

CONTROLLABILITY ANALYSIS OF THE CHEMOTHERAPY OF HIV/AIDS

A.M. Jeffrey, X. Xia and I.K. Craig

*Department of Electrical, Electronic and Computer Engineering,
University of Pretoria, Pretoria 0002, South Africa,
e-mail: {mjjeffrey, xxia, icraig}@postino.up.ac.za.*

Abstract: Using mathematical models that show the host-pathogen interaction of the immune system with the HIV virus, this paper identifies the extent to which the stages in the progression of HIV/AIDS are controllable, given that the available treatment strategies are constrained. These constraints are the imperfect inhibition of the replication of the virus by the available drugs, undesirable side effects and the ability of the virus to become resistant to drugs. This paper shows how controllability analysis can be applied to HIV/AIDS models to identify stages where therapy initiation can benefit the patient more. ©2002 IFAC

Keywords: Controllability analysis, chemotherapy, HIV, biomedical, treatment.

1. INTRODUCTION

Mathematical models that describe the interaction between the immune system and HIV have been developed and explained in (Perelson and Nelson, 1999; Kirschner, Lenhart and Serbin, 1997; Kirschner and Webb, 1996; Kirschner and Webb, 1997; Nowak and May, 2000; Hraba, Dolezal and Celikovsky, 1990). Modeling has substantially assisted in understanding the virus and immune system dynamics and with formulating therapy schedules for infected persons. None of these models however, can account for the full course of the disease. The main reason for the models' limitation is lack of a good understanding of the immunology of the human body against HIV. The accuracy of the models though, is increasing with new medical discoveries (Kirschner, Webb and Cloyd, 2000).

HIV chemotherapy is initiated either in the asymptomatic stage, termed early therapy or in the advanced stage and referred to as late therapy. The objective is to prolong the life of the infected person by suppressing the viral load and maintaining an acceptable T cell count. The issues of when

best to initiate therapy and the necessary dosage have been studied by (Perelson, Kirschner and De Boer, 1993; Kirschner and Webb, 1996; Concord, 1994). Some authors, (e.g. (Kirschner and Webb, 1996)) believe that early therapy, when the T cell count is still high is best, while some (Concord, 1994) believe late therapy during the final decline of the T cells is best. Not much consideration however, has been paid to initiating therapy in the early days of infection.

The application of control theory to HIV dynamics has been explored from an optimal control point of view in (Kirschner, Lenhart and Serbin, 1997; Wein, Zenios and Nowak, 1997; Felipe de Souza, Caetano and Yoneyama, 2000). (Alvarez-Ramirez, Meraz and Velasco-Hernandez, 2000) adopted a feedback control point of view. Most of these works are aimed at controlling the plasma viral load of infected persons, and this paper adds to them by determining the extent to which the virus is controllable using controllability analysis. Measures of controllability are standard issues in control system theory (Ming, 2000). Some aspects of controllability of HIV/AIDS however, have only

been touched upon heuristically by most of the above mentioned works.

This paper deals specifically with identifying the stages of the disease progression that are more controllable than others. Analysis will be done from the day of initial infection to the advanced stages. The question to be addressed is; if some stages are more controllable than other stages and given the constraints on treatment strategies, when then would it be best to initiate therapy and how strong should the dosage be? The authors of this paper believe that therapy is best initiated at the stage when the viral load is easier to control. An easier to control viral load implies less control effort in the form of lower drug doses. Lower drug doses in turn imply that therapy can be administered and be effective with milder side effects over a longer period of time. Simulations will be used to demonstrate the effect on the viral load of initiating therapy at various stages.

2. THE WORKING MODEL

The model as presented by (Kirschner, Lenhart and Serbin, 1997) was adopted for this paper and the following is a summary of that model.

$$\dot{x}_1 = s + \phi(x_1) - dx_1 - kx_1x_3 \quad (1)$$

$$\dot{x}_2 = kx_1x_3 - \delta x_2 \quad (2)$$

$$\dot{x}_3 = N\delta x_2 - cx_3 \quad (3)$$

where $\phi(x_1) = px_1(1 - x_1/T_m)$. The state variables x_1, x_2 and x_3 are the plasma concentrations of the uninfected CD4+ T cells, the infected CD4+ T cells and the free virus particles respectively. Equation (1) describes the population dynamics of the uninfected CD4+ T cells. It shows that they are produced from a source at a constant rate s and proliferate to a maximum given by T_m , at a rate that is proportional to their abundance, with p as the proliferation constant. Uninfected CD4+ T cells die at a rate d and are infected by the virus at a rate that is proportional to the product of their abundance and the amount of free virus particles. The proportionality constant k is an indication of the effectiveness of the infection process. Equation (2) describes the population dynamics of the infected CD4+ T cells and shows that infection of healthy CD4+ T cells produces infected CD4+ T cells that die at a rate δ . Equation (3) similarly describes the population dynamics of the free virus particles, which are also known as virions. It can be seen that an infected CD4+ T cell produces N free virus particles when it bursts. The free virus particles die at a rate c .

