Implementation of a Highly Nonlinear, Multi-scaled and Long-term HIV Dynamic Model with Treatment Interruptions and Non-static BQL Data for Population Analysis

Shuhua Hu, Kevin Feng, Bob Leary, Mike Dunlavey, Bill Poland

Certara/Pharsight, Cary, NC

Background

- Antiretroviral therapy (ART) is able to suppress the viral load to below the detection limit, but it is not able to eradicate the latent reservoir. The HIV model in [1] was built with an intention to investigate possible pharmacological strategies that may be beneficial to reduce or possibly eradicate the latent reservoir [2].

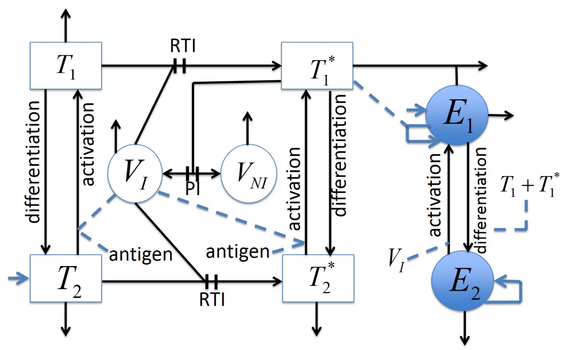

Figure 1: Diagram of HIV model proposed in [1]. Model states T_1 and T_1^* respectively denote the uninfected and infected activated CD4+ T cells, and T_2 and T_2^* respectively represent uninfected resting CD4+ T cells and latently infected CD4+ T cells. Model states V_I and V_{NI} respectively denote infectious and non-infectious virus, and E_1 and E_2 respectively represent activated and memory HIV-specific CD8+ T cells. PI and RTI denote protease inhibitor and reverse transcriptase inhibitor, respectively.

$$\dot{T}_1 = -d_1 T_1 - (1-\xi_1(t))k_1 V_I T_1 - \gamma_T T_1 + p_T\left(\tfrac{a_T V_I}{V_I+K_V} + a_A\right) T_2,$$

$$\dot{T}_1^* = (1-\xi_1(t))k_1 V_I T_1 - \delta T_1^* - mE_1 T_1^* - \gamma_T T_1^* + p_T\left(\tfrac{a_T V_I}{V_I+K_V} + a_A\right) T_2^*,$$

$$\dot{T}_2 = \lambda_T \tfrac{K_s}{V_I+K_s} + \gamma_T T_1 - d_2 T_2 - (1-f\xi_1(t))k_2 V_I T_2 - \left(\tfrac{a_T V_I}{V_I+K_V} + a_A\right) T_2,$$

$$\dot{T}_2^* = \gamma_T T_1^* + (1-f\xi_1(t))k_2 V_I T_2 - d_2 T_2^* - \left(\tfrac{a_T V_I}{V_I+K_V} + a_A\right) T_2^*,$$

$$\dot{V}_I = (1-\xi_2(t))10^3 N_T \delta T_1^* - cV_I - 10^3(1-\xi_1(t))\rho_1 k_1 T_1 V_I$$
$$-10^3(1-f\xi_1(t))\rho_2 k_2 T_2 V_I,$$

$$\dot{V}_{NI} = \xi_2(t)10^3 N_T \delta T_1^* - cV_{NI},$$

$$\dot{E}_1 = \lambda_E + \tfrac{b_{E1}T_1^*}{T_1^*+K_{b1}}E_1 - \tfrac{d_E T_1^*}{T_1^*+K_d}E_1 - \delta_{E1}E_1 - \gamma_E \tfrac{T_1+T_1^*}{T_1+T_1^*+K_\gamma}E_1 + \tfrac{p_E a_E V_I}{V_I+K_V}E_2,$$

$$\dot{E}_2 = \gamma_E \tfrac{T_1+T_1^*}{T_1+T_1^*+K_\gamma}E_1 + \tfrac{b_{E2}K_{b2}}{E_2+K_{b2}}E_2 - \delta_{E2}E_2 - \tfrac{a_E V_I}{V_I+K_V}E_2,$$

with $(T_1(0), T_1^*(0), T_2(0), T_2^*(0), V_I(0), V_{NI}(0), E_1(0), E_2(0))^T = (T_1^0, T_1^{*0}, T_2^0, T_2^{*0}, V_I^0, V_{NI}^0, E_1^0, E_2^0)^T$.

Here $\xi_1(t) = \epsilon_1 u(t)$ and $\xi_2(t) = \epsilon_2 u(t)$, where ϵ_1 and ϵ_2 denotes the relative effectiveness of reverse transcriptase inhibitor and protease inhibitor, respectively, and $0 \le \epsilon_1, \epsilon_2 \le 1$.

- Function u $(0 \le u(t) \le 1)$ is used to describe treatment interruption with $u(t) = 0$ representing fully off and $u(t) = 1$ be fully on.

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- A simpler HIV model was considered in [3] for population analysis using stochastic approximation expectation maximization (SAEM) algorithm. Specifically, this model does not incorporate some important features of HIV pathogenesis and cellular immune response such as HIV-specific CD8+ T cells and another possible source of latency that is established through transition of activated CD4+ T cells to a resting state following infection.

Objective

To apply the quasi-random parametric expectation maximization (QRPEM) method in Phoenix® NLME™ (Pharsight/Certara) to this highly nonlinear and multi-scaled HIV dynamic model for population analysis with clinical data [1]

- consisting of 14 patients followed for varying lengths of time between 2 and 6 years who all underwent ART and had at least one treatment interruption;
- including the total CD4+ T-cells and non-static BQL viral load (due to different assays used in the investigated period).

