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Closed-loop minimal sampling method for determining viral-load minima during switching

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Abstract

In previous work, we have developed optimal-control based approaches that seek to minimize the risk of subsequent virological failure by "pre-conditioning" the viral load during therapy switches. These techniques result in the transient susceptibility of the total viral load, and rely on finding the minimum of a dip in viral load and switching before viral load rebound. Model uncertainty necessitates a closed-loop approach to minimum-finding. Blood measurements are costly in terms of money, inconvenience and risk. In this paper, we introduce an iterative parameter estimation approach to find the viral load minimum, and measure the degree of optimality of minimum-seeking under conditions of measurement noise. We evaluate the cost-savings of this approach in terms of number of samples saved from a constant measurement rate.

I. INTRODUCTION

HIV replication is effectively contained by combination antiviral therapy, known as Highly Active Antiretroviral Therapy, or HAART. The emergence of drug-resistant strains, however, necessitate a change in therapy in order to reestablish control. Virological failure due to drug resistance occurs in some 30-50% of all cases [1], and subsequent failures are also common.

Drug-resistance that is due to micro-populations of preexisting resistant virus is likely a major cause of these failures. The probability that these micro-populations exist is proportional to the population sizes of the various strains present, modulated by the genetic distance of the various strains to the resistant strain [2]. It is possible to transiently manipulate the population levels of these resistant strains using residual effectiveness of the failing drugs, achieving local minima in the viral load [3]. Risk of subsequent virological failure can be significantly reduced by switching to the new HAART regimen at these minima.

In previous work, models and algorithms have been developed which calculate optimal schedules of treatment application to create these minima [4],[5],[6]. These schedules utilize treatment interruptions or treatment permutations to set up a viral load decline at an approximately exponential rate, until a resistant strain emerges and grows at an approximately exponential rate. Reduction of risk requires the minimum of this viral load curve to be detected, so that treatment can be switched before viral load rebound.

The uncertainty in HIV measurements and the dynamics necessitate the use of a closed-loop approach to minima finding. Frequent sampling accomplishes this, but sampling is costly and hazardous to the patient. It is important to use the minimum number of samples necessary

to find the minima. In this paper, we introduce a parameter-independent closed-loop algorithm for finding the viral load minimum. Our method exhibits tunable robustness to measurement noise, and good overall performance when tested against simulated data.

II. MODEL

A. Viral strain competition model

The treatment scheduling algorithms presented in [4],[5],[6] use dynamic models of HIV strain-strain competition that incorporate viral reservoir dynamics. A simple form of this model can be written:

$$\begin{aligned}\dot{x} &= \lambda - dx - \beta_s (1 - u_1) (1 - u_2) xv_s - \beta_r (1 - u_2) xv_r \\ \dot{y}_w &= \beta_w (1 - u_1) (1 - u_2) xv_w - a_w y_w + \lambda_w \\ \dot{y}_r &= \beta_r (1 - u_2) xv_r - a_r y_r + \lambda_r \\ \dot{v}_w &= k_w a_w y_w - u_w v_w \\ \dot{v}_r &= k_r a_r y_r - u_r v_r\end{aligned}\quad (1)$$

where v_w, y_w are the populations of virus and infected cells, respectively, susceptible to drug regimen u_1 , v_r and y_r the populations of virus and infected cells resistant to u_1 , respectively, and x is the uninfected target cell population.

B. Approximate Solution

The differential equation model of Equation 1 has twelve parameters and five states, making parameter estimation difficult. The strategies described always result in an approximately exponential decline of one virus population followed by the approximately exponential rise of a second virus population. The solutions of the total viral load $y_s(t) + y_r(t)$ during this time can be well approximated by the equation:

$$y(t) = y_w(0)e^{-k_w(t-\delta)} + y_r(0)e^{k_r(t-\delta)} \quad (2)$$

the plot of which is shown in Figure 1.

III. ALGORITHM

A priori estimation of the minimum location will be too imprecise. A closed-loop algorithm is necessary to find the minimum. The necessary fixed sampling rate for acceptable performance would be 1-3 days, which would be too invasive. A method to minimize the number of samples and the error in minimum-time estimation is necessary.