Estimates are available for the parameters described above in (Wein, Zenios and Nowak, 1997;

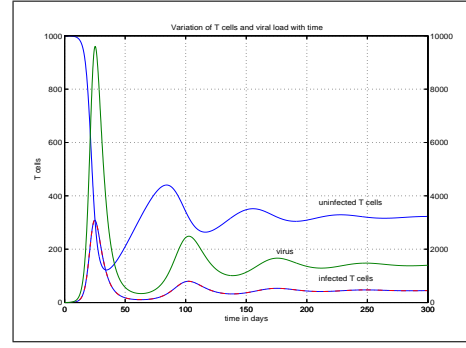


Fig. 1. Variation of T cells and viral load.

Kirschner, Lenhart and Serbin, 1997; Nowak and May, 2000; Kirschner and Webb, 1996; Perelson and Nelson, 1999) Online estimates obtained by using control techniques can be found in (Xia, 2001). For this paper, the estimates used are in Table 1 and are as presented in (Kirschner, Lenhart and Serbin, 1997). The conclusions drawn for this paper however, are not parameter dependent.

Table 1: Parameter estimations

s	$10mm^{-3}d^{-1}$	k	$2.4 \times 10^{-5}mm^{-3}d^{-1}$
p	$0.03d^{-1}$	δ	$0.24d^{-1}$
T_m	$1500mm^{-3}$	N	1200 counts cell ⁻¹
d	$0.02d^{-1}$	c	$2.4d^{-1}$

Figure 1 shows how the plasma concentrations of the uninfected CD4+ T cell, infected CD4+ T cell and free virus particles vary with time from initial infection.

The uninfected CD4+ T cell concentration declines rapidly from an initial uninfected steady state value of $1000mm^{-3}$ of plasma and eventually settles in damped oscillations to an infected steady state. The virus profile shows a very sharp initial increase to a very high peak value of over 10,000 particles mm^{-3} of plasma and eventually settles, also in damped oscillations to a steady state value that is much lower than the peak value. The infected CD4+ T cell profile is similar to that of the free virus particles. The stage from initial infection to before the viral load settles is known as the acute infection or pre-asymptomatic stage. This stage is characterized by fever like symptoms. The stage when the viral load has settled is known as the asymptomatic or latent stage and can last for up to 10 years with the patient showing no symptoms of the disease. The limitation of this model as stated before, is that it does not account for the later stages of the disease when the CD4+ T cell count does go down to zero and the associated rapid increase in the viral load. This later or advanced stage of the disease is when the patient is said to have AIDS.

Therapy is initiated in an attempt to maintain the viral load and CD4+ T cell counts at ac-

ceptable levels and it entails using drugs that inhibit the growth of virus particles. The commonly used drugs are Reverse Transcriptase –RT Inhibitors and Protease Inhibitors. Refer to for example, (Perelson and Nelson, 1999; McLeod and Hammer, 1992) on which model parameters are affected by therapy. RT Inhibitors block infection by reducing the constant k . Perfect inhibition occurs when $k = 0$. In practice however, perfect inhibition is not attainable.

Equations (1 –3) under imperfect RT Inhibitors can be modified to

$$\dot{x}_1 = s + \phi(x_1) - dx_1 - u_1 k x_1 x_3 \quad (4)$$

$$\dot{x}_2 = u_1 k x_1 x_3 - \delta x_2 \quad (5)$$

$$\dot{x}_3 = N \delta x_2 - c x_3 \quad (6)$$

where $u_1 = 1 - \eta_{RT}$ is the control law and $0 \leq \eta_{RT} \leq 1$, and therefore, $0 < u_1 \leq 1$. Perfect inhibition occurs therefore when $\eta_{RT} = 1$ and there is no inhibition when $\eta_{RT} = 0$.

