Optimality Conditions to Mitigate HIV escape

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INTRODUCTION

Highly active antiretroviral therapies (HAARTs) provide a rapid drop in plasma viral load with a large reduction of infected cells in patients with HIV infection. Even though long periods of HAART are provided, latently infected cells are still detectable. Therefore, cellular reservoirs may contribute to HIV persistence promoting the emergence of resistant mutants.

Using simplified switched linear system models of HIV mutation and treatment with certain class of symmetry and finite horizon cost functions, we demonstrate that the optimal state and co-state trajectories lie on a sliding surface where infinitely fast switching may occur. Results suggest that in the absence of other practical constraints, switching rapidly between therapies is relevant. Simulations show the potential benefits of a proactive switching strategy to minimize viral load and delay the emergence of resistant mutant viruses

HIV TREATMENT

The process of reverse transcription is extremely error-prone and it is during this step that mutations can occur. In the absence of ongoing viral replication, the generation of new variants is also arrested. Therefore, the authors of [1] noted that stronger suppression of viral replication reduces the chance that a resistant mutant will emerge. Therefore, a strong suppression of the total viral load (V_T) increases the probability of viral extinction.

$$J := c'x(t_f) \qquad (1)$$

where c is a strictly positive vector. Note that this final time penalty is motivated by the observation that frequently the final viral escape is at an exponential rate that is largely independent of the treatment selection.

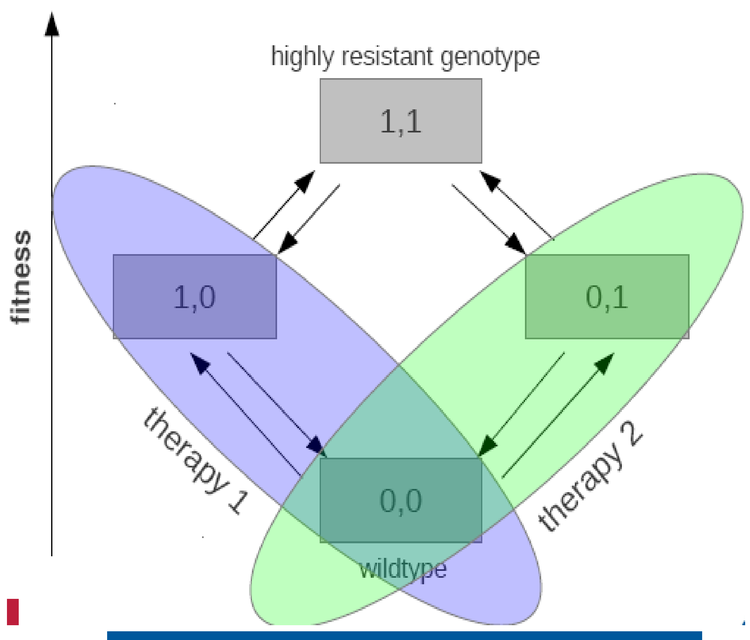

Figure 1: Mutation Graph

Simulations and clinical data suggest that once the patient is using HAART and until virological failure, macrophage and CD4+T cell counts are approximately constant. Under this assumption, most nonlinear HIV models are rendered linear. We use the linear model that includes *n* different viral genotypes (*i*), with viral populations, x_i. *N* is the different possible drug therapies that can be administered, represented by $\sigma(t) \in \{1, \ldots, N\}$. The viral dynamics are represented by the following simplified equation:

$$\Sigma_A : \dot{x}(t) = A_{\sigma(x(t))}x(t), \qquad x(0) = x_0 \qquad (2)$$

where $\sigma(t)$ is the therapy combination for viral genotype (*i*), μ represents the mutation rate, and the matrix *A* can be written as follows:

$$A_\sigma = \begin{bmatrix} \lambda_1 & 0 & 0 & 0 \\ 0 & \lambda_{2\sigma} & 0 & 0 \\ 0 & 0 & \lambda_{3\sigma} & 0 \\ 0 & 0 & 0 & \lambda_4 \end{bmatrix} + \mu \begin{bmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix}. \qquad (3)$$

