

# Bibliography

- [1] US Department of Health and Human Services: “Guidelines for the Use of Antiretroviral Agents in HIV-infected Adults and Adolescents”, AIDSinfo, April, 2005, <http://www.aidsinfo.nih.gov/>.
- [2] Altfeld M., Rosenburg E.S., Shankarappa R., Mukherjee J., *et al.* “Cellular immune responses and viral diversity in individuals treated during acute and early HIV-1 infection,” *J Exp Med*, **193(2)**, pp. 169-180, 2001.
- [3] Concord Coordinating Committee, “MRC /ANRS randomized double-blind controlled trial of immediate and deferred AZT in symptom free HIV infection”, *Lancet*, **343**, pp. 871-881, 1994.
- [4] Hogg R.S., Yip B., Chan K., Wood E., *et al.*, “Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy,” *JAMA*, **286(20)**, pp. 2568-2577, 2001.
- [5] Hogg R.S., Yip B., Wood E., Chan K., Craib K.J.P., O’Shaughnessy M.V. and Montaner J.S.G. “Diminished effectiveness of antiretroviral therapy among patients initiating therapy with CD4<sup>+</sup> cell counts below 200/mm<sup>3</sup>,” *Proc. 8th Conference on Retroviruses and Opportunistic Infections*, Chicago, USA, 4 –8 Feb 2001.
- [6] Kaplan J., D. Hanson, J. Karon, D. Cohn, M. Thompson, S. Buskin, P. Fleming, and M. Dworkin, “Late initiation of antiretroviral therapy (at CD4<sup>+</sup> lymphocyte count < 200 cells/mL) is associated with increased risk of death,” *Proc. 8th Conference on Retroviruses and Opportunistic Infections*, Chicago, USA, 4 –8 Feb 2001.
- [7] Kirschner D. and Webb G.F. “A model for treatment strategy in the chemotherapy of AIDS”, *Bull. Math. Biol.*, **58(2)**, pp. 367-390, 1996.
- [8] Opravil M., B. Ledergerber, H. Furrer, S. Gallant, B. Hirscher, F. Meienberg, T. Wagels, E. Bernasconi, M. Rickenbach, R. Weberand The Swiss HIV Cohort Study

- (SHCS). “Clinical benefit of early initiation of HAART in patients with asymptomatic HIV infection and CD4<sup>+</sup> Counts > 350/mm<sup>3</sup>”. *Proc. 8th Conference on Retroviruses and Opportunistic Infections*, Chicago, USA, 4-8 Feb. 2001.
- [9] Phillips A.N., Staszewski S., Weber R., Kirk O., *et al.* “HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load” *JAMA*, **286(20)**, pp. 2560-2567, 2001.
- [10] Plana M., Garcia F., Gallart T., Tortajada C., *et al.* “Immunological benefits of antiretroviral therapy in very early stages of asymptomatic chronic HIV-1 infection,” *AIDS*, pp. -, 2000.
- [11] Pomerantz R.J. “Initiating antiretroviral therapy during HIV infection : confusion and clarity”, *JAMA* **286(20)**, pp. 2597-2599, 2001.
- [12] Sterling T.R., Chaisson R.E., Bartlett J.G. and Moore R.D. “CD4<sup>+</sup> Lymphocyte level is better than HIV-1 plasma viral load in determining when to initiate HAART,” *Proc. 8th Conference on Retroviruses and Opportunistic Infections*, Chicago, USA, 4-8 Feb 2001.
- [13] Lisziewicz J., Rosenberg E., Lieberman J., Jessen H., *et al.* “Control of HIV despite the discontinuation of antiretroviral therapy”, *New Engl. J. Med.*, **340(21)**, pp. 1683-1694, 1999.
- [14] Lori F., Maserati R., Foli A., Siminari E., Timpone J. and Lisziewicz J. “Structured treatment interruptions to control HIV-1 infection”, *Lancet*, **355**, pp. 287-288, 2000.
- [15] Ortiz G.M., Nixon D.F., Trkola A., Binley J., *et al.* “HIV-1 specific immune responses in subjects who temporarily contain virus replication after discontinuation of highly active antiretroviral therapy”, *J Clin. Invest.*, **104**, pp. R13-R18, 1999.
- [16] Rosenberg E.S., Altfeld M., Poon S.H., Phillips M., *et al.* “Immune control of HIV-1 after early treatment of acute infection” *Nature*, **407**, pp. 523-526, 2000.
- [17] Wodarz D., Arnaout R., Nowak M.A. and Lifson J. “Transient antiretroviral treatment during acute simian immunodeficiency virus infection facilitates long-term control of the virus”, *Philos Trans Royal Soc Lond B Biol Sci*, **355**, pp. 1021-1029, 2000.
- [18] Wodarz D. and Nowak M.A. “Specific therapy regimens could lead to long-term immunologic control of HIV,” *PNAS*, **96(25)**, pp. 14464-14469, 1999.