Some authors (McLeod and Hammer, 1992; Kirschner, Lenhart and Serbin, 1997; Alvarez-Ramirez, Meraz and Velasco-Hernandez, 2000) assume that the control variable represents the percentage effect of the chemotherapy on viral production, and the effect of inverse transcriptase inhibitors and protease inhibitors can be lumped into the parameter N . The controllability study of this control model as well as the model of combined chemotherapy will be presented elsewhere.

3. CONTROLLABILITY ANALYSIS

3.1 Admissible Controls

Controllability analysis can be applied to the above HIV models to determine the stages when effective therapy can be initiated or when initiating therapy will not be beneficial. It can also be used to identify stages of the disease progression that are more controllable than others. Controllability analysis is essential because if the initial condition of interest lies outside the controllable region, then there is no point in designing a controller, unless of course if the capabilities of the system are modified so that the initial condition of interest is included. HIV therapy schemes have a lot of constraints. These constraints are due to the fact that available drugs are not perfect inhibitors, the drugs have undesirable side effects on the patients like nausea and diarrhea and the virus has the ability to mutate and effectively become immune to the drugs. The control law in use should therefore take these constraints into consideration since the models used above do not, apart for imperfect inhibition, take them into consideration. Another point to consider is that these

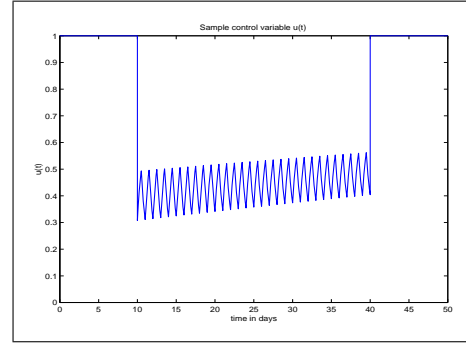


Fig. 2. Sample control variable $u(t)$.

drugs are administered periodically. In this paper, it is assumed that the interval between doses is constant and that the drug potency from the dosing time rises then decreases exponentially with time. The drug is usually effective until the time when resistance emerges and the effectiveness η , can also be assumed to decline exponentially with time. The decay time constant for the effectiveness η are drug and dosage dependant and it has been shown by (Perelson and Nelson, 1999) that large drug doses lead to early emergence of resistance. The admissible control for the chemotherapy of HIV in this paper is therefore an oscillatory and decaying function of time that can be represented as

$$u(t) = \begin{cases} 1 & t < t_i, t > t_f \\ 1 - \eta(t) & t_1 \leq t \leq t_f \end{cases} \quad (7)$$

where t_i is the time from initial infection to when therapy is initiated and t_f is when therapy is ended. Figure 2 shows a sample control variable $u(t)$ for when therapy is on for 30 days from day 10 to 40.

3.2 Controllability of HIV

For this paper, the variable to be controlled is the viral load. The viral load is considered to be controllable if the control law in use can reduce it by 90% from the time treatment is initiated in 8 weeks and continue to suppress it to below 50 copies per milliliter of plasma in 6 months.

The Jacobians for equations (4–6) when evaluated at an operating point x^0 are given by

$$A_{RT} = \begin{bmatrix} \alpha & 0 & -u_1 k x_1^0 \\ u_1 k x_3^0 & -\delta & u_1 k x_1^0 \\ 0 & N \delta & -c \end{bmatrix}$$

$$B_{RT} = k x_1^0 x_3^0 \begin{bmatrix} -1 \\ 1 \\ 0 \end{bmatrix}$$

where $\alpha = p(1 - 2x_1^0/T_m) - d - u_1 k x_3^0$. The controllability matrix M_{RT} is

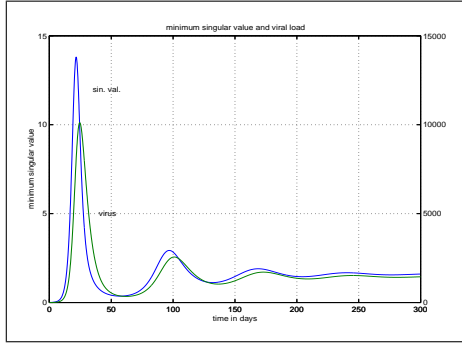


Fig. 3. Minimum singular value and viral load.

$$kx_1^0 x_3^0 \begin{bmatrix} -1 & -\alpha & -\alpha^2 - N\delta u_1 k x_1^0 \\ 1 & -(u_1 k x_3^0 + \delta) & \beta \\ 0 & N\delta & -N\delta(u_1 k x_3^0 + \delta + c) \end{bmatrix}$$

where $\beta = -u_1 k x_3^0 \alpha + \delta(u_1 k x_3^0 + \delta) + N\delta u_1 k x_1^0$.