OPTIMAL CONTROL

Definition 1. A triple $u^o(t) : [0, t_f] \times \mathcal{U}, x^o(t), \pi^o(t)$, that satisfies (for almost all t) the system of equations:

$$\dot{x}^o(t) = \sum_{i=1}^{N} u_i^o(t) A_i x^o(t) \qquad (4)$$

$$-\dot{\pi}^o(t) = \sum_{i=1}^{N} u_i^o(t) A_i' \pi^o(t) \qquad (5)$$

$$u^o(t) \in \operatorname*{argmin}_{u \in \mathcal{U}} \left\{ \pi^{o\prime}(t) \sum_{i=1}^{N} u_i A_i x^o(t) \right\} \qquad (6)$$

with the boundary conditions $x^o(0) = x_0$ and $\pi^o(t_f) = c$, is called a Pontryagin solution for the optimal control problem.

Theorem 1. Assume that there exists a unique Pontryagin solution (u_o, x_o, π_o) for the optimal control defined by system (2) and cost (1). Then $u_o(t)$ is an optimal control signal relative to x_0 and the value of the optimal cost functional is $\pi_o'(0)x_0$.

Lemma 1. *Consider the dynamic system (1) with initial condition $x(0) = x_0$, $N = 2$ and cost function $J = c'x(t_f)$. Suppose there exist $A_\alpha := \alpha A_1 + (1-\alpha)A_2$ ($\alpha \in (0,1)$); and tall matrices $v_x, w_x, v_\pi, w_\pi \in \mathbb{R}^{n \times m}$ (for any $m \leq n$) such that:*

i. v_x' *is a left invariant of* A_α;
ii. $v_x'x_0 = 0$;
iii. v_π *is a right invariant of* A_α;
iv. $c'v_\pi = 0$; *and*
v. $A_1 - A_2 = w_x v_x' + v_\pi w_\pi'$.

Then there exists a Pontryagin solution over $t \in [0, t_f]$ that is a sliding mode.

Assumption 1. The matrix A_2 may be obtained as a (generalized) transposition of A_1, namely, there exists a transposition T such that:

$$A_2 = TA_1T.$$

Lemma 2. *Under Assumption 1, v' is a basis for a left invariant subspace of $A_\alpha = \alpha A_1 + (1-\alpha)A_2$; in particular $v'A_\alpha = \alpha(v'A_1v)v'$ where $\alpha = \frac{k-1}{k}$.*

Theorem 2. *Under the following conditions:*

i. *Assumption 1;*
ii. *The initial conditions and cost satisfy $v'x_0 = 0$ and $v'c = 0$, with v as in Definition 2; and*
iii. *A_1 and A_2 are symmetric;*

Then a Pontryagin solution is given by the trajectory along the plane $v'x(t) = 0$ with dynamical matrix A_α.

Assumption 2. $\lambda_{21} > 0, \lambda_{22} < 0, \lambda_{31} < 0, \lambda_{32} > 0.$

In addition, we make the following symmetry assumption:

Assumption 3. $\lambda_{21} - \lambda_{22} + \lambda_{31} - \lambda_{32} = 0.$

Lemma 4. *Consider any time interval, $[t_1, t_2]$ and suppose that $x_2(t_1) = x_3(t_1)$, $\pi_2(t_2) = \pi_3(t_2)$. Under Assumption 3, there is a Pontryagin solution over $[t_1, t_2]$ such that $x_2(t) = x_3(t)$, $\pi_2(t) = \pi_3(t)$ with $\alpha = \frac{\lambda_{32}-\lambda_{22}}{\lambda_{32}-\lambda_{22}+\lambda_{21}-\lambda_{31}}$.*

Theorem 3 (*Long Horizon Case*). *Let Assumptions 2 and 3 be met, let $\mu > 0$ and assume that $T_1 \leq T_2$. Then, the optimal control associated with the initial state $x(0)$ and cost $c'x(t_f)$ is given by $\sigma(t) = k_1, t \in [0, T_1]$ and $\sigma(t) = k_2, t \in [T_2, t_f]$. For $t \in [T_1, T_2]$, the optimal control is given by the trajectory along the plane $x_2 = x_3$, with dynamical matrix $A_\alpha = \alpha A_1 + (1-\alpha)A_2$ and α as given in Lemma 2.*