- [19] Abbas U.L. and Mellors J.W. “Interruption of antiretroviral therapy to augment immune control of chronic HIV-1 infection: risk without reward,” *Proc Natl Acad Sci USA*, **99(21)**, pp. 13377-13378, 2002.
- [20] Ananworanich J., Nuesch R., Braz M.L., Chetchotisakd P., *et al.* “Failures of 1 week on, 1 week off antiretroviral therapies in a randomized trial” *AIDS*, **17(15)**, pp. F33-37, 2003.
- [21] Oxenius A. and Hirscher B. “Structured treatment interruptions in HIV infection: benefit or disappointment?”, *Anti-Infect. Ther.*, **1(1)**, pp. 129-139, 2003.
- [22] Bean P. “Role of viral load blips, drug boosting, and therapeutic holidays in HIV patient management”, *American Clin. Lab.*, **20(8)**, pp. 11-13, 2001.
- [23] Di Mascio M., Markowitz M., Louie M., Hogan C., *et al.*, “Viral blip dynamics during highly active antiretroviral therapy”, *J. Virology*, **77**, pp. 12165-12172. 2003.
- [24] Havlir D.V., Bassett R., Levitan D., *et al.*, “Prevalence and predictive value of intermittent viremia with combination HIV therapy”, *J. American Med. Ass.*; **286(2)**, pp. 171-179, 2001.
- [25] Moore A.L., Youle M., Lipman M., Cozzi-Lepri A., Lampe F., *et al.* “Raised viral load in patients with viral suppression on highly active antiretroviral therapy: transient increase or treatment failure?”, *AIDS*; **16(4)**, pp. 615-618, 2002.
- [26] Embretson J., Zupancic M., Beneke J., Till M., Wolinski S., Ribas J.L., *et al.* “Analysis of HIV infected tissues by amplification and *in situ* hybridization reveals latent and permissive infections at single-cell resolution”. *Proc. Natl. Acad. Sci.*, **90**, pp. 357-61, 1993.
- [27] Finzi D., Blackson J., Siliciano J., Margolick J., *et al.* “Latent infection of CD4<sup>+</sup> T cells provides a mechanism for lifelong persistence of HIV-1, even on patients on effective combination therapy”, *Nature Med.*, **5(5)**, pp. 512-517, 1999.
- [28] Furtado M.R., Callaway D.S., Phair J.P., Kunstman K.J., *et al.* “Persistence of HIV-1 transcription in peripheral blood mononuclear cells in patients receiving potent antiretroviral therapy”, *New England J. Med.*, **340(21)**, pp. 1614-1622, 1999.
- [29] Grossman Z., Polis M., Feinberg M.B., Levi I., Jankelevich S., Yarchoan R., *et al.* “Ongoing dissemination during HAART”, *Nature Med.*, **5**, pp. 1099-104, 1999.

- [30] Natarajan V., Bosche M., Metcalf J.A., Ward D.J., Lane H.C. and Kovacs J.A. “HIV-1 replicates in patients with undetectable plasma virus receiving HAART”, *Lancet*, **353**, pp. 119-120, 1999.
- [31] Ngo-Giang-Huong N., Deveau C., Da Silva I., Pellegrin I., *et al.* “Proviral HIV-1 DNA in subjects followed since primary HIV-1 infection who suppress plasma viral load after one year of highly active antiretroviral therapy”, *AIDS*, **15**, pp. 665-673, 2001.
- [32] Wong J.K., Hezareh M., Gunthard H.F., Havlir D.V., Ignacio C.C., Spina C.A. and Richman D.D. “Recovery of replication-competent HIV despite prolonged suppression of plasma viremia,” *Science*, **278**, 1291-1295, 1997.
- [33] Zhang L., Ramratnam B., Tenner-Racz K., He Y., Vesanen M., Lewin S., *et al.* “Quantifying residual HIV-1 replication in patients receiving combination antiretroviral therapy”, *New Eng. J. Med.*, **340(21)**, pp. 1605-1613, 1999.
- [34] Aweeka F., Jayewardene A., Staprans S., *et al.* “Failure to detect nelfinavir in the cerebrospinal fluid of HIV-1 infected patients with and without AIDS dementia complex”. *J AIDS Hum. Retrovir.* **20**, pp. 39-43, 1999.
- [35] Kepler T.B. and Perelson A.S. “Drug concentration heterogeneity facilitates the evolution of drug resistance”, *Proc. Natl. Acad. Sci. USA*, **95**, pp. 11514-11519, 1998.
- [36] Mansky L.M., Le Rouzic E., Benichou S. and Gajary L.C. “Influence of reverse transcriptase variants, drugs and Vpr on human immunodeficiency virus type 1 mutant frequencies,” *J. Virology*, **77(3)**, pp. 2071-2080, 2003.
- [37] Perno C-F., Newcomb F.M., Davis D.A., Aquaro S., *et al.* “Relative potency of protease inhibitors in monocytes/macrophages acutely and chronically infected with human immunodeficiency virus.” *J. Infect. Diseases*, **178**, pp. 413-422, 1998.
- [38] Taylor S., Back D., Workman J., *et al.* “Poor penetration of the male genital tract by HIV-1 protease inhibitors”. *AIDS*, **13**, pp. 859-860, 1999.
- [39] Chun T-W., Engel D., Berrey M.M., Shea T., Corey L. and Fauci A.S. “Early establishment of a pool of latently infected, resting CD4<sup>+</sup> T cells during primary HIV-1 infection”, *Proc. Natl. Acad. Scie. USA*, **95**, pp. 8869-8873, 1998.

