A Generalized Multi-strain Model of HIV Evolution with Implications for Drug-resistance Management

Rutao Luo, Michael J. Piovoso and Ryan Zurakowski

Abstract— Since 1996, the National Institutes of Health and other organizations have recommended offering Highly Active Antiretroviral Therapy (HAART) to all patients infected with HIV. Although HAART provides a powerful strategy for HIV treatment, it does not prevent completely the development of multi-drug resistant strains, and drug resistance is the primary reason for treatment failure. A better control of drug-resistance risk is critical for the success of long-term antiviral therapy in HIV patients. Recent research focuses on how to develop new drugs, but little has been done to control resistance risk by using an appropriate treatment regime. In this paper, we propose a generalized multi-strain model of HIV evolution with viral mutations. Based on this model, we suggest a drug switching strategy to minimize resistance risk and preserve long-term control of the HIV infection for the case in which the patient only has one kind of drug-resistance virus. Though simulations, this model can also be used for detecting and minimizing the resistance risk for the patients who develops multiple drug-regimen resistance.

I. INTRODUCTION

Highly Active Antiretroviral Therapy (HAART) uses a combination of multiple antiretrovirals, chosen to interfere with different stages of the HIV life cycle. This technique is highly effective at reducing viral load and restoring immune function, and its use has drastically reduced AIDS-related deaths in the United States and other first-world nations. However, it is not without its drawbacks. The treatment must be continued for the life of the patient, as complete viral eradication cannot be achieved under current therapies. This is due to the existence of untouchable reservoirs. The primary reservoir consists of resting, or latently-infected CD4 cells with a memory phenotype [1], [2], and is established at the beginning of infection [3]. Other reservoir subtypes are also known to exist. These long-lived reservoirs provide a mechanism for virus persistence during antiretroviral therapy even when active replication is suppressed by drugs.

The mutation rate between two different strains is related to their genetic distance. The primary purpose of HAART is to increase the genetic distance to the closest viral variant through the use of multiple antiviral drugs, making drug resistance theoretically unlikely to emerge. Although a successful HAART regimen reduces the possibility of the emergence of resistant strains of the virus, it does not completely block their emergence. In fact, drug resistance affects up to 30 to 50% of all individuals being treated with HAART [4]. The possible reasons may be either a preexisting resistant strain or poor adherence to the treatment regimen [5]. The impact of drug resistance to patient health is such that the International AIDS Society-US Panel now suggests resistance testing as part of the initial comprehensive patient assessment [6] [7] [8].

The development of resistance to a particular therapy necessitates a change in regimen, and the new therapy must consist of drugs for which there is no cross-resistance with the last failing therapy. As of 2007 at least 23 drugs were available as therapy for treatment-naive patients [9]. However, the number of sequentially available combination therapies is only 6-7 due to drug cross-resistances. The biggest challenge for long term successful treatment is how to prevent and/or accommodate the emergence of drug-resistant strains without running out of treatment options [4].

In the case of a particular regimen failure, there has been significant research on how to choose a new regimen or a new form of antiviral combination, based on the probability of cross resistance between the new regimen and the failing regimen [10] [11] [12] [13]. Other research has focused on the design of an optimal sequencing of therapy to avoid resistance emergence [14]. However, little research has been done on the effect of the timing of the therapy switch relative to the possibility of resistance emerging to the new regimen. Current recommendations either suggest switching regimens as soon as resistant virus is detected, or waiting until a particular disease marker (either viral load increase in some level or CD4 T-Cell count decrease to some level) is reached [13].

The research of Bonhoeffer and Ribeiro [5], [15] show the likelihood of emergence of drug resistance to a regimen is proportional to the amount of virus present at the start of application of this regimen. Furthermore, the concentration of virus is proportional to the number of infected cells by HIV virus. Therefore, the goal of restraining the drug resistance occurrence can be achieved by minimizing the number of infected cells at the time of starting a new therapy. In 2007, Luo and Zurakowski proposed that a pattern of structured treatment interruptions using the failing regimen preceding the introduction of the new regimen can significantly decrease the risk of resistance emerging to the new regimen [16][17].

In this paper, we extend these results to a generalized multi-strain infection model. This new model attempts to

Rutao Luo is a PhD student in Electrical Engineering, University of Delaware, Newark, DE 19716, USA rutaoluo@udel.edu

Michael J. Piovoso is a Professor of Electrical Engineering, Penn State University Great Valley, 30E. Swedesford Road, Malvern, PA 19355, USA mjp5@gv.psu.edu

Ryan Zurakowski is an Assistant Professor of Electrical and Computer Engineering, University of Delaware, Newark, DE 19716, USA ryanz@udel.edu

address the following issues critical to the design of a successful optimal treatment:

1. How to represent the reservoirs' effects in the mathematical model?

2. What is the frequency of mutations among different virus strains?

3. What is the likelihood of emergence of drug resistance for a new therapy?

We develop a generalized multi-strain model in section II-B, which includes a description of the mutation process during HIV evolution. In section III, simulation results using the therapy switching strategy proposed by Luo and Zurakowski [16][17] to minimize the risk of drug resistance occurrence illustrate the model and its utility. Conclusions are drawn in the last section.