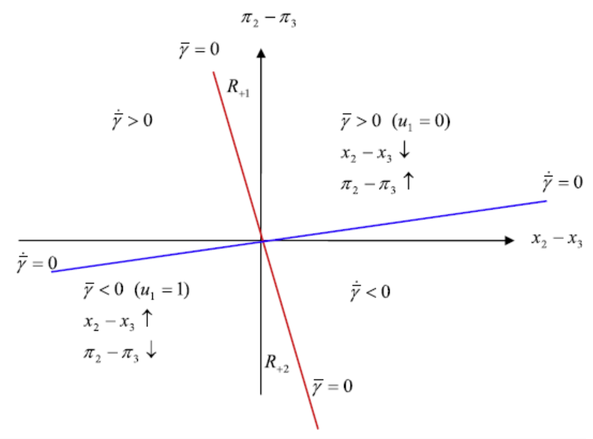

Figure 2: Plane $x_2 - x_3$, $\pi_2 - \pi_3$.

SIMULATION RESULTS

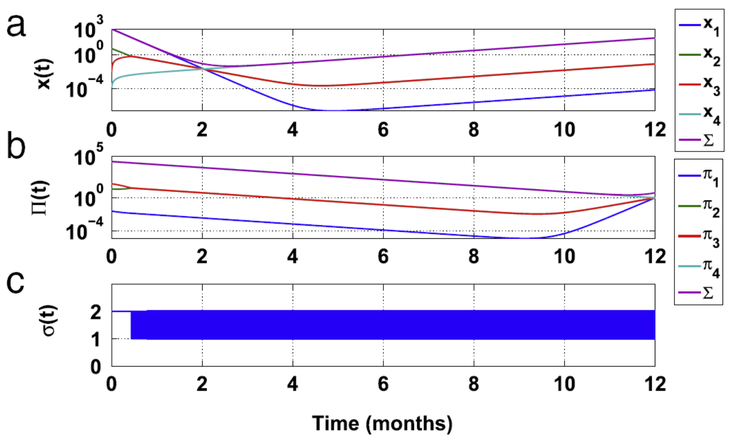

Figure 3: Optimal trajectories. (a) genotype dynamics (b) adjoint state variables (c) switching rules.

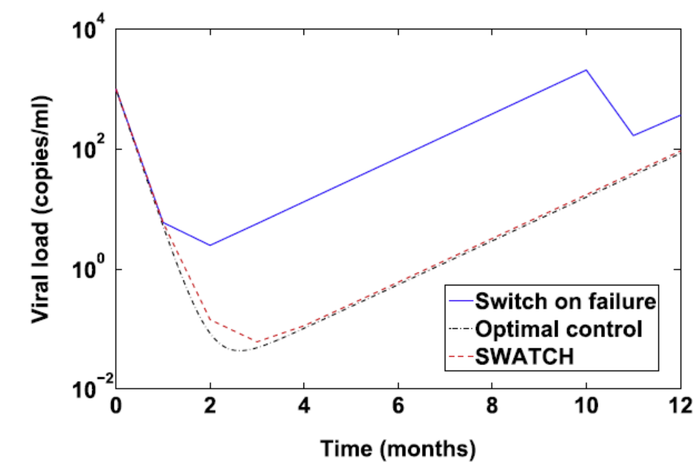

Figure 4: Different treatment strategies.

CONCLUSIONS

For the proposed models of treatment in HIV and simplifying assumptions in the proliferation rate and the mutation graph, we show that the optimal control for a class of positive switched systems is given by the trajectory along the plane $v'x(t)=0$.

Such behaviour suggests that in the absence of other practical constraints, switching rapidly between therapies may be desirable. This work provides the speculative possibility that therapy alternation may sustain viral suppression to very low levels inhibiting the emergence of resistant mutant viruses. Further research will include more realistic models and cost functions that penalise the switching.

References

[1] E.A. Hernandez-Vargas, P. Colaneri, R. Middleton, Optimal therapy scheduling for a simplified HIV infection model, Automatica, In press, 2013

[2] E.A. Hernandez-Vargas, P. Colaneri, R. Middleton, Control strategies to mitigate HIV mutation, IEEE transactions on control systems technology, In press, 2013