- [40] Finzi D., Hermankova M., Pierson T., Carruth L.M., Buck C., *et al.* “Identification of a reservoir for HIV-1 in patients on highly active antiretroviral therapy”, *Science*, **278**, pp. 1295-1300, 1997.
- [41] Roden D.M. and George A.L. Jr. “The genetic basis of variability in drug responses,” *Nature Revs. - Drug Discovery*, **1**, pp. 37-44, 2002.
- [42] “Guest Editorial: Special Issue on Systems and Control Problems in Medicine,” *IEEE Trans. AC*, **43(6)**, pp. 763-764, 1998.
- [43] Jeffrey A.M., Xia X. and Craig I.K. “When to initiate HIV therapy : a control theoretic approach,” *IEEE Trans. BME*, **50(11)**, pp. 1213-1220, 2003.
- [44] Ko J.H., Kim W.H., and Chung C.C. “Optimized structured treatment interruption for HIV therapy and its performance analysis on controllability”, *IEEE Trans BME*, **53(3)**, pp. 380-386, 2006
- [45] Kim J, Kim W.H., Chung H.B., and Chung C.C. “Constant drug dose leading long-term non-progressor for HIV-infected patients with RTI and PI,” *Proc. IEEE Conf. on Decision and Control and European Control Conf.*, Seville, Spain. pp. 909-916, Dec 12-15 2005.
- [46] Alvarez-Ramirez J., Meraz M. and Velasco-Hernandez J.X. “Feedback control of the chemotherapy of HIV”, *Int. J. of Bifurc. and Chaos*, **10(9)**, pp. 2207-2219, 2000.
- [47] Brandt M.E. and Chen G. “Feedback control of a biodynamical model of HIV-1”, *IEEE Trans. BME*, **48(7)**, pp. 754-759, 2001.
- [48] Butler S., Kirschner D. and Lenhart S. “Optimal control of chemotherapy affecting the infectivity of HIV”, *Advances in Mathematical Populations Dynamics: Molecules, Cells, Man*. World Scientific Publishing, pp. 104-120, 1997.
- [49] de Souza J.A.M.F., Caetano M.A.L. and Yoneyama T. “Optimal control theory applied to the anti-viral treatment of AIDS”, *Proc. 39<sup>th</sup> IEEE Conf. on Decision and Control*, Sydney, Australia, pp. 4839-4844, 2000.
- [50] Kirschner D., Lenhart S. and Serbin S. “Optimal control of the chemotherapy of HIV”, *J. Math. Biol.*, **35**, pp. 775-792, 1997.

- [51] Wein L.M., Zenios S.A. and Nowak M.A. “Dynamic multidrug therapies for HIV: a control theoretic approach”, *J. Theor. Biol.*, **185**, pp. 15-29, 1997.
- [52] Shim H., Han S.J., Chung C.C., Nam S.W. and Seo J.H. “Optimal scheduling of drug treatment for HIV infection: continuous dose control and receding horizon control”, *International Journal of Control, Automation and Systems*, **1(3)**, pp. 282-288, 2003.
- [53] Zurakowski R. and Teel A.R. “A model predictive control based scheduling method for HIV therapy”, *J. Theor. Biol.*, **238(2)**, pp. 368-382, 2006.
- [54] Chang H.J., Shim H. and Seo J.H. “Control of immune response of HIV infection model by gradual reduction of drug dose”, *In proc. 43<sup>rd</sup> IEEE Conf. Decision and Control*, (Atlantis, Bahamas), pp. 1048-1054, 14-17 December, 2004.
- [55] Jeffrey A.M., Xia X. and Craig I.K. “A Model Predictive Control Approach to Drug Dosage Design for HIV Therapy,” Submitted: *IEEE Trans. CST*, 2005.
- [56] Zhiling T., Ge S.S. and Tong H.L, “Globally stable nonlinear control of HIV-1 systems,” *Proc. American Control Conf.*, **(2)**, pp. 1633-1638, 2004.
- [57] Jeffrey A.M., Xia X. and Craig I.K. “Structured treatment interruptions: a control mathematical approach to protocol design,” Submitted: *J. Process Control*, 2005.
- [58] Gumel A.B., Twizell E.H. and Yu P. “Numerical and bifurcation analysis for a population model of HIV chemotherapy”, *Math. and Comp. in Sim.*, **54**, pp. 169-181, 2000.
- [59] De Leenheer P. and Smith H.L. “Virus dynamics: a global analysis”, *SIAM J. App. Math.*, **63(4)**, pp. 1313-1327, 2003.
- [60] Jeffrey A.M., Xia X. and Craig I.K. “A viral load time response analysis to antiretroviral therapy,” *SAIEE Trans.*, **96(3)**, pp. 234-239, 2005.
- [61] Jeffrey A.M. and Xia X. “Identifiability of HIV/AIDS models”, In: *Deterministic and Stochastic Models of AIDS Epidemics and HIV Infections with Intervention*, Eds. Wai-Yuan Tan and Hulin Wu. World Scientific Publishing, Singapore. pp. 255-286, 2005.
- [62] Xia X. “Estimation of HIV/AIDS parameters,” *Automatica*, **39**, 1983-1988, 2003.

- [63] Xia X. and Moog C.H. “Identifiability of nonlinear systems with application to HIV/AIDS models,” *IEEE Tran. Auto. Contr.*, **48(2)**, pp. 330-336, 2003.
- [64] Filter R.A., Xia X. and Gray C.M. “Dynamic HIV/AIDS parameter estimation with application to a vaccine readiness study in Southern Africa”, *IEEE Trans. BME.*, **51**, pp. 784-791, 2005.
- [65] Ouattara D.A. “Mathematical analysis of the HIV-1 infection : parameter estimation, therapies effectiveness and therapeutical failures”, *27th Annual International Conference of the IEEE EMB Society* Shanghai, China, 1-4 September 2005.
- [66] Ouattara D.A., Bugnon F., Moog C.H. and Raffi F. “Parameter identification of an HIV/AIDS dynamical model”, *13th International Symp. on HIV and Emerging Infectious Diseases*, Toulon, France. pp. 186-192, 2004.
- [67] Xia X. “Modelling of HIV infection: vaccine readiness, drug effectiveness and therapeutic failures”, In *Proc. Int. Symp. on Advanced Control of Chemical Processes*, Gramado, Brazil. **(2)**, pp. 485-492, 2-5 April, 2006.
- [68] Craig I.K., Xia X. and Venter J.W. “Introducing HIV/AIDS education into the electrical engineering curriculum at the University of Pretoria”, *IEEE Transactions in Education*, **47(1)**, pp. 65-73, 2004.
- [69] Craig I.K. and Xia X. “Can HIV/AIDS be controlled?”, *IEEE Control Sys Mag*, **25(1)**, pp. 80-83, 2005.
- [70] Bonhoeffer S., Coffin J.M. and Nowak M.A. “Human immunodeficiency virus drug therapy and virus load” *J. Virol.*, **71**, pp. 3275-3278, 1997.
- [71] Callaway D.S. and Perelson A.S. “HIV-1 infection and low steady state viral loads”, *Bull. Math. Biol.*, **64**, pp. 29-64, 2002.
- [72] Culshaw R.V. and Ruan S. “A delay-differential equation model of HIV infection of CD4<sup>+</sup> T cells”, *Mathematical Biosciences*, **165**, pp. 27-39, 2000.
- [73] de Souza F.M.C. “Modeling the dynamics of HIV-1 and CD4 and CD8 lymphocytes”, *IEEE Eng. Med. and Bio.*, Jan/Feb, pp. 21-24, 1999.
- [74] Ding A.A. and Wu H. “Relationships between antiviral treatment effects and biphasic viral decay rates in modeling HIV dynamics”, *Math. Bioscie.*, **160**, pp. 63-82. 1999.

