Project ODE 37

MODEL OF THE HIV DYNAMICS AND ANTIVIRAL RESPONSE IN THE PRESENCE OF TIME-VARIABLE PHARMACOLOGICAL TREATMENT

1. Introduction to the problem

The human immunodeficiency virus or HIV (Human Immunodeficiency Virus) belongs to the class of retroviruses and, as such, exploits the transcriptional apparatus of the cells it attacks to propagate. In particular, the viral amplification process is mediated by a specific enzyme, reverse transcriptase, which converts the genetic material of the virus, consisting of RNA, into a double-stranded DNA molecule, which can integrate with the genome of the host cell. or give rise to numerous copies of viral RNA.

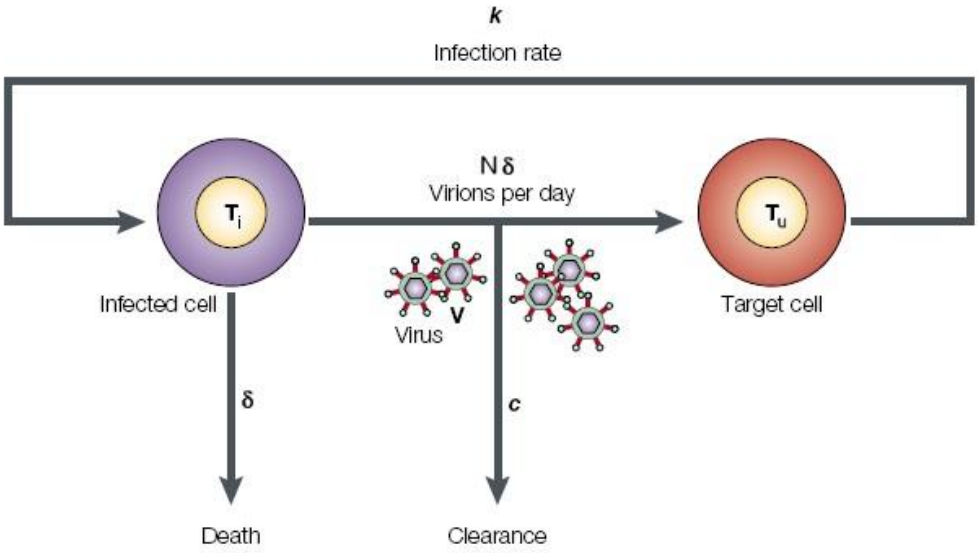
The main target of HIV are T helper lymphocytes, cells that regulate the antibody response by interacting with B lymphocytes (antibody producers) and inducing them to proliferate. The attack of the T helper lymphocytes by the virus therefore causes a marked reduction in the immune defenses which makes the body extremely vulnerable and susceptible to infections.

The treatment of HIV involves the use of a combination therapy (HAART, Highly Active Antiretroviral Therapy) which consists of the combination of several classes of drugs, including reverse transcriptase inhibitors (RTI, Reverse Transcriptase Inhibitors) and inhibitors protease inhibitors (PIs): the former prevent the infection of new T cells by blocking the reverse transcription of viral RNA, while the latter reduce the production of infectious viral particles (virions) by T cells already attacked by the virus . This therapy, which must be modulated on the characteristics of individual patients, while not constituting a definitive cure, is capable of slowing the progression of the disease, while improving the quality of life of the sick.

2. Mathematical Model

In HIV-infected patients, the viral load tends to settle around a constant value and remain around it for years, but for this to happen the body must be able to produce and eliminate viruses at the same time1. Fig.1 shows a diagram of the viral dynamics of HIV that describes this mechanism: the virus (V), which infects healthy T cells (T_U) with speed k, is eliminated from the body with speed c; in parallel, new viral particles are produced by infected T cells (T_I) with Nδ velocity. The equations that describe the viral dynamics model are as follows:

Fig.1: Scheme of the viral dynamics of HIV



$$\begin{aligned}\frac{dT_U}{dt} &= \lambda - \rho T_U - kT_U V \\ \frac{dT_I}{dt} &= kT_U V - \delta T_I \\ \frac{dV}{dt} &= N\delta T_I - cV\end{aligned} \tag{1}$$

where λ represents the rate at which new cells are generated T, ρ and δ indicate the mortality rate of the cells T_U and T_I respectively, while N is the number of virions produced by each infected cell.

The introduction of antiretroviral therapy can be described by model1:

$$\begin{aligned}\frac{dT_U}{dt} &= \lambda - \rho T_U - \big(1-\gamma(t)\big)kT_U V_I \\ \frac{dT_I}{dt} &= \big(1-\gamma(t)\big)kT_U V_I - \delta T_I \\ \frac{dV_I}{dt} &= \big(1-\eta(t)\big)N\delta T_I - cV_I \\ \frac{dV_{NI}}{dt} &= \eta(t)N\delta T_I - cV_{NI}\end{aligned} \tag{2}$$

where V_I represents the concentration of infectious viral particles, V_{NI} the concentration of non-infectious virions produced following the administration of the PI drug (the total amount of virus is therefore given by $V = V_I + V_{NI}$), while $\gamma(t)$ and $\eta(t)$ represent the efficacy of RTI and PI drugs