A. Nonlinear constrained optimization solution

Once we have three measurements, we can perform nonlinear least-squares estimation. We use the MATLAB function *fmincon*. We assume we have an initial measurement $y(0)$, and use the fact that $y(0) = y_w(0) + y_r(0)$ to reduce the unknown parameters. We are trying to find parameters $\theta = [y_w(0) k_w k_r]$ to match the sampled data, s.t. the linear constraints: $y_w(0) > 0$, $k_w > 0$, $k_r > 0$, $k_w > \alpha k_r$, $y_r(0) > y_{r0min}$. k_w is greater than k_r because the previously dominant virus was fitter. $y_r(0)$ is nonzero, else it would not emerge.

B. Closed-loop sampling criterion

In order to avoid the errors of sampling too frequently and overshooting the minimum, we implement a binary sampling algorithm. A minimum interval T_{min} and a maximum interval T_{max} are defined. After three samples, nonlinear least-squares estimation of the parameters is done and the minimum time t_{min}^* is calculated. If $t_{min}^* > t_s + T_{max}$, the next sample is taken at

$t_S + T_{max}$. If $\tilde{t}_{min} < t_S + T_{min}$, the next sample is taken at $t_S + T_{min}$. If $t_S + T_{min} < \tilde{t}_{min} < t_S + T_{max}$, the next sample is taken at $\tilde{t}_{min}$. The algorithm terminates when $\tilde{t}_{min} \geq t_S$.

For reasonable measurement noise, the number of samples needed is reduced by approximately 50% compared to a fixed 3-day interval, and maintains a ± 3 -day accuracy. Figure 2 shows three algorithm runs on a nominal parameter set with Gaussian noise. The blue curve is the actual viral load, the red circles are the measurements, and the numbered green curves are the successive estimates generated by the algorithm. The results are summarized in Table I.

IV. CONCLUSIONS AND FUTURE WORKS

We have shown that an adaptive sampling scheme allows the same accuracy in minimum-finding as a fixed-interval scheme, but with half the total number of samples. This demonstrates the feasibility of implementing the intervention described in [6].

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References

1. Perrin L, Telenti A. Hiv treatment failure: testing for hiv resistance in clinical practice. *Science*. Jun; 1998 280(5371):1871–1873. [PubMed: 9669946]
2. Ribeiro RM, Bonhoeffer S. Production of resistant hiv mutants during antiretroviral therapy. *Proc Natl Acad Sci U S A*. Jul; 2000 97(14):7681–7686. [PubMed: 10884399]
3. Zurakowski R, Wodarz D. Treatment interruptions to decrease risk of resistance emerging during therapy switching in hiv treatment. *Decision and Control, 2007 46th IEEE Conference on*. Nov. 2007 :5174–5179.
4. Luo, R.; Zurakowski, R. A new strategy to decrease risk of resistance emerging during therapy switching in hiv treatment. *Proc. American Control Conference*; 11–13 June 2008; p. 2112–2117.
5. Luo, R.; Zurakowski, R. Resistance risk management in hiv therapy switching with explicit quiescent t-cell modeling. *Proc. The International Federation of Automatic Control*; 6–11 July 2008; p. 10 325–10 330.
6. Luo R, Piovoso MJ, Zurakowski R. A generalized multi-strain model of hiv evolution with implications for drug-resistance management. *American Control Conference, 2009. ACC '09*. May. 2009 :2295–2300.

Fig. 1.
Approximate solution of viral load for minima finding

Fig. 2.
Closed-loop sampling. Arrows indicate successive estimates.

TABLE I

Parameters	Nominal	Sim 1	Sim 2	Sim 3
y_{w0}	22000	22400	22400	22400
k_w	0.067	0.064	0.060	0.063
k_r	0.025	0.037	0.032	0.035
t_{min}	44	41	46	43
$y(t_{min})$	4158	4198	4168	4164
t_{minerr}	0	3	-2	1
$y(t_{min})_{err}$	0	40	10	6
samples	15	7	8	7