- [75] Gumel A.B., Shivakumar P.N. and Sahai B.M. “A mathematical model for the dynamics of HIV-1 during the typical course of infection”, *Nonlin. Anal.*, **47**, pp. 1773-1783, 2001.
- [76] Hraba T. and J. Dolezal, “A mathematical model and CD4<sup>+</sup> lymphocyte dynamics in HIV infection.” *Emerging Infectious Diseases*, **2(4)**, pp. 299-305, 1996.
- [77] Kirschner D. “Using mathematics to understand HIV immune dynamics”, *AMS Notices*, **43(2)**, pp. 191-202, 1996.
- [78] Kirschner D. and Perelson A.S. “A model for the immune system response to HIV: AZT treatment studies”, in: *Mathematical Population Dynamics: Analysis of Heterogeneity*, **1**, pp. 295-310, 1995. Eds. Arino O., Axelrod D., Kimmel M. and Langlais M. Wuerz Publishing, Winnipeg.
- [79] Kirschner D. and Webb G.F. “Resistance, remission, and qualitative differences in HIV chemotherapy”, *Emerging Infectious Diseases*, **3(3)**, pp. 273-283, 1997.
- [80] Kramer I., “Modeling the dynamical impact of HIV on the immune system: viral clearance, infection, and AIDS,” *Math. and Comp. Mod.*, **29**, pp. 95-112, 1999.
- [81] Murray J.M., Kuafmann G., Kelleher A.D. and Cooper D.A., “A model of primary HIV-1 infection,” *Math. Biosci.*, **154**, pp. 57-85, 1998.
- [82] Nelson P.W., Murray J.D. and Perelson A.S., “A model of HIV-1 pathogenesis that includes an intracellular delay,” *Math. Bioscie.*, **163**, pp. 201-215, 2000.
- [83] Nelson P.W. and Perelson A.S. “Mathematical analysis of delay differential equation models of HIV-1 infection”, *Math. Biosci.*, **179**, pp. 73-94, 2002.
- [84] Nowak M.A. and May R.M. *Virus Dynamics: mathematical principles of immunology and virology*, Oxford University Press. New York, 2000.
- [85] Perelson A.S. and Nelson P.W. “Mathematical analysis of HIV-1 dynamics in vivo”, *SIAM Rev*, **41(1)**, pp. 3-44, 1999.
- [86] Tan W-Y. and Wu H. “Stochastic modeling of the dynamics of CD4<sup>+</sup> T-cell infection by HIV and some Monte Carlo studies”, *Math. Biosci.*, **147**, pp. 173-205, 1998.
- [87] Wodarz D. “Helper-dependent vs. helper-independent CTL responses in HIV infection: implications for drug therapy and resistance”, *J. Theor. Biol.*, **213**, pp. 447-459, 2001.

- [88] De Boer R.J., Mohri H., Ho D.D. and Perelson A.S. “Estimating average cellular turnover from 5-bromo-2'-deoxyuridine (BrdU) measurements.” *Proc. Royal Soc. London B*, **270**, pp. 849-858, 2003.
- [89] Gray C.M., Williamson C., Bredell H, Puren A., Filter R., Xia X., *et al.* “Viral dynamics, CD4 counts and human leukocyte antigen types in subtype human immunodeficiency virus type-1 infected individuals from Southern Africa: significance for vaccine trials.” *AIDS Research and Human Retroviruses*, **21(4)**, pp. 285-291, 2005.
- [90] Ho. D.D., Neumann A.U., Perelson A.S., *et al.* “Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection,” *Nature*, **373**, pp. 123-126(abstract), 1995.
- [91] Mittler J.E., Markowitz M., Ho D.D. and Perelson A.S. “Improved estimates for HIV-1 clearance rate and intracellular delay”. *AIDS*. **13** pp. 1415-1417, 1999.
- [92] Mohri H., Perelson A.S., Tung K., Ribeiro R.M., *et al.* “Increased turnover of T lymphocytes in HIV-1 infection and its reduction by antiretroviral therapy,” *J. Exp. Med.*, **194(9)**, pp. 1277-1287, 2001.
- [93] Ramratnam B., Bonhoeffer S., Mittler J.E., Zhang L., Boden D., Hurley A., *et al.* “The decay of the latent reservoir of replication-competent HIV-1 is inversely correlated with the extent of residual viral replication during prolonged anti-retroviral therapy”, *Nature Med.*, **6(1)**, pp. 82-85, 2000.
- [94] Wang, L., J. Chen, B. Gelman, R. Konig and M. Cloyd. “A novel mechanisms of CD4 lymphocyte depletion involves effects of HIV on resting lymphocytes: induction of lymph node homing and apoptosis upon secondary signaling through homing receptors.” *J. Immunol.*, **162**, pp. 268-276, 1999.
- [95] Hoetelmans R.M.W., Reijers M.H., Weverling G.J., *et al.* “The effect of plasma drug concentrations on HIV-1 clearance rate during quadruple drug therapy”, *AIDS*; **12**, pp. 111-115, 1998.
- [96] Hraba T., Dolezal J. and Celikovsky S. “Model based analysis of CD4<sup>+</sup> lymphocyte dynamics in HIV infected individuals,” *Immunobiology*, **181** , pp. 108-118, 1990.
- [97] Huang Y., Rosenkranz S.L. and Wu H., “Modeling HIV dynamics and antiviral response with consideration of time-varying drug exposures, adherence and phenotypic sensitivity”, *Math. Biosciences* **184** pp. 165-186, 2003.