respectively. In particular, the variable parameters γ(t) and η(t) can vary between 0 (completely ineffective drug) and 1 (ideal drug) and take the form:

$$\gamma(t) = \frac{\prod_{i=1}^{n} A_i \, IQ_i(t)}{\phi + \prod_{i=1}^{n} A_i \, IQ_i(t)}\Bigg|_{RTI} \tag{3}$$

$$\eta(t) = \frac{\prod_{j=1}^{m} A_j \, IQ_j(t)}{\phi + \prod_{j=1}^{m} A_j \, IQ_j(t)}\Bigg|_{PI} \tag{4}$$

where ϕ represents a conversion factor between in vivo and in vitro measurements, n and m respectively indicate the number of RTI and PI drugs administered simultaneously, while A_i, i=1,...,n and A_j, j=1,...,m represent, for the i-th drug RTI and for the j-th drug PI respectively, the adherence to treatment, or the percentage of doses taken with respect to the dosage ($0 < A < 1$). The variable parameters $IQ_i(t)$ and $IQ_j(t)$ indicate, for the i-th drug RTI and the j-th drug PI respectively, the inhibitory coefficient of the drug, which has an expression such as:

$$IQ(t) = \frac{C_{max}}{IC_{50}(t)} \tag{5}$$

where C_{max} represents the maximum plasma concentration of the drug and $IC_{50}(t)$ the amount of drug needed to inhibit viral replication by 50% (mean inhibitory concentration). To take into account the variations of this parameter over time, related to the onset of mutant versions of the virus with reduced sensitivity to drug treatment, Huang et al.2 proposed the following expression:

$$IC_{50}(t) = \begin{cases} I_0 + \dfrac{I_r - I_0}{t_r} t & per \quad 0 < t < t_r \\ I_r & per \quad t \geq t_r \end{cases} \tag{6}$$

where I_0 and I_r represent the respective values of $IC_{50}(t)$ at the beginning of treatment and at time t_r, that is, the instant in which drug-resistant mutations dominate.

In the case of combined treatment between RTI and PI drugs, the overall effectiveness is given by: (7)

$$e(t) = 1 - \big(1 - \gamma(t)\big)(1 - \eta(t))$$

If the treatment is powerful enough, that is, if $e(t) > e_c \ \forall t$ (e_c drug efficacy threshold), then we have that $dV_I/dt < 0$ and thus the virus can eventually be eradicated ($V = V_I + V_{NI} = 0$).

Realization of the project in Matlab

To simulate the viral dynamics described in system (2), use the parameters shown in Tab.1. These values have been obtained from studies [3-5] estimating the parameters for fitting experimental data relating to patients with HIV.

Parameter	Description	Value
$\boldsymbol{\lambda}$	new cell generation rate T	36(days^{-1}mm^{-3})
$\boldsymbol{\rho}$	non-infected T cell death rate	0.108(days^{-1})
$\boldsymbol{k}$	rate of T cell infection	$1.7\cdot10^{-5}$(mm^{3}days^{-1})
$\boldsymbol{\delta}$	Infected cell death rate T	0.5(days^{-1})
$\boldsymbol{N}$	number of virions produced per infected cell	1000
$\boldsymbol{c}$	clearance of free virions	3 (days^{-1})
$\boldsymbol{\gamma(t)}$	medicine efficacy RTI	$0<\gamma(t)<1$
$\boldsymbol{\eta(t)}$	medicine efficacy PI	$0<\eta(t)<1$

Tab.1: Parameters of the HIV viral dynamics model.

Given the initial conditions[7] $T_U(0) = 600$, $T_I(0) = 30$, $V_I(0) = 10^5$ and $V_{NI}(0) = 9.9 \cdot 10^4$, the simulation models of the various pharmacological treatments are solved numerically for:

1) the dynamics of the untreated virus;
2) the dynamics of the virus treated with PI drug (Ritonavir);
3) the dynamics of the virus treated with RTI, to be studied in the two cases: a) administration of a single drug (ZDV); b) combination of two drugs (ZDV + 3TC);
4) the dynamics of the virus subjected to combined pharmacological treatment between PI (Ritonavir) and RTI (ZDV and 3TC), analyzed in two cases: a) Ritonavir + ZDV; b) Ritonavir + (ZDV + 3TC);
5) the dynamics of the virus subjected to hypothetical PI "killer" pharmacological treatment capable of canceling the viral load (efficacy $e > 0.7$).

The parameters to be used for the simulations conducted at points 2), 3) and 4), obtained from the literature [2,6], are reported in Tab.2. For all treatments, assume ϕ = 1, which is equivalent to considering the values of IC_{50} measured in vivo. Furthermore, at points 3-b) and 4-b) choose - for simplicity - the same treatment adherence value (A) for both RTI drugs.

Medicine	Kind	C_{max} (mg/L)	I_0 (mg/L)	I_r (mg/L)	t_r (days)
Ritonavir	PI	5.14	0.11	7.7	21
ZDV	RTI	1.57	0.13	9.75	84
3TC	RTI	1.37	0.34	23.8	84

Tab.2: Pharmacokinetic parameters of the PI and RTI treatments considered.

Finally check if the problem is characterized by stiffness.

1. References

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