II. MATH MODEL

A. Genetic distance and mutation rate:

Predicting the rate at which certain strains of the virus give rise to new strains is a complicated problem involving the notions of mutation rate and genetic distance. Genetic distance is a measure of distance between two genetic sequences, defined as the number of mutation events necessary to change one sequence into the other. Mutation rate is the probability of a given mutation event occurring. There are a number of different kinds of mutation events, including point mutation, deletion, translocation, and inversion. Each of these has an associated mutation rate, which may not be constant. Indeed, mutation rates can be highly dependent on the particular base location in the DNA or RNA sequence. In HIV evolution, this is complicated by the fact that different viral strains may infect the same host cell, yielding recombinant virus which further increases the variability. However, it is generally accepted that point mutations are the dominant mutation type in HIV replication. The average point-mutation rate of the HIV reverse transcriptase enzyme is 3×10^{-5} mutations per base pair per replication cycle [18].

If we simplify the problem by assuming that all mutations are point mutations, and that their probability is fixed, the notion of genetic distance reduces to the classical Hamming distance between the two sequences, and the probability of one strain giving rise to another strain is $(r)^m$, where r is the mutation rate when the genetic distance is 1 and m is the genetic distance between these two strains.

B. Competition model:

In this paper we introduce an ODE model of HIV dynamics. This model depicts the interactions between a wild-type virus population sensitive to all antiviral drug regimens and any resistant mutant virus population only sensitive to treatment with some, if any, antiviral drug combinations. We model the generation of new strains through mutation as well.

$$
\begin{aligned}
\dot{x} &= \lambda - dx - \sum_{0 \le j \le n} \beta_j x y_j (\prod_{0 \le i \le n} (1 - \xi_{j,i} u_i)) \\
\dot{y}_0 &= \beta_0 (1 - f_0)(\prod_{0 \le i \le n} (1 - \xi_{0,i} u_i)) x y_0 + \sum_{i \ne 0} (r)^{m_{0,i}} y_i \\
&\quad + \alpha_0 l_0 - a_0 y_0 \\
\dot{y}_1 &= \beta_1 (1 - f_1)(\prod_{0 \le i \le n} (1 - \xi_{1,i} u_i)) x y_1 + \sum_{i \ne 1} (r)^{m_{1,i}} y_i \\
&\quad + \alpha_1 l_1 - a_1 y_1 \\
\dot{y}_2 &= \beta_2 (1 - f_2)(\prod_{0 \le i \le n} (1 - \xi_{2,i} u_i)) x y_2 + \sum_{i \ne 2} (r)^{m_{2,i}} y_i \\
&\quad + \alpha_2 l_2 - a_2 y_2 \\
&\cdots\cdots \\
&\cdots\cdots \\
&\cdots\cdots \\
\dot{y}_n &= \beta_n (1 - f_n)(\prod_{0 \le i \le n} (1 - \xi_{n,i} u_i)) x y_n + \sum_{i \ne n} (r)^{m_{n,i}} y_i \\
&\quad + \alpha_n l_n - a_n y_n \\
\dot{l}_0 &= \beta_0 f_0 (\prod_{0 \le i \le n} (1 - \xi_{0,i} u_i)) x y_0 + r_0 l_0 - \alpha_0 l_0 \\
\dot{l}_1 &= \beta_1 f_1 (\prod_{0 \le i \le n} (1 - \xi_{1,i} u_i)) x y_1 + r_1 l_1 - \alpha_1 l_1 \\
\dot{l}_2 &= \beta_2 f_2 (\prod_{0 \le i \le n} (1 - \xi_{2,i} u_i)) x y_2 + r_2 l_2 - \alpha_2 l_2 \\
&\cdots\cdots \\
&\cdots\cdots \\
&\cdots\cdots \\
\dot{l}_n &= \beta_n f_n (\prod_{0 \le i \le n} (1 - \xi_{n,i} u_i)) x y_n + r_n l_n - \alpha_n l_n
\end{aligned}
\tag{1}
$$

This model includes x representing CD4+ T cells that are susceptible to infection, y_i, CD4+ T cells infected by the ith type of virus and l_i, the long-live reservoir of y_i.