- [98] Little S.J., McLean A.R., Spina C.A., Richman D.D. and Havlir D.V., "Viral dynamics of acute HIV-1 infection," *J. Exp. Med.*, **190**(6), pp. 841-850, 1999.
- [99] Perelson A.S., Kirschner D. and De Boer R. "Dynamics of HIV infection of CD4<sup>+</sup> T cells," *Mathematical Biosciences*, **114**, pp. 81-125, 1993.
- [100] Perelson A.S. Neumann A.W., Markowitz M. and *et al.*, "HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time", *Science Mag. (online abstract)*, **271**, pp. 1582-1586, 1996.
- [101] University of Pretoria, "HIV/AIDS educational CD-ROM", Available [online]: <http://www.be.up.co.za>, 2002.
- [102] Jeffrey A.M., Xia X. and Craig I.K. "A model based analysis of anti-CD4 therapy as adjuvant to HAART interruption," *16th IFAC World Congress*, Prague, Czech Republic, 04-09 July 2005a.
- [103] Jeffrey A.M., Xia X. and Craig I.K. "Drug dosage level design to maximize the benefits of therapy", *Proc. IEEE 7<sup>th</sup> Africon Conf.*, Gaborone, Botswana, 15-17 September 2004.
- [104] Jeffrey A.M., Xia X. and Craig I.K. "On attaining maximal and durable suppression of the viral load ,," *1st African Control Conference AFCON*, Cape Town, South Africa, 03-05 December 2003c.
- [105] Jeffrey A.M., Xia X. and Craig I.K. "Identifiability of an extended HIV model", *Proc. 5<sup>th</sup> IFAC Symp. Modelling and Control in Biomedical Systems*, Melbourne, Australia, pp. 507-512, 21-23 August 2003a.
- [106] Jeffrey A.M. and Xia X. "Estimating the viral load response time after HIV chemotherapy", *Proc. IEEE 6<sup>th</sup> Africon Conf.*, George, South Africa, **1**, pp. 77-80, 02-04 October 2002.
- [107] Jeffrey A.M., Xia X. and Craig I.K. "Controllability analysis of the chemotherapy of HIV," *15th IFAC World Congress*, Barcelona, Spain, 21-26 July 2002.
- [108] ATIS : Department of Health and Human Services. *Glossary of HIV/AIDS-Related Terms* 4th Edition [online] [www.hivatis.org](http://www.hivatis.org), September 2002.
- [109] AIDS.ORG "FactSheets: HIV life cycle," *AIDS.ORG*, available [online] <http://www.aids.org/factSheets/400-HIV-Life-Cycle.html> Accessed December 14, 2005.

- [110] Jennings C., *Understanding and preventing AIDS: a book for everyone*, Health Alert Press, Cambridge, MA, 1996. Available [online]: [http://www.aproposinc.com/hap/toc\\_long.htm](http://www.aproposinc.com/hap/toc_long.htm)
- [111] Wodarz D., Lloyd A.L., Jansen V.A.A., and Nowak M.A. “Dynamics of macrophage and T cell infection by HIV”, *J. Theor. Biol.*, **196**, pp. 101-113, 1999.
- [112] Igarashi T., Brown C.R., Endo Y., Buckler-White A., *et al.* “Macrophage are the principal reservoir and sustain high virus loads in rhesus macaques after the depletion of CD4<sup>+</sup> T cells by a highly pathogenic simian immunodeficiency virus/HIV type 1 chimera (SHIV): Implications for HIV-1 infections of humans,” *Proc. Natl. Acad. Scie.*, **98(2)**, pp. 658-663, 2001.
- [113] Muller V., Maree A.F.M. and De Boer R.J. “Release of virus from lymphoid tissue affects human immunodeficiency virus type 1 and hepatitis C virus kinetics in the blood”, *J. Virol.*, **75(6)**, pp. 2597-2603, 2001.
- [114] Hlavacek W.S., Stilianakis N.I., Notermans D.W., Danner S.A. and Perelson A.S. “Influence of follicular dendritic cells on decay of HIV during antiretroviral therapy”, *PNAS*, **97(20)**, pp. 10966-10971, 2000.
- [115] Hunt R. “Virology - chapter seven: human immunodeficiency virus and AIDS”, *Microbiology and Immunology On-line* University of South Carolina, School of Medicine [online]: <http://www.med.sc.edu:85/lecture/hiv2000.htm> Accessed 04 November 2005.
- [116] De Boer R.J., Mohri H., Ho D.D. and Perelson A.S. “Turnover rates of B cells, T cells, and NK cells in simian immunodeficiency virus-infected and uninfected rhesus macaques1.” *The Journal of Immunology*, 2003, **170**, pp. 2479-2487, 2003.
- [117] Clarke J.R., White N.C. and Webber J.N. “HIV compartmentalization: pathogenesis and clinical implications”, *AIDS Rev.*, **2**, pp. 15-22, 2000.
- [118] Bonhoeffer S. and Nowak M.A. “Pre-existence and emergence of drug resistance in HIV-1 infection”, *Proc. Roy. Soc. London B*, **264**, pp. 631-637, 1997.
- [119] Bangsberg D.R., Charlebois E.D., Grant R.M., Holodniy M., Deeks S.G., *et al.* “High levels of adherence do not prevent accumulation of HIV drug resistant mutants,” *AIDS*, **17**, pp. 1925-1932, 2003.

