An integrated modelling approach for R5-X4 mutation and HAART therapy assessment

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Abstract: We have modelled the within-patient evolutionary process during HIV infection using different methodologies. During the HIV infection the arising of viral multi-strain of the virus able to use different coreceptors, in particular the CCR5 and CXCR4 (R5 and X4 phenotypes, respectively) influences the progression of the disease to the AIDS phase.

We present a model of HIV early infection and CTLs response which describes the dynamics of R5 quasispecie and a model of HIV late infection, specifying the R5 to X4 switch and effect of immune response. We illustrate dynamics of HIV multiple strains on HAART and multidrug HAART therapy. The HAART combined with X4 strain blocker drug might help to reduce infectivity and that leads slower progression of disease.

On the methodology side, our model represents a paradigm of integrating formal methods and mathematical models as a general framework to study HIV multiple strains during disease progression, and will inch towards providing help in selecting among vaccines and drug therapies. The results here presented are one of the rare cases of methodological cross comparison (stochastic and deterministic) and the first implementation of model checking in therapy validation.

Description of Biological phenomena

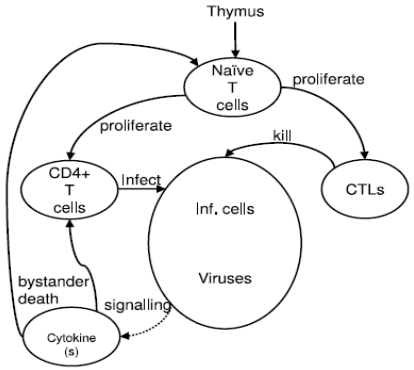

Fig 1: Schematic description of interaction among the cells and viruses. Circle ○ represents population of cells/virons, → abundance of cells/viral particles from one type to the other, either directly from single cell population or through interaction of two different type of cell populations.

Model

The interactions among the immature T cells (U), uninfected mature T cells (T), CTL response (Z), infected cells (I), viral strains (V) and TNF (F) are translated into ordinary differential equations (ODEs).

$$\frac{dU}{dt} = \lambda + \sigma_1 \left(\sum_k I_k Z_k \right) - \delta_{ut} U - \delta_{uf} U F - \delta_{uz} U$$

$$\frac{dT}{dt} = \delta_{ut} U - \left(\sum_{k \in R5} (1 - \eta_{RT}) \beta_{k5} V_k + \sum_{k \in X4} (1 - \eta_{RT}) \beta_{k4} V_k \right) T - \delta_{tf} T F - \delta_t T$$

$$\frac{dZ_k}{dt} = \delta_{uz} U + \sigma_2 I_k - \delta_z Z_k$$

$$\frac{dI_k}{dt} = \left(\sum_{k'} \mu_{kk'} (1 - \eta_{RT}) \beta_{k'} V_{k'} \right) T - \delta_{iz} I_k Z_k - \delta_i I_k$$

$$\frac{dV_k}{dt} = (1 - \eta_{PI}) \pi I_k - \delta_v V_k$$

$$\frac{dF}{dt} = \sigma_3 \sum_{k \in X4} V_k$$

Stochastic Model

We employ a *population-based* approach where number of each type of species or cells are modelled, rather than the state of each individual component. Agents are interact directly or indirectly through environment. The combined behaviour of these agents is observed in a discrete-time or event-driven simulation.