CD4+ T cells are generated from their source at rate λ and disappear at rate d. The target cells are infected by j^{th} kind of virus at rate of β_i and the therapy suppresses the infection by the jth type of virus with efficacy $\xi_{i,j} u_i$, where $\xi_{i,j}$ is the effective fact of the ith type multidrug antiviral regimen on the jth type of virus and u_i is the drug efficacy of the ith type multidrug antiviral regimen.

The infected CD4+ cells y_i are created by the infection from target cells x, the mutation from any other virus at rate $(r)^{m_{i,j}}$ and the activation from long-live reservoirs at rate α_i. And then, they die with a rate of a_i.

The long-live reservoirs l_i are produced by a fraction f_i of the infected CD4+ cells y_i. Their net regeneration rate is r_i and they are activated into y_i at rate of α_i.

C. Model simplification:

To simplify the problem and from the simulation results of [16][17], the influence of long-live reservoirs on the each kind of infected CD4+ cells y_i is replaced by a constant λ_i. The reason is that compared with the changing of virus infection, the fluctuation of reservoirs is much slower and smaller. The validity of this reduction has been verified through simulation [16][17]. Therefore, the original math

model is reduced as follows:

$$
\begin{aligned}
\dot{x} &= \lambda - dx - \sum_{0 \le j \le n} \beta_j x y_j \left(\prod_{0 \le i \le n} (1 - \xi_{j,i} u_i) \right) \\
\dot{y}_0 &= \beta_0 \left(\prod_{0 \le i \le n} (1 - \xi_{0,i} u_i) \right) x y_0 \\
&\quad + \sum_{i \ne 0} (r)^{m_{0,i}} y_i + \lambda_0 - a_0 y_0 \\
\dot{y}_1 &= \beta_1 \left(\prod_{0 \le i \le n} (1 - \xi_{1,i} u_i) \right) x y_1 \\
&\quad + \sum_{i \ne 1} (r)^{m_{1,i}} y_i + \lambda_1 - a_1 y_1 \\
\dot{y}_2 &= \beta_2 \left(\prod_{0 \le i \le n} (1 - \xi_{2,i} u_i) \right) x y_2 \qquad (2) \\
&\quad + \sum_{i \ne 2} (r)^{m_{2,i}} y_i + \lambda_2 - a_2 y_2 \\
&\quad \cdots \cdots \\
&\quad \cdots \cdots \\
&\quad \cdots \cdots \\
\dot{y}_n &= \beta_n \left(\prod_{0 \le i \le n} (1 - \xi_{n,i} u_i) \right) x y_n \\
&\quad + \sum_{i \ne n} (r)^{m_{n,i}} y_i + \lambda_n - a_n y_n
\end{aligned}
$$

Table I shows the definition of each symbol in the simplified model.

TABLE I
THE DEFINITION OF EACH SYMBOL IN MODEL 2

Symbol	Definition
x	CD4+ T cells that are susceptible to infection (target cells)
y_0	The CD4+ T cells infected by wide-type virus
y_i	The CD4+ T cells infected by the ith type of drug-resistant virus
d	The Natural death rate of target cells
λ	The generation rate of target cells
β_0	The infection rates of wild-type virus
β_i	The infection rates of the ith type of drug-resistant virus
$\xi_{i,j}$	The effective fact of the ith type multidrug antiviral regimen on the jth type of virus
u_i	The drug efficacy of the ith type multidrug antiviral regimen
a_0	The death rates of cells infected by wild-type virus
a_i	The death rates of cells infected by the ith type of drug-resistant virus
r	Unit mutation probability
$m_{i,j}$	The genetic distance between the ith type of virus and the jth type of virus
λ_0	The generation rate of wild-type virus from long-lived reservoirs
λ_i	The generation rate of the ith type of drug-resistant virus from long-lived reservoirs

D. Switching Strategy

Normally, at the beginning of antiretroviral treatment, the amount of HIV in patients' body goes down dramatically. The reason for this is most of the virus is wild-type, broadly sensitive to antiretroviral treatment. When treatment begins, viruses with certain mutations have a survival advantage. The drug cannot stop these kinds of viruses from reproducing.

Drug-resistant virus will become the dominant strain over time. It has been shown that for any sufficiently potent antiviral therapy, the number of mutation events occurring after the start of anti-viral therapy is insignificant compared to the genetic diversity present at the start of anti-viral therapy. The reason is that the therapy reduces the chance of mutation by lowering the virus reproduction rate. Therefore, the risk of resistance emerging to a new regimen is proportional to the amount of virus present at the start of application of this regimen [5], [15].
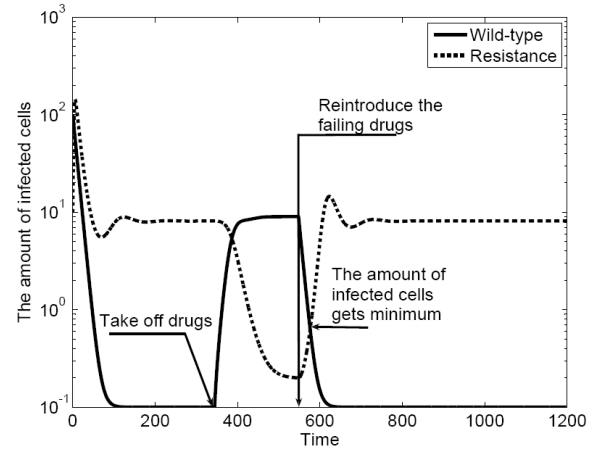