The matrix M_{RT} is singular only when the viral load x_3 is zero or when the T cell count x_1 is zero. A zero viral load is invalid since the patient is assumed to be actively infected. The singular point when the T cell count is zero implies that when the immune system is completely damaged, there is no point trying to control the virus. All other states apart from when the T cell count or the viral load is zero are therefore controllable. This paper demonstrates that for the controllable states, some of them are more controllable than others, in the sense that, given a control objective, some states require more control effort than other states to meet the control objectives. When singular value decomposition is applied to the controllability matrix M_{RT} , an estimate measure of how controllable the viral load is at a particular time during the progression of the disease can be obtained. Figure 3 is a plot of the minimum singular value for the virus and T cell pairs as depicted in Figure 1.

From Figure 3, it can be seen that the early stages of the acute infection stage between the 1st and the 15th day from initial infection are relatively more difficult to control as compared to the asymptomatic or steady state stage. The section of the acute infection stage where the viral load is much higher than the steady state viral load is relatively the easiest to control. It can also be seen that controllability and viral load are correlated.

Model parameters are known to vary with time as it has been shown in (Nowak and May, 2000; Douek, McFarland and Keiser, 1998). For this paper, in an attempt to account for the rapid increase of the viral load at the later stages of the disease, parameters N and k are assumed to increase with time and parameter s to decrease with time. However, all parameters are taken to be constant from the time of infection until a time when the immune system breaks down. When this

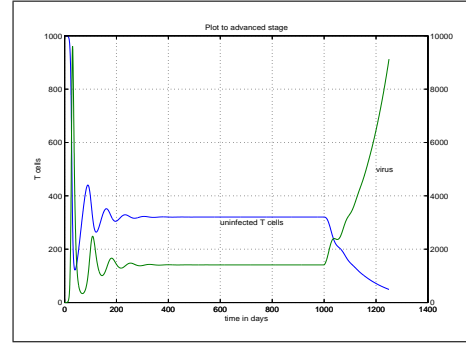


Fig. 4. Plot to advanced stage.

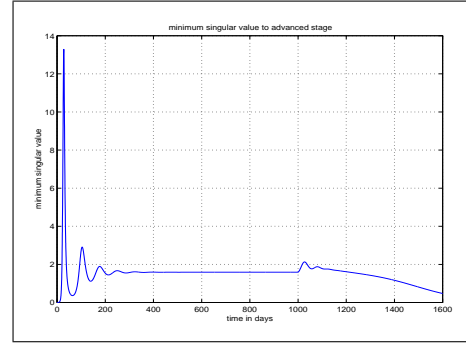


Fig. 5. Minimum singular value to advanced stage.

breakdown occurs, parameters are taken to vary linearly with time. These assumptions, though not clinically proven, do give a virus profile that complies with clinical observations as illustrated in Figure 4. For illustrative purposes, the immune system is taken to break down at 1000 days from initial infection.

Figure 5 is the minimum singular value plot for the steady state and advanced stages using the virus T cell pairs generated in Figure 4. It can be seen that the advanced stage is not as controllable as the steady state stage.

4. SIMULATION

The previous section is an approximate analysis based on linearization and control constraints are not taken into consideration. Simulation was done in a Matlab/Simulink environment and the models took the nonlinearities of the HIV dynamics and control constraints into consideration. The control variable $u(t)$ is as presented in section 3.1 with therapy on for 200 days. Therapy is assumed to be administered once daily as it has been shown in (Kirschner and Webb, 1996) that it is just as effective as when administered thrice daily. Simulation results are presentation here for when therapy is initiated from the acute infection stage to the steady state stage. In particular, simulation was performed from days 5, 10, 15 and 20 before the viral load reached its natural peak value and from days 25, 30, 40 and 50 when the viral load is on the decline. These simulations were compared

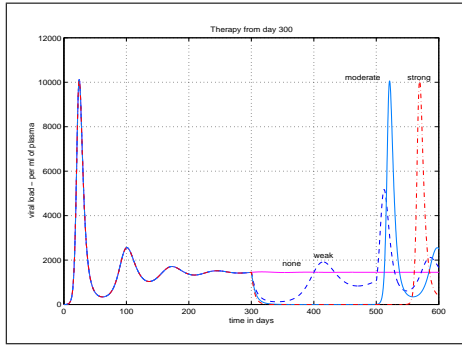


Fig. 6. Therapy from day 300.

