, new infections occur proportional to virus levels. However, due to the fast dynamics of virus particles, the level of the virus follows the level of infected cells and can therefore be replaced with it in the infection term, by appropriate scaling of the infectivity rate.

[b] You may compare this to the module "Within-host HIV dynamics: the estimation of parameters". In that module, we investigate the short-term dynamics ($\sim$ 1 week) of the virus level after the start of effective therapy. During that time frame, resistance does not arise, and potential residual replication due to incomplete suppression hardly matters. Therefore, it is justified to use the simplifying assumption of complete virus suppression (i.e. $b = 0$), which also makes the use of a separate variable for the target cells unnecessary. In this module, however, we will describe the emergence of drug resistance, which is also affected by the efficacy of the drugs; therefore, we have to allow for $\epsilon < 1$ and will need also an explicit equation for the target cells.

[c] You may consult the script of Sebastian Bonhoeffer's course "Ecology and Evolution II: Populations" for an analytical solution to this problem.

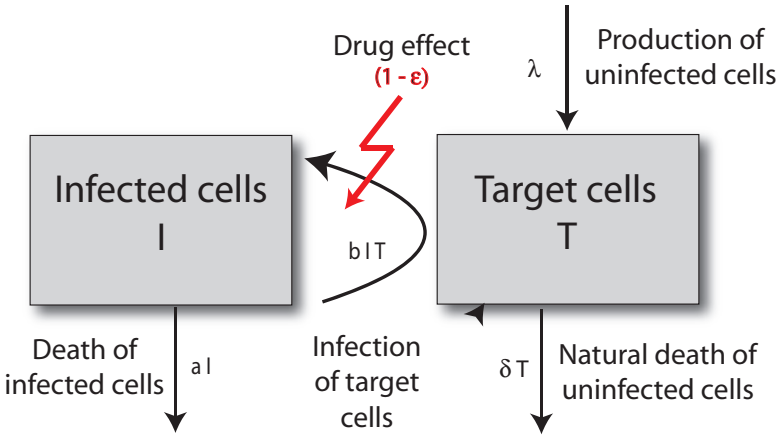

Figure 1: Schematic illustration of the virus dynamics model given by Eqs 1-2. New infections occur proportional to the level of target cells and infected cells.

I_s and I_r denote the levels of cells infected with wild type and resistant virus, respectively, which have the same death rate a, but different infectivities: b_s and b_r. The parameter ϵ characterises the efficacy of the drug in inhibiting the replication of sensitive virus; for simplicity, we assume complete resistance for the resistant virus. Finally, μ is the mutation rate at which wild type virus mutates into resistant mutant virus. (Note that we ignore back mutations from resistant to wild type virus, which is justified as long as the sensitive virus is much more abundant than the resistant mutant). Implement this model by extending the R script. Initially, set additional parameters as $b_s = 0.25$, $b_r = 0.24$ (i.e. the resistant variant is slightly less infectious than the wild type in the absence of the drugs, which is the typical situation for most resistance mutations) and $\mu = 10^{-5}$. Start simulations from an infected steady state with only wild type virus present initially (you can find this steady state from Eqs 1-2 either analytically, or by letting the original model attain a steady state). Figure 2 shows an example for $\epsilon = 0.9$.

3 Exercises

3.1 Basic exercises

Eb1. How does the efficacy of the drugs affect the time to the emergence of drug resistance? Run simulations with different values of the efficacy parameter ϵ. Plot the fraction of resistant virus over time in the simulations.

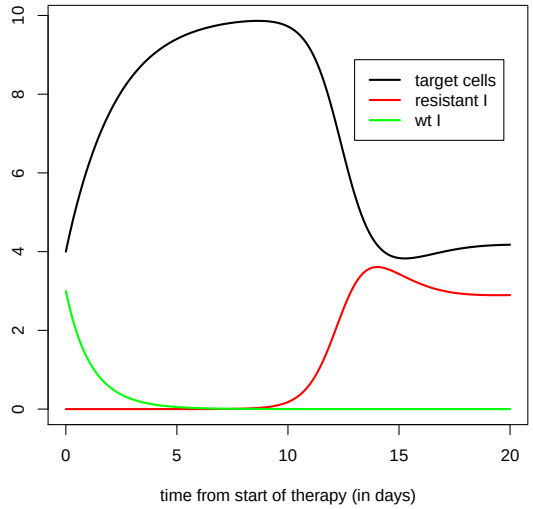

Figure 2: The time course of effective drug treatment ($\epsilon = 0.9$) with emerging drug resistance as modelled by Eqs 3-5. The figure shows the levels of uninfected target cells and of cells infected with resistant and wild type virus, respectively.