$U_0 \xrightarrow{\lambda} U_0 + U$	$T + F \xrightarrow{\delta_{tf}} F$	$I_5 \xrightarrow{\sigma_2} I_5 + Z_5$	$I_5 \xrightarrow{\pi} V_5 \times 200$
$U + F \xrightarrow{\delta_{uf}} F$	$T + V_5 \xrightarrow{\beta_{R5}} I_5$	$I_4 \xrightarrow{\sigma_2} I_4 + Z_4$	$I_4 \xrightarrow{\pi} V_4 \times 200$
$U \xrightarrow{\delta_{ut}} T$	$T + V_4 \xrightarrow{\beta_{X4}} I_4$	$I_5 + Z_5 \xrightarrow{\sigma_1} U + I_5 + Z_5$	$V_4 \xrightarrow{\sigma_3} F + V_4$
$U \xrightarrow{\delta_{uz}} Z_4$	$I_4 + Z_4 \xrightarrow{\sigma_1} U + I_4 + Z_4$	$I_5 \xrightarrow{\delta_i} 0$	$V_4 \xrightarrow{\delta_v} 0$
$U \xrightarrow{\delta_{uz}} Z_5$	$I_5 + Z_5 \xrightarrow{\delta_{iz}} Z_5$	$I_4 \xrightarrow{\delta_i} 0$	$V_5 \xrightarrow{\delta_v} 0$
$T \xrightarrow{\delta_t} 0$	$Z_5 \xrightarrow{\delta_z} 0$	$I_4 + Z_4 \xrightarrow{\delta_{iz}} Z_4$	
	$Z_4 \xrightarrow{\delta_z} 0$	$V_5 \xrightarrow{\mu} V_4$	

Embedding HAART therapy

According to the representation of HAART therapy described by the equations of the deterministic model. Here, a notion of time flow is essential to express the degradation of the efficacy of the therapy during the treatment period.

The coefficient varies in time, starting from a 60% reduction of these reactions and degrading to a null effect over a time span of 400 days. Simulation results are described in Fig 2.

Stochastic simulation Results

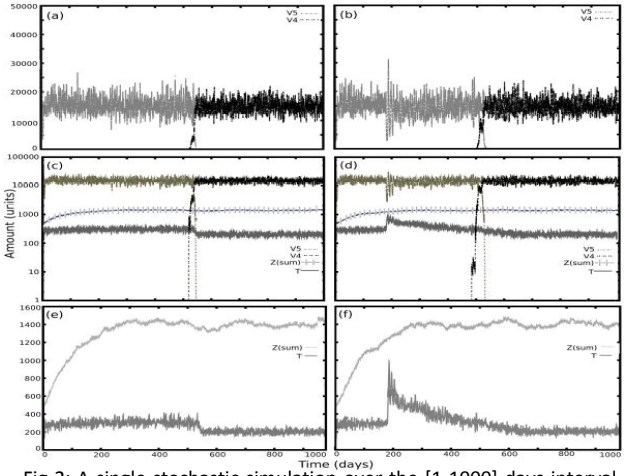

Fig 2: A single stochastic simulation over the [1-1000] days interval. (a) illustrates the overall dynamics of infective dynamics. The viral develops initially based on a V5 population (light grey). At about day 500 the mutation occurs, V4 (black) prevails, and the system locally perturbed. (c) highlights the simulation results on log scale. (e) reports only data on T cells and sum of Z cells. Figures on right (b, d, f) represent stochastic simulation in the presence of HAART treatment during approximate interval [200, 600] days.

Model checking

We have adopted the open-source PRISM probabilistic model checker, one of the reference existing model checkers for the analysis of systems which exhibit random or probabilistic behaviour. We discuss two properties of interest: 1) number of infected cells leading to virus replication as a measure of the spread of infection 2) the amount of healthy T cells t as a measure of resistance to the virus attach. Results are describe in below tab.

	Plain model	Therapy model
$R\{\text{"i\_to\_v"}\} =? \ [200.0 <= C <= 600.0]$	50 157	47 465
$P =? \ [F[200.0, 600.0] tc <= 200.0]$	**0.8032**	**0.3293**

Conclusion

1) To illustrate how properties of interest for the study of viral infections can be formalised in a general purpose logic using PRISM. 2) how their verification can precisely numerical results of simulations 3) how this can be helpful in comparing and assessing different therapies.

References

- Kwiatkowska, et. al. The PRISM model checker. http://www.prismmodelchecker.org
- M. Kwiatkowska, G. Norman, and D. Parker. Algorithmic Bioprocesses : Quantitative Verification Techniques for Biological Processes, Natural Computing Series, Springer, 391–409, 2009
- A. Sorathiya, A. Bracciali, and P. Lio'. Formal reasoning on qualitative models of coinfection of HIV and Tuberculosis and HAART therapy. BMC Bioinformatics, 11(1):S67, 2010