- [120] Fumero E., Garcia F. and Gatell J.M. "Immunosuppressive drugs as an adjuvant to HIV treatment", *J. Antimicrobial Chemo.*, **53**, pp. 415-417, 2004.
- [121] Lane H.C. "Immunopathogenesis and immune reconstitution", *Medscape*, 2002, [online] <http://www.medscape.com/viewarticle/440466>. Accessed 14 Nov. 2002.
- [122] Cepeda J.A. and Wilks D. "Excess peripheral neuropathy in patients treated with hydroxyurea plus didanosine and stavudine for HIV infection". *AIDS*, **14(3)** pp. 332-333, 2000.
- [123] Havlir D.V., Gilbert P.B., Bennett K., *et al.* "Effects of treatment intensification with hydroxyurea in HIV infected patients with virologic suppression". *AIDS*, **15(11)**, pp. 1379-1388, 2001.
- [124] Zala C., Salomon H., Ochoa C., *et al.* "Higher rate of toxicity with no increased efficacy when hydroxyurea is added to a regimen of stavudine plus didanosine and nevirapine in primary HIV infection". *J Acquired Immune Deficiency Syndrome*, **29(4)**, pp. 368-373, 2002.
- [125] De Boer R.J. and Boucher C.A.B. "Anti-CD4 therapy for AIDS suggested by mathematical models", *Proc. Biol. Scie.*, **263(1372)**, pp. 899-905, 1996.
- [126] Pirmohamed M. and Back D.J. "The pharmacogenomics of HIV therapy," *Pharmacogen. J.*, **1**, pp. 243-253, 2001.
- [127] Lori F. and Lisziewicz J. "Structured treatment interruptions for the management of HIV infection", *JAMA*, **286(23)**, pp. 2981-2987, 2001.
- [128] Dorman K., Kaplan A., Lange K. and Sinsheimer J. "Mutation takes no vacation: can structured treatment interruptions increase the risk of drug resistant HIV-1?" *J Acquir Immune Defic Syndr*, **24(5)**, pp. 398-402, 2000.
- [129] Martinez-Picado J., Morales-Lopetegi K., Wrin T., Prado J.G., *et al.* "Selection of drug-resistant HIV-1 mutants in response to repeated structured treatment interruptions", *AIDS*, **16**, pp. 895-899, 2002.
- [130] Metzner K.J., Bonhoeffer S., Fischer M., Karanicolas R., Weber R., Hirschel B., *et al.* "Detection of minor populations of drug-resistant-viruses in patients undergoing structured treatment interruptions". *Antiviral. Ther.*, **7**, pp. 73, 2002.

- [131] Schweighardt B., Ortiz G.M., Grant R.M., Wellons M., *et al.* “Emergence of drug-resistant HIV-1 mutants in patients undergoing structured treatment interruptions” *AIDS*, **16(17)**, pp. 2342-2344, 2002.
- [132] Dybul M., Chun T-W., Yoder C., Hidalgo B., and *et al.* “Short-cycle structured intermittent treatment of chronic HIV infection with highly active antiretroviral therapy: effects on virologic, immunologic and toxicity parameters”. *Proc. Natl Acad Sci - USA*, **98(26)**, pp. 15161-15166, 2001.
- [133] NIH News Release, “The SMART Way to Fight AIDS”, <http://www.nih.gov/news/pr/jan2002/niaid-10.html>, 10 January 2002.
- [134] Bonhoeffer S., Rembiszewski M., Ortiz G.M. and Nixon D.F. “Risks and benefits of structured antiretroviral drug therapy interruptions in HIV-1 infection”, *AIDS*, **14**, pp. 2313-2322, 2000.
- [135] Davey R.T. Jr., Bhat N., Yoder C., Chun T-W., Metcalf J.A., Dewar R., *et al.* “HIV-1 and T cell dynamics after interruption of highly active antiretroviral therapy (HAART) in patients with a history of sustained viral suppression”, *PNAS*, **96(26)**, pp. 15109-15114, 1999.
- [136] Fagard C., Oxenius A., Günthard H., Garcia F., *et al.* “A prospective trial of structured treatment interruptions in human immunodeficiency virus infection” *Arch. Intern. Med.*, **163(10)**, pp. 1220-1226, 2003.
- [137] Fischer M., Hafner R., Schneider C., Trkola A., *et al.* “HIV RNA in plasma re-bounds within days during structured treatment interruptions” *AIDS*, **17(2)**, pp. 195-199, 2003.
- [138] Frost S.D.W., Martinez-Picado J., Ruiz L., Clotet B. and Brown A.J.L. “Viral dynamics during structured treatment interruptions of chronic human immunodeficiency virus type 1 infection”, *J. Virology*, vol. 76(3), pp. 968-979, 2002.
- [139] Garcia F., Plana M., Ortiz G.M., Bonhoeffer S., *et al.* “The virological and immunological consequences of structured treatment interruptions in chronic HIV-1 infection”, *AIDS*, **15(9)**, pp. F29-F40, 2001.
- [140] Hirschel B., Faggard C., Oxenius A., *et al.* “A Prospective Trial of Treatment Interruption in HIV Infection”, *Programmes and abstracts of the 9th Conference on Opportunistic Infections* (Seattle, USA), Feb. 24-28, 2002.