Eb2. Consider a resistance mutation that reduces the replication capacity or infectivity of the mutant considerably, e.g. let $b_r = 0.2$. Run a series of simulations with different drug efficacies, ranging from weak (e.g. $\epsilon = 0.1$) to strong drugs. Let the simulations run to a steady state and record the levels of target cells, resistant and mutant infected cells at the end point. Does resistant virus always take over? If not, what is the condition for the emergence of drug resistance? What is the maximum effect of drug treatment given that the resistant mutant can appear?

Eb3. Mutations are being generated all the time: resistance mutations arise also in the absence of therapy. Considering the large population size and fast mutation rate of HIV, mutants resistant to individual drugs can be present ("pre-exist") at the start of treatment. Set $\epsilon = 0$ and let the simulation run until the fraction of mutants attains a steady-state[d]. Use the endpoint as a new initial condition and simulate treatment. Compare the time to the emergence of drug resistance with previous simulations.

Eb4. What is the advantage of administering a combination of different drugs? Extend the equations to simulate treatment with a combination of two drugs that act independently. Let new infections be blocked by the factor $(1 - \epsilon_1)(1 - \epsilon_2)$ according to the efficacy of both drugs, and introduce variables for viruses that are resistant to one, the other, or both drugs. (For simplicity, allow for forward mutations only). In real life, drug combinations can inhibit the emergence of resistance for longer periods of time. How can you explain this? Can you reproduce this effect in the model?

[d]The steady-state fraction of mutants can be shown analytically to be $f = \frac{\mu}{1-b_r/b_s}$. Check this in your simulations.

3.2 Advanced/additional exercises

Ea1. Begin with a model of long-term suppressive combination treatment as implemented in the last basic exercise. Introduce variables for the concentration of the drugs, and define efficacy as some saturating function of the concentration[e] ("dose-response curve"). Let also mutants be affected by the drugs, i.e. define different drug response curves for all mutants and the wild type. Find the critical concentrations at which single and double mutants can grow. Implement drug dosing: "administer" drugs once or several times per day. Show how the nadir of the concentration curve can result in the emergence of resistance. Try to devise an optimal dosing strategy. Consider also side effects, which increase with increasing drug concentration.

Ea2. Implement the two major classes of drugs, protease (PR) and reverse transcriptase (RT) inhibitors, explicitly. PR inhibitors make produced virus particles non-infectious, while RT inhibitors prevent infectious virions from infecting cells. Expand the model accordingly: you will need variables to track the levels of infectious and non-infectious viruses. Compare the effect of the two drug classes on the dynamics of the total virus level after the start of therapy.

Ea3. Some evidence indicates that virus replication may still occur in well-suppressed patients in whom the virus has been undetectable by standard techniques for many years. In terms of our models, these patients may have attained a new steady state with extremely low virus levels under therapy. However, such a low steady state is only possible for a very narrow range of the efficacy parameter in the models: why would the efficacy stay in exactly this small regime, why do we not see deviations in either direction, which would imply eradication or failure to suppress the virus? A possible explanation is that under therapy HIV can still replicate in a special cell type or in a special compartment of the body which drugs do not penetrate. Model such a "drug sanctuary" and show how it could maintain a low steady state virus level in the blood.

Ea4. Model compensatory mutations. Such mutations can restore the efficiency of the drug resistant viral enzymes, which is impaired by the primary resistance mutations. Consider a single primary (P) and a single compensatory (C) mutation, and implement wild type, single and double mutant virus variants. Overall replication capacity should follow the order wt>C>PC$\gg$P in the absence of therapy and PC>P$\gg$C$\simeq$wt in the presence of therapy. Observe the time course of the evolution of drug resistance during therapy.

[e] One frequently used, realistic approximation works with the flexibly tunable Hill equation, in which the effect equals $\frac{a*x^c}{b^c+x^c}$, where x is the drug concentration in this case.