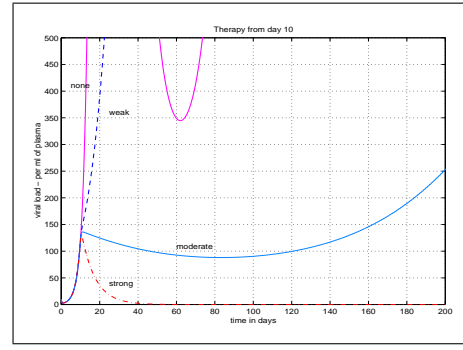


Fig. 8. Therapy from day 10.

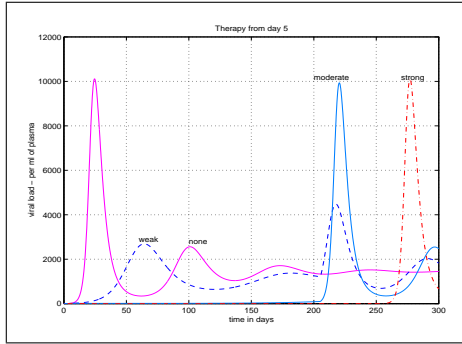


Fig. 7. Therapy from day 5.

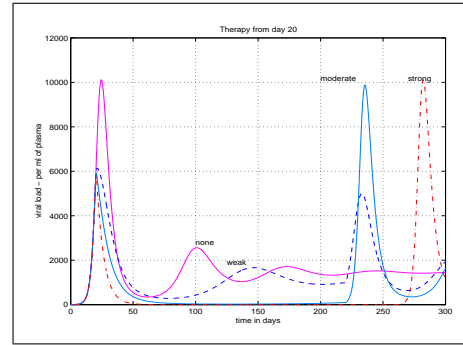


Fig. 9. Therapy from day 20.

with when therapy is initiated in steady state at day 300 from initial infection.

Using the asymptomatic stage as a reference, “moderate” therapy was taken as the minimal dosage that is required at the asymptomatic stage in order to meet the control objectives. This means that moderate therapy can reduce the viral load by 90% in eight weeks and continue to suppress it to below 50 copies in 6 months when initiated at day 300. This corresponded to a control input that fluctuated between 0.25 and 0.4 when therapy is on (70% effective). “Weak” therapy was selected such that it can reduce the viral load by 90% but can not keep it below 50 copies for the duration of the treatment and fluctuated between 0.4 and 0.6 (50% effective). “Strong” therapy fluctuated between 0.05 and 0.15 (90% effective).

Figure 6, showing the virus response when therapy is initiated from day 300, was used as the reference response graph. Moderate therapy does manage to reduce and maintain the viral load. Figure 7 shows the virus response to therapy from day 5. It can be seen that the viral load is already below 50 copies, but neither the moderate or weak therapies can maintain it at that level. In fact, the viral load continuously increases for the duration of the moderate therapy. This shows that therapy that is sufficient at the asymptomatic stage is insufficient at the very early days of infection. Stronger therapy is therefore needed at the early stages to keep such a low viral load under control.

There is a clear benefit however from initiating therapy at the very early days of infection as illustrated in Figure 7. It can be seen that early therapy significantly reduces the peak viral load, and consequently the symptoms associated with the acute infection stage.

Figure 8, which is the zoomed out version of the complete graph, shows that at day 10, the virus is still more difficult to control than at day 300, but is more controllable than at day 5. It is more controllable in the sense that with moderate therapy, the viral load does not continuously increase for the entire duration of the therapy as it did at day 5. A more controllable viral load is shown in Figure 9 when therapy is initiated from day 20. The viral load at day 20 is more controllable than at days 10 and 300 considering that the viral load at day 20 is 4 times the load at day 300.

5. CONCLUSIONS

The following conclusions can be drawn from this study.