- [141] Lori F., Foli A., Maserati R., Siminari E., *et al.* “Control of HIV during a structured treatment interruption in chronically infected individuals with vigorous T cell responses”, *HIV Clin. Trials*, **3**, pp. 115-124, 2002.
- [142] Ortiz G.M., Wellons M., Brancato J., Vo H.T.T., *et al.* “Structured antiretroviral treatment interruptions in chronically HIV-1-infected subjects”, *PNAS*, **98(23)**, pp. 13288-13293, 2001.
- [143] Oxenius A., Price D.A., Günthard H.F., Dawson S.J., *et al.* “Stimulation of HIV-specific cellular immunity by structured treatment interruption fails to enhance viral control in chronic HIV infection”, *Proc. Natl. Acad. Sci.*, **99(21)**, pp. 13747-13752, 2002.
- [144] Oxenius A., McLean A., Fischer M., Price D.A., *et al.* “HIV-specific CD8+ T cell responses do not predict viral growth and clearance rates during structured intermittent antiretroviral therapy”, *J Virol.*, **76**, pp. 10169-10175, 2002b.
- [145] Ruiz L., Carcelian G., Martnez-Picado J., Frost S., *et al.* “HIV dynamics and T-cell immunity after three structured treatment interruptions in chronic HIV-1 infection”, *AIDS*, **15(9)**, pp. 19-27, 2001.
- [146] Stellbrink H.J., van Lunzen J., Westby M., OSullivan E., Schneider C., Adam A., *et al.* “Effects of interleukin-2 plus highly active antiretroviral therapy on HIV-1 replication and proviral DNA (COSMIC trial)”. *AIDS*, **16**, pp. 1479-1487, 2002.
- [147] Katlama C., Dominguez S., Duvivier C., Delaugerre C., *et al.* “Long-term benefit of treatment interruption in salvage therapy,” *Proc. 10th Conference on Retroviruses and Opportunistic Infections*, Abstract 68, 2003.
- [148] Miller V., Sabin C., Hertogs K., Bloor S., Martinez-Picado J., DAquila R., *et al.* “Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure”. *AIDS*, **14**, pp. 2857-2867, 2000.
- [149] Mussini C., Bugarini R., Perno C., *et al.* “Virological and immunological effects of discontinuation of antiretroviral therapy in patients with virological failure”, *Programmes and abstracts of the 9th Conference on Opportunistic Infections* (Seattle, USA), Feb. 24-28, 2002.
- [150] Ruiz L., Martnez-Picado J., Romeu J., Paredes R., *et al.* “Structured treatment interruptions in chronically HIV-1 infected patients after long-term viral suppression”, *AIDS*, **14(4)**, pp. 397-403, 2000.

- [151] Bajaria S.H., Webb G. and Kirschner D.E. “Predicting differential responses to structured treatment interruptions during HAART,” *Bull. Math. Bio.*, **66**, pp. 1093-1118, 2004.
- [152] Hatano H., Vogel S., Yoder C., Metcalf J., *et al.* “Pre-HAART HIV burden approximates post-HAART viral levels following interruption of therapy in patients with sustained viral suppression” *AIDS*, **14(10)**, pp. 1357-1363, 2000.
- [153] Blankson J., Siliciano J., Finzi D., Quinn T., Gallant J. and Siliciano R. “Rapid initial decay of latently infected cells following re-initiation of HAART in chronically HIV-1 infected patients with treatment interruptions,” *Abstracts from the 9th Conference on Retroviruses and Opportunistic Infections*, Abstract 491-M, 2002.
- [154] Neumann A., R. Tubiana, V. Calvez, C. Robert, T.-S. Li, H. Agut, B. Autran, C. Katlama and The Comet Study Group. “HIV-1 rebound during interruption of highly active antiretroviral therapy has no deleterious effect on reinitiated treatment,” *AIDS* **13**, pp. 677683, 1999.
- [155] Carcelain G., Tubiana R., Samri A., Calvez V., *et al.* “Transient mobilization of human immunodeficiency virus (HIV)- specific CD4 T-helper cells fails to control virus rebounds during intermittent antiretroviral therapy in chronic HIV type 1 infection,” *J Virology*, **75**, pp. 234-241, 2001.
- [156] Papasavvas E., Grant R., Sun J., Mackiewicz A., Pistilli M., Gallo C., Kostman J., Mounzer K., Shull J. and Montaner L. “Lack of persistent drug-resistant mutations evaluated within and between treatment interruptions in chronically HIV-1-infected patients”, *AIDS*, **17**, pp. 2337-2343, 2003.
- [157] Dybul M., *et al.* “A randomized controlled trial of long cycle structured intermittent versus continuous ARV therapy for chronic HIV infection,” *Abstracts from the 10th Conference on Retroviruses and Opportunistic Infections*, Abstract 681b.
- [158] Poulton, M., Sabin C. and Fischer M. “Immunological changes during treatment interruptions: risk factors and clinical sequelae.” *AIDS*, **17**, pp. 126128, 2003.
- [159] Blankson J., Gallant J., Quinn T., Bartlett J. and Siliciano R. “Loss of HIV-1 specific immunity during treatment interruption in 2 chronically infected patients,” *JAMA*, **288**, pp. 162-164, 2002.