We do not try to compare the QRPEM estimation with methods used in other software but rather show the capability of the QRPEM in implementing such a complex model with complicated data.

Methods

To incorporate treatment interruptions, we added treatment as a time-varying covariate using a linear-interpolation approach.

Challenges

Due to the complexity of the problem, this model cannot be directly implemented in Phoenix® NLME™.

- Model states may become unrealistically negative in numerically solving it due to round-off error caused by large-scale differences among model states and parameters.
- ODE solvers often failed due to some unrealistic parameter values obtained during the optimization process.
- A large number of free parameters in this model brings significant challenges in parameter estimation. For example, the standard error estimates, if they can be computed at all, are very large.

Techniques

- To avoid the issue caused by the scale difference, we converted the model into a log-transformed system by log-transformation of all model states and parameters.
- To avoid obtaining unrealistic parameter values, we imposed lower and upper bounds on posthoc parameters. This is achieved through transformation of constrained parameters to unconstrained ones. We then modified Mu-models for the QRPEM estimation.

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- To alleviate the difficulty caused by the large number of free parameters, we first performed sensitivity analysis to identify the parameters to which the model outputs are least sensitive. Those least sensitive parameters were fixed with values given in [1] and the rest of the parameters were estimated. Next we identified the parameters with least inter-individual variability and fixed them with the values justed estimated and then re-estimated the remaining parameters.

Results

Through proposed methods, we successfully implemented this model, and obtained reasonably good model fitting results for all patients (see Figure 2 for two example patients) and reliable parameter estimates (with coefficient of variation less than 36%).

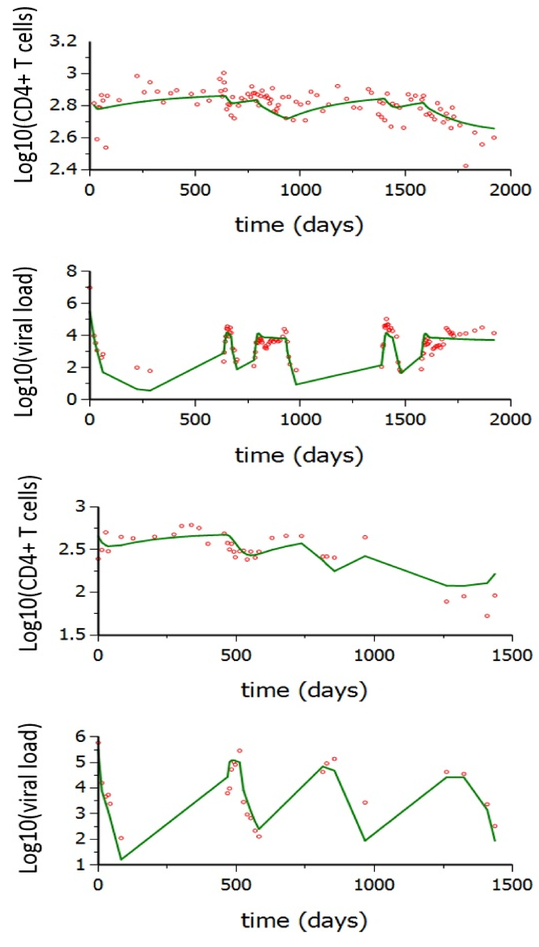

Figure 2: Model fitting results for two example patients, where red circles are the actual observations, and green solid line denotes the predicated model solution.

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Figure 3 shows visual predicted checks (VPC) for $\log_{10}$(CD4+ T cells) and $\log_{10}$(viral load) obtained using Phoenix® NLME™ with K-means binning option and 1000 replicates. It suggests that this model has satisfactory predictive capability. This is consistent with the conclusion made in [1] where model simulations with parameters estimated using only half of the longitudinal observations agreed with the corresponding ones obtained using parameters estimated from full longitudinal data.

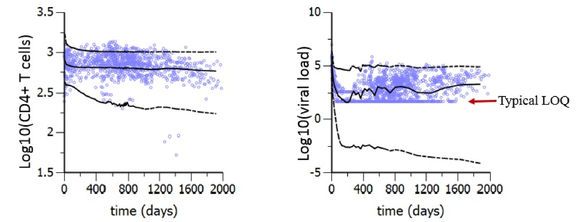

Figure 3: (left panel): plot of VPC for $\log_{10}$(CD4+ T cells); (right panel): plot of VPC for $\log_{10}$(viral load). Open circles represent actual observations. The solid line represents the 50th percentile of the simulated ones, and the dashed lines represent the 5th and 95th percentiles.

Conclusions and Future Work

- Numerical results demonstrate the capability of the QRPEM estimation in analyzing a complex dynamic model with complicated data.
- It is worth noting that the HIV model in [1] can be used in the case where integrase inhibitors are also given to patients. In the future, we plan to apply this HIV model to such data set and continue investigating possible pharmacological strategies for viral eradication.
- We also plan to investigate a hierarchical HIV disease model repository as workflow and then use these models to design adaptive dosing regimens via the Phoenix modeling language engine.

References

[1] H.T. Banks, M. Davidian, S. Hu, G.M. Kepler and E.S. Rosenberg, Modeling HIV immune response and validation with clinical data, *Journal of Biological Dynamics*, 2 (2008), 357–385.

[2] H.T. Banks, K.B. Flores, S. Hu, E. Rosenberg, M. Buzon, X. Yu and M. Lichterfeld, Immuno-modulatory strategies for reduction of HIV reservoir cells, *Journal of Theoretical Biology*, 372 (2015), 146–158.

[3] M. Lavielle, A. Samson, A.K. Fermin, and F. Mentre, Maximum Likelihood Estimation of Long-Term HIV Dynamic Models and Antiviral Response, *Biometrics*, 67 (2011), 250–259.

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