Fig. 1. **Dynamics of infected cells by using our drug-switch strategy**

Our objective is to find a drug-switching schedule that yields the minimum total amount of infected cells for starting a new regimen, reducing the risk of resistance emerging. We use the simplest model to explain how this strategy works(3).

$$
\begin{aligned}
\dot{x} &= \lambda - dx - \beta_w (1 - u_1)(1 - u_2) x y_w \\
&\quad - \beta_r (1 - u_2) x y_r \\
\dot{y}_w &= \beta_w (1 - u_1)(1 - u_2) x y_w - a_w y_w + \lambda_w \qquad (3) \\
\dot{y}_r &= \beta_r (1 - u_2) x y_r - a_r y_r + \lambda_r
\end{aligned}
$$

where y_w are those cells infected by wide-type virus and y_r are the cells infected by resistant virus. u_1 and u_2 represent the drug efficacies. When the first drug combination is failing, the system approaches a new steady state (see Fig.1). Notice that wild-type virus outcompetes resistant virus in the absence of suppressive therapy. Therefore, if the patient is taken off the drugs, the wild-type virus will grow exponentially and the resistant virus will decay exponentially. Our strategy is to reintroduce the failing drugs at a time which results in the smallest number of all infected cells (both wild-type and resistant) as shown in Fig.1. A new regimen started at this time minimizes the risk of resistance emergence because the total viral load is minimized.

III. SIMULATION

This section consists of two subsections. The first subsection illustrates how to find the optimal treatment schedule for a patient who has a single previously failed regimen. In the second subsection, several cases illustrate minimizing the

resistance risk for patients who have failed one or more drug regimens.

A. One Previously Failed Regimen:

Initially, we use a simple model. This model is an ordinary differential equation describing the interactions between a wild-type virus population sensitive to treatment with both the original antiviral regimen u_1 and a new antiviral regimen u_2, and a resistant mutant virus population, sensitive only to treatment with the new antiviral regiman u_2. It takes the form:

$$
\begin{aligned}
\dot{x} &= \lambda - dx - \beta_w(1-u_1)(1-u_2)xy_w \\
&\quad -\beta_r(1-u_2)xy_r \\
\dot{y_w} &= \beta_w(1-u_1)(1-u_2)xy_w + ry_r - a_wy_w + \lambda_w \\
\dot{y_r} &= \beta_r(1-u_2)xy_r + ry_w - a_ry_r + \lambda_r
\end{aligned} \quad (4)
$$

The values of u_1, u_2, are applied 0 or 1 during the simulation. We do not apply the both regimens at the same time because of the excessive toxicity. We show how to find the optimal treatment schedule for this patient based on the switch strategy stated above. In the following figures, T1 represents the time for waiting before the failing therapy is reintroduced; T2 represents the time to get the minimum resistance risk after the failing therapy is reintroduced; M point means the moment for getting the minimum resistance risk.

Case I: Resistant strain has the same properties with wild-type strain except the infection rates ($\beta_w = 0.01$, $\beta_r = 0.005$) and the death rate ($a_w = 0.1$, $a_r = 0.3$). Parameter values: $\lambda = 1$, $\lambda_w = 0.01$, $\lambda_r = 0.01$, $d = 0.01$, $\beta_w = 0.01$, $\beta_r = 0.005$, $a_w = 0.1$, $a_r = 0.3$. The simulation results are shown in Fig.2 and Fig.3.
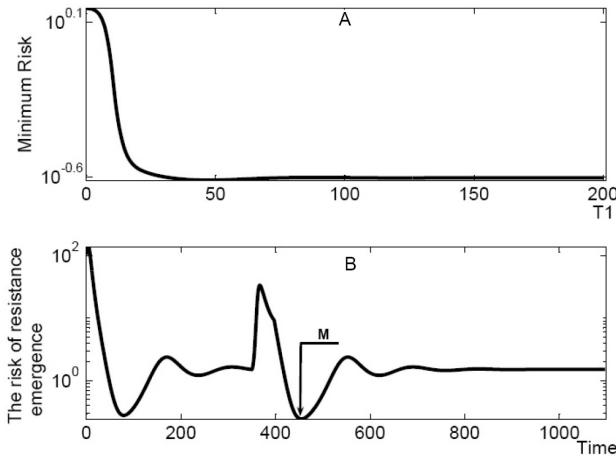