- (1) Even though any viral load for all stages of the disease, apart from when the associated T cell count is zero, is theoretically controllable, some stages are more controllable than others.
- (2) The early acute infection stage and the late advanced stages are the most difficult to control stages

- (3) The acute infection stage, when the viral load is very high is the easiest stage to control
- (4) The restrictions placed on the control variable make control of the viral load attainable for a limited period of time.
- (5) The clear benefit of initiating therapy early in the acute infection stage is that the actual peak viral load is significantly lowered. This point could be investigated further towards a “morning after” treatment strategy for individuals who have been, or potentially been exposed to the virus.
- (6) When people have been exposed to the virus, results indicate that they would benefit from taking initial strong doses as soon as possible. If however, the intention is to just minimize the peak viral load, then a lower dose is suitable.
- (7) Initiating therapy within a few days from infection does not seem to, in any way, make the eradication of the virus possible.
- (8) Initiating therapy during the acute infection stage, but after the viral load has reached its peak value has no clear benefit (graph not shown). This seems to be because the viral load is already declining due to the immune response. If therapy must be initiated, then lower doses are better.
- (9) When therapy is stopped or when the virus is totally resistant, the viral load increases to another peak value before settling to the same steady state value as when no therapy was initiated.
- (10) The simulation results indicate that when the therapy is strong or moderate, the after treatment viral load peak is higher than when therapy was weak. Strong doses therefore, though better than weak doses at controlling the viral load, are potentially harmful to the immune system in that when resistance does emerge, or therapy is discontinued, the virus rebounds more forcefully.
- (11) The results also agree with previous observations by (Kirschner and Webb, 1996) that there is a significant time delay after strong therapy is terminated before the virus starts to rebound.
- (12) Therapy is best initiated when the viral load is easier to control because this implies the use of lower drug doses and consequently bearable side effects. This would be in the asymptomatic stage since most people do not know when they are infected.

6. REFERENCES

- Alvarez-Ramirez, J., M. Meraz and J. X. Velasco-Hernandez (2000), Feedback control of the chemotherapy of HIV, *International Journal of Bifurcation and Chaos*, 10, pp. 2207–2219.
- Concord Coordinating Committee (1994). MRC/ANRS randomized double-blind controlled trial of immediate and deferred AZT in symptom free HIV infection. *Lancet* **343**, pp. 871–881.
- Douek, D. C., R. D. McFarland and P. H. Keiser (1998). Changes in thymic function with the age and during treatment of HIV infection. *Nature* **396**, pp. 690–695.
- Felippe de Souza, J. A. M., Marco Antonio Leonel Caetano and T Yoneyama (2000), Optimal control theory applied to the anti-viral treatment of AIDS, *Proc. IEEE Conference on Decision and Control*, Sydney, Australia.
- Hraba, T., J. Dolezal and S. Celikovskiy (1990). Model based analysis of CD4+ lymphocyte dynamics in HIV infected individuals. *Immunology* **181**, pp. 108–118.
- Kirschner, D. (1996). Using mathematics to understand HIV immune dynamics. *AMS Notices*, pp. 191–202.
- Kirschner, D., S. Lenhart and S. Serbin (1997), Optimal control of the chemotherapy of HIV, *J. Math. Biol.*, **35**, pp. 775–792.
- Kirschner, D., G. F. Webb (1996). A model for treatment strategy in the chemotherapy of AIDS, *J. Math. Biol.* **58** pp. 367–390.
- Kirschner, D., G. F. Webb (1997), A mathematical model of combined drug therapy of HIV infection. *Journal of Theoretical Medicine* **1**, pp. 25–34.
- Kirschner, D., G. F. Webb and M. Cloyd (2000). Model of HIV-1 disease progression based on virus-induced lymph node homing and homing-induced apoptosis of CD4+ lymphocytes. *JAIDS*, **24**, pp. 352–362.
- McLeod, G. X., S. M Hammer (1992), Zidovudine: 5 years later, *Ann. Int. Med.*, **117**, pp. 487–501.
- Ming, G. (2000). New methods for estimating the distance to uncontrollability. *SIAM J. Matrix Appl* **21**, pp. 989–1003.
- Nowak, M. A., R. M. May (2000), *Virus Dynamics: mathematical principles of immunology and virology*, Oxford University Press, New York.
- Perelson, A. S., D. Kirschner and R. De Boer (1993), Dynamics of HIV infection of CD4+ T cells, *Mathematical Biosciences*, **114**, pp. 81–125.
- Perelson A. S., P. W. Nelson (1999), Mathematical analysis of HIV-1 dynamics *in vivo*, *SIAM Review*, **41**, pp. 3–44.
- Wein, L. M., S. A. Zenios and M. A. Nowak (1997), Dynamic multidrug therapies for HIV: a control theoretic approach, *J. Theor. Bio.*, **185**, pp. 15–29.
- Xia, X. Estimation of HIV/AIDS parameters. submitted.