Fig. 2. **(A) Minimum Risk vs. T1; (B) The dynamics of total amount of infected cells by reintroducing the failing therapy**

Fig.2(A) gives us the following important information: for this case, we can control the minimum resistance risk by manipulating how long we wait before reintroducing the failing therapy (T1). In this case, because the death rate of the cells infected by resistant virus is larger than that of the cells infected by wild-type virus, after the patient takes off the therapy, the increasing rate of the cells infected by wild-type
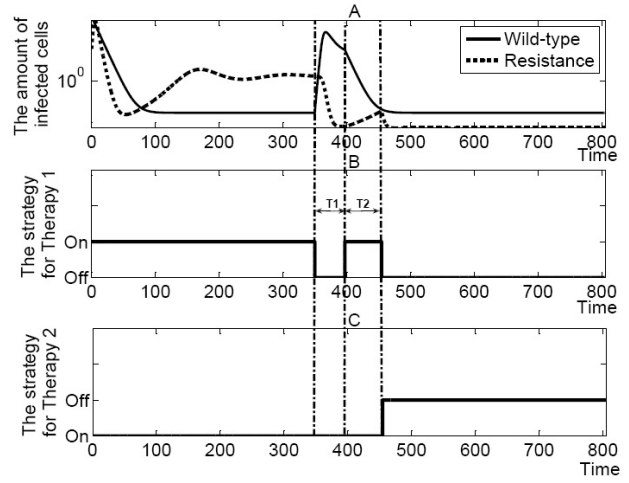

Fig. 3. **(A) The dynamics of infected cells under our strategy; (B) The schedule of therapy 1; (C) The schedule of therapy 2;**

virus and the decay rate of the cells infected by resistant virus are almost in the same level. The minimum total amount of infected cells occurs before the system reaches its steady state.

Fig.2(B) illustrates that after we reintroduce the failing therapy, there is a minimum value for the total amount of infected cells, which means if new therapy is introduced at this moment, we minimize the risk for resistance emerging to the new therapy. We can manipulate the size of this this minimum according to how long we wait before reintroducing our failing therapy.

B. Multiple Previously Failed Regimens:

In the case of patients who have failed one or more drug regimens previously, the need to preserve the remaining regimens becomes all the more important. Interestingly, the previously failed regimens provide us additional control inputs which can be used to achieve our goal of reduced risk of failure for the new regimen at a lower systemic cost than in the case where we have only one failing regimen to use. Consider a variation of the following model, which includes three viral strains:

$$
\begin{aligned}
\dot{x} &= \lambda - dx - \beta_0(1-u_0)(1-u_1)(1-u_2)xy_0 \\
&\quad -\beta_1(1-u_1)(1-u_2)xy_1 - \beta_2(1-u_2)xy_2 \\
\dot{y_0} &= \beta_0(1-u_0)(1-u_1)(1-u_2)xy_0 + (r)^{m_{0,1}}y_1 \\
&\quad +(r)^{m_{0,2}}y_2 + \lambda_0 - a_0y_0 \\
\dot{y_1} &= \beta_1(1-u_1)(1-u_2)xy_1 + (r)^{m_{1,0}}y_0 \\
&\quad +(r)^{m_{1,2}}y_2 + \lambda_1 - a_1y_1 \\
\dot{y_2} &= \beta_2(1-u_2)xy_2 + (r)^{m_{2,0}}y_0 \\
&\quad +(r)^{m_{2,1}}y_1 + \lambda_2 - a_2y_2
\end{aligned} \quad (5)
$$

In this model, a wild-type virus population is sensitive to all regimens: u_0, u_1 and u_3; the first resistant mutant is sensitive to regimens: u_2 and u_3; the second resistant mutant is only sensitive to regimen 3. Similarly in section III-A, because of the excessive toxicity, we only apply one regimen at the one time. The values of other parameters will be given. In the

following two cases, we emphasize how to use the multiple resistant-strain model to minimize the risk of drug resistance.

Case I: Parameter values: $\beta_0 = 0.01$, $\beta_1 = 0.01$, $\beta_2 = 0.01$, $\lambda = 1$, $\lambda_0 = 0.01$, $\lambda_1 = 0.01$, $\lambda_2 = 0.01$, $d = 0.01$, $a_0 = 0.1$, $a_1 = 0.1$, $a_2 = 0.3$. Treatment strategy: there are 3 available regimens and their drug efficacies are represented by u_0, u_1, and u_2 respectively. When regimen 1 is found to be failing, the patient is taken off all drugs (at time a) and some time later reintroducing regimen 1(at time b). Still later, regimen 2 is begun (at time c). When regimen 2 starts to fail, regimen 3 is applied (at time d). The optimization goal is to determine the switching times to minimize the risk of resistance emergence at point T by minimizing the total viral load. The simulation results are shown in Fig.4 and Fig.5 illustrates the dynamics.
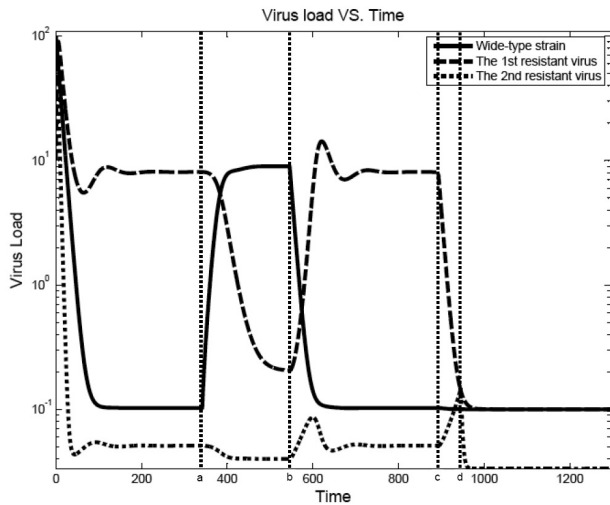
Case II: Parameter values: All values are the same as those in case I; Treatment strategy: All schemes are the same as that in case I except that we use regimen 2 to replace regimen 1 as the failing therapy which is reintroduced. The sequencing of this treatment is: at time a, switch regimen 1 to regimen 2; at time b, take off regimen 2; at time c, reintroduce regimen 2; at time d, apply regimen 3. The simulation results for case II are shown in Fig.6 and Fig.7.

Fig. 6.   **The relationship between each virus load and treatment time**

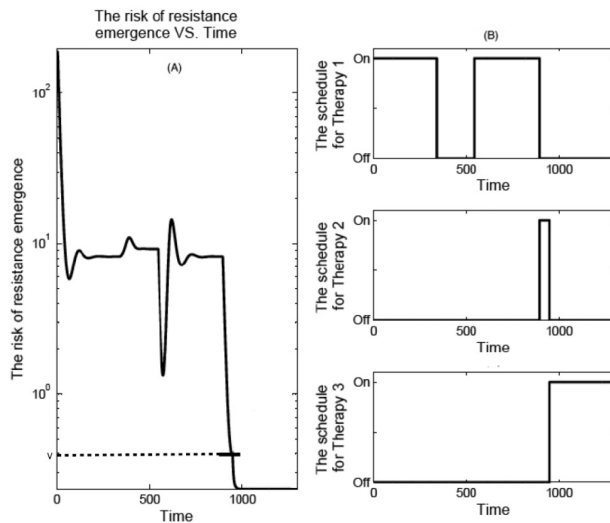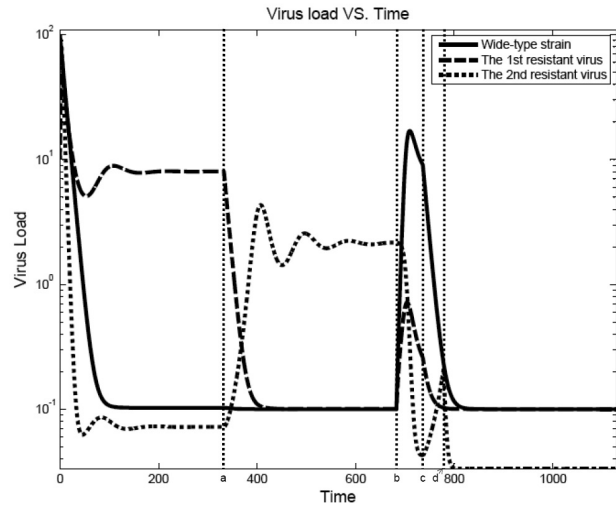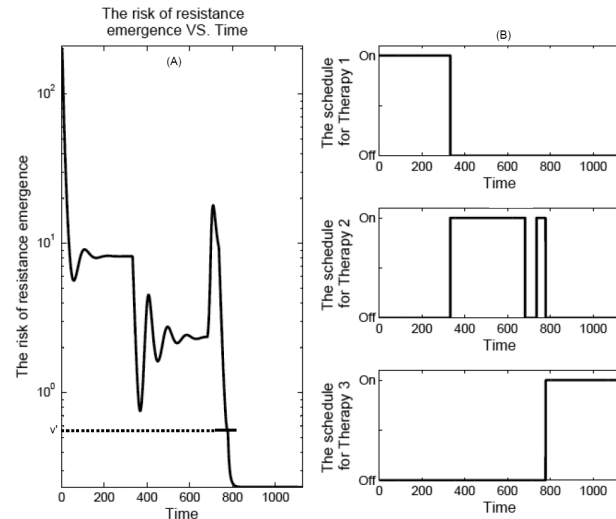Fig. 4.   **The relationship between each virus load and treatment time**

Fig. 7.   **(A) The relationship between resistance emergence risk and treatment time; (B) The schedule of therapy 1, therapy 2 and therapy 3**

For patients who have failed one or more drug regimens previously, our goal is to minimize the likelihood of resistance emergence at the time of applying the last regimen (Here is regimen 3). Therefore, observe from Fig.5 and Fig.7 that for the patient in case I and case II, the first treatment switching strategy is more advantageous than the second strategy because the value of v (the resistance emergence

Fig. 5.   **(A) The relationship between resistance emergence risk and treatment time; (B) The schedule of therapy 1, therapy 2 and therapy 3**

risk) in Fig.5 is smaller than that of v' Fig.7. In the same manner, it is not difficult to know for this patient, the first treatment strategy can create a better moment for introducing the last available regimen. Therefore, from the simulation results, we find that this model not only can be used to find a good schedule for a fixed treatment, but also can be used to evaluate the performance of different therapy-switching strategies.

IV. CONCLUSIONS AND FUTURE WORKS

A. Conclusions

In this paper, we propose a generalized mathematical model to describe HIV dynamics, which include some items to represent the mutation among different virus strain. Combining this model with our treatment switching strategy, we not only can find the best time for reintroducing the failing therapy to obtain the minimum resistance risk for a particular treatment scheme, but also are able to find the best treatment plan from all available treatment schemes for a patient based on the resistance risk. Furthermore, the previously failed regimens provide another manipulation variable which can be used for optimizing the likelihood of resistance emergence.

This paper introduces an arbitrary scaling of the number of resistant strains and allows strain-strain mutation events. We have also shown that the notion of resistance management introduced in previous papers scales well to increasing numbers of previously failed treatments; indeed, the achievable performance benefits from this situation. Also, we have shown that the notion is robust to genetic drift between species, and that it is possible to consider this drift while choosing optimal therapy switching schedules.

B. Future Works

In order to implement the treatment approach described in this paper, we will need to be able to better anticipate the evolutionary effects of our drug choices. Therefore, in the future, we will develop predictive stochastic models of HIV genetic distribution. We will also using data from two studies provided by our collaborator, Dr. Martinez-Picado, to identify reasonable parameter ranges and distributions for our mathematical models of HIV quasispecies competition. Implementation issues also involve robustness to model uncertainty, event detection, and minimum sampling. We are exploring solutions to these problems as well.

REFERENCES

[1] T. W. Chun, L. Carruth, D. Finzi, X. Shen, J. A. DiGiuseppe, H. Taylor, M. Hermankova, K. Chadwick, J. Margolick, T. C. Quinn, Y. H. Kuo, R. Brookmeyer, M. A. Zeiger, P. Barditch-Crovo, and R. F. Siliciano, "Quantification of latent tissue reservoirs and total body viral load in hiv-1 infection." *Nature*, vol. 387, no. 6629, pp. 183–188, May 1997. [Online]. Available: http://dx.doi.org/10.1038/387183a0

[2] T. Pierson, T. L. Hoffman, J. Blankson, D. Finzi, K. Chadwick, J. B. Margolick, C. Buck, J. D. Siliciano, R. W. Doms, and R. F. Siliciano, "Characterization of chemokine receptor utilization of viruses in the latent reservoir for human immunodeficiency virus type 1." *J Virol*, vol. 74, no. 17, pp. 7824–7833, Sep 2000.

[3] D. Finzi, M. Hermankova, T. Pierson, L. M. Carruth, C. Buck, R. E. Chaisson, T. C. Quinn, K. Chadwick, J. Margolick, R. Brookmeyer, J. Gallant, M. Markowitz, D. D. Ho, D. D. Richman, and R. F. Siliciano, "Identification of a reservoir for hiv-1 in patients on highly active antiretroviral therapy." *Science*, vol. 278, no. 5341, pp. 1295–1300, Nov 1997.

[4] L. Perrin and A. Telenti, "Hiv treatment failure: testing for hiv resistance in clinical practice." *Science*, vol. 280, no. 5371, pp. 1871–1873, Jun 1998.

[5] S. Bonhoeffer and M. A. Nowak, "Pre-existence and emergence of drug resistance in hiv-1 infection." *Proc Biol Sci*, vol. 264, no. 1382, pp. 631–637, May 1997. [Online]. Available: http://dx.doi.org/10.1098/rspb.1997.0089

[6] M. S. Hirsch, F. Brun-Vzinet, R. T. D'Aquila, S. M. Hammer, V. A. Johnson, D. R. Kuritzkes, C. Loveday, J. W. Mellors, B. Clotet, B. Conway, L. M. Demeter, S. Vella, D. M. Jacobsen, and D. D. Richman, "Antiretroviral drug resistance testing in adult hiv-1 infection: recommendations of an international aids society-usa panel." *JAMA*, vol. 283, no. 18, pp. 2417–2426, May 2000.

[7] M. S. Hirsch, F. Brun-Vzinet, B. Clotet, B. Conway, D. R. Kuritzkes, R. T. D'Aquila, L. M. Demeter, S. M. Hammer, V. A. Johnson, C. Loveday, J. W. Mellors, D. M. Jacobsen, and D. D. Richman, "Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an international aids society-usa panel." *Clin Infect Dis*, vol. 37, no. 1, pp. 113–128, Jul 2003.

[8] M. S. Hirsch, H. F. Gnthard, J. M. Schapiro, F. Brun-Vzinet, B. Clotet, S. M. Hammer, V. A. Johnson, D. R. Kuritzkes, J. W. Mellors, D. Pillay, P. G. Yeni, D. M. Jacobsen, and D. D. Richman, "Antiretroviral drug resistance testing in adult hiv-1 infection: 2008 recommendations of an international aids society-usa panel." *Clin Infect Dis*, vol. 47, no. 2, pp. 266–285, Jul 2008. [Online]. Available: http://dx.doi.org/10.1086/589297

[9] S. Orsega, "Treatment of adult hiv infection: Antiretroviral update and overview," *The Journal for Nurse Practitioners*, vol. 3, no. 9, pp. 612–624, 2007.

[10] W. F. Mangel, W. J. McGrath, M. T. Brown, M. L. Baniecki, D. L. Barnard, and Y. P. Pang, "A new form of antiviral combination therapy predicted to prevent resistance from arising, and a model system to test it." *Curr Med Chem*, vol. 8, no. 8, pp. 933–939, Jul 2001.

[11] P. G. Yeni, S. M. Hammer, C. C. J. Carpenter, D. A. Cooper, M. A. Fischl, J. M. Gatell, B. G. Gazzard, M. S. Hirsch, D. M. Jacobsen, D. A. Katzenstein, J. S. G. Montaner, D. D. Richman, M. S. Saag, M. Schechter, R. T. Schooley, M. A. Thompson, S. Vella, and P. A. Volberding, "Antiretroviral treatment for adult hiv infection in 2002: updated recommendations of the international aids society-usa panel." *JAMA*, vol. 288, no. 2, pp. 222–235, Jul 2002.

[12] P. G. Yeni, S. M. Hammer, M. S. Hirsch, M. S. Saag, M. Schechter, C. C. J. Carpenter, M. A. Fischl, J. M. Gatell, B. G. Gazzard, D. M. Jacobsen, D. A. Katzenstein, J. S. G. Montaner, D. D. Richman, R. T. Schooley, M. A. Thompson, S. Vella, and P. A. Volberding, "Treatment for adult hiv infection: 2004 recommendations of the international aids society-usa panel." *JAMA*, vol. 292, no. 2, pp. 251–265, Jul 2004. [Online]. Available: http://dx.doi.org/10.1001/jama.292.2.251

[13] S. M. Hammer, M. S. Saag, M. Schechter, J. S. G. Montaner, R. T. Schooley, D. M. Jacobsen, M. A. Thompson, C. C. J. Carpenter, M. A. Fischl, B. G. Gazzard, J. M. Gatell, M. S. Hirsch, D. A. Katzenstein, D. D. Richman, S. Vella, P. G. Yeni, P. A. Volberding, and I. A. S.-U. panel, "Treatment for adult hiv infection: 2006 recommendations of the international aids society-usa panel." *JAMA*, vol. 296, no. 7, pp. 827–843, Aug 2006.

[14] J. L. Martinez-Cajas and M. A. Wainberg, "Antiretroviral therapy : optimal sequencing of therapy to avoid resistance." *Drugs*, vol. 68, no. 1, pp. 43–72, 2008.

[15] R. M. Ribeiro and S. Bonhoeffer, "Production of resistant hiv mutants during antiretroviral therapy." *Proc Natl Acad Sci U S A*, vol. 97, no. 14, pp. 7681–7686, Jul 2000.

[16] R. Luo and R. Zurakowski, "A new strategy to decrease risk of resistance emerging during therapy switching in hiv treatment," in *Proc. American Control Conference*, 11–13 June 2008, pp. 2112–2117.

[17] ——, "Resistance risk management in hiv therapy switching with explicit quiescent t-cell modeling," in *Proc. The International Federation of Automatic Control*, 6–11 July 2008, pp. 10 325–10 330.

[18] R. M. Martin A. Nowak, *Virus dynamics: Mathematical principles of immunology and virology*. Oxford University Press, USA, 2001.