- [160] Perelson A.S. “Modelling the interaction of the immune system with HIV,” in *Mathematical and Statistical Approaches to AIDS Epidemiology*, (Lect. Notes Biomath.), C. Castillo-Chavez, Ed., Springer Verlag, New York, **83**, pp. 350-370, 1989.
- [161] Chun T-W., Carruth L., Finzi D., Xhen X., et al. “Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection”. *Nature*, **387**, pp. 183-188, 1997.
- [162] Perelson, A.S., Essunger P., Cao Y., Vesanen M., Hurley A., Saksela K., Markowitz M. and Ho D.D. “Decay characteristics of HIV-1 infected compartments during combination therapy”, *Nature*, **387**, pp. 188-191, 1997.
- [163] Perelson A.S., Essunger P., Markowitz M. and Ho D.D., “How long should treatment be given if we had an antiretroviral regimen that completely blocked HIV replication?”, *XIth Intl. Conf. AIDS Abstracts*, 1996.
- [164] Filter R.A. “Dynamic HIV/AIDS parameter estimation with applications”, *MEng(Electronic Eng) Dissertation*, University of Pretoria, Pretoria, South Africa. 2005.
- [165] Haase A.T., Henry K., Zupancic M., Sedgewick G., Faust R., et al. “Quantitative image analysis of HIV-1 infection in lymphoid tissue”, *Science*, **274**, pp. 985-989, 1996.
- [166] Dewhurst S., da Cruz R.L.W. and Whetter L. “Pathogenesis and treatment of HIV-1 infection: recent developments (Y2K update)”, *Front. Biosci.*, **5**, pp. 30-49. 2001.
- [167] Douek D.C., McFarland R.D., Keiser P.H., et al. “Changes in thymic function with the age and during treatment of HIV infection”, *Nature*, **396**, pp. 690-695, 1998.
- [168] Stilianakis N.I., Dietz K. and Schenzle D. “Analysis of a model of the pathogenesis of AIDS” *Math. Biosci.*, **145**, pp. 27-46, 1997.
- [169] McLeod G.X. and Hammer S.M. “Zidovudine: 5 years later,” *Ann. Intern. Med.*, **117**, pp. 487-501, 1992.
- [170] Nise N.S. *Control Systems Engineering*. John Wiley and Sons, New York, 2000.

- [171] Muller V., Maree A.F.M. and De Boer R.J. “Small variations in multiple parameters account for wide variations in HIV-1 set-points: a novel modelling approach ,” *Proc. Royal Soc. Lond. B. Biol. Sci.*, **268**, pp. 235-242, 2001.
- [172] Rizzardi G.P., De Boer R.J., Hoover S., Tambussi G., *et al.* “Predicting the duration of antiviral treatment needed to suppress plasma HIV-1 RNA”, *J. Clin. Investigation.* **105(6)**, pp. 777-782, 2000.
- [173] Hoetelmans R.M.W. “Clinical pharmacokinetics of antiretroviral drugs”, *AIDS Rev*; **1**, pp. 167-178, 1999.
- [174] De Boer R.J. and Perelson A.S. “Target cell limited and immune control models of HIV infection: a comparison”, *J. Theor. Biol.*, **190**, pp. 201-214, 1998.
- [175] Skogestad S. and Postlethwaite I. *Multivariable Feedback Control : Analysis and Design*, John Wiley & Sons, Chichester, England, 1996.
- [176] Ramratnam B., Bonhoeffer S., Binley J., Hurley A., *et al.* “Rapid production and clearance of HIV-1 and hepatitis C virus assessed by large volume plasma apheresis”, *Lancet*, **354(20)**, pp. 1782-1785, 1999.
- [177] Becker S.L. and Hoetelmas R.M.W. “Exploiting pharmacokinetics to optimize antiretroviral therapy”, *Medscape’s CME activity*, [online] <http://www.medscape.com/viewprogram/703>. Accessed 11/7/2002.
- [178] Lindpainter K., “Pharmacogenetics and the future of medical practice: conceptual considerations,” *Pharmacogen. J.*, **1**, pp. 23-26, 2001.
- [179] Wei X., Ghosh S.K., Taylor M.E., Johnson V.A., *et al.* . “Viral dynamics in HIV-1 infection,” *Nature*. **273**, pp. 117-121, 1995.
- [180] Jelliffe R.W., “Optimal design of drug dosage regimens” *Ann. Int. Conf. IEEE in Med. and Biol. Society*, **13(5)**, pp. 2164-2165, 1991.
- [181] Mahfouf M., Linkens D.A. and Xue D, “A new generic approach to model reduction for complex physiologically based drug models,” *Control Eng. Pract.*, **10**, pp. 67-81, 2002.
- [182] Ferguson N.M., Fraser C. and Anderson R.M. “Viral dynamics and anti-viral pharmacodynamics: rethinking in vitro measures of drug potency”, *Trends in Pharm. Scie.*, **22(2)**, pp. 97-100, 2001.

- [183] Joshi A.S., Barrett J.S., Fiske W.D., *et al*, “Population pharmacokinetics of efavirenz phase II studies and relationship with efficacy”, *Prog. and abstr. 30<sup>th</sup> ICAAC*, San Francisco, USA, 26—29 Sept. 1999.
- [184] Gerber J.G. and Acosta E.P. “Therapeutic drug monitoring in the treatment of HIV infection”, *J. Clin. Virol.*, **27**, pp. 117-128, 2003.
- [185] Mathworks, “Model predictive toolbox - users guide”, 2006.
- [186] Maciejowski J.M. *Predictive Control with Constraints*, Prentice Hall, Harlow, England, 2002.
- [187] Camacho E.F. and Bordons C. *Model Predictive Control*, Springer-Verlag. London, 1999.
- [188] Goodwin G.C., Graebe S.F. and Salgado M.E. *Control System Design*, Prentice Hall, Upper Saddle River, New Jersey, 2001.
- [189] Gallant J.E. and Squires K.E. “Non-nucleoside reverse transcriptase inhibitors in the treatment of HIV: focus on efficacy”, *Medscape’s CME activity*, Available [online]: <http://www.medscape.com/viewprogram/2853>. Accessed 10 June 2004.

# Appendix A

## Parameter Estimates

Table A.1: Parameter estimates for the latently infected model : Set 1.

Parameter	Value
$s_T$	10 mm <sup>-3</sup> day <sup>-1</sup>
$p$	0.03 day <sup>-1</sup>
$T_{max}$	1500 mm <sup>-3</sup>
$d_T$	0.01 day <sup>-1</sup>
$\beta_T$	$7.5 \times 10^{-6}$ mm <sup>3</sup> day <sup>-1</sup>
$\delta_l$	0.01 day <sup>-1</sup>
$\delta_a$	0.5 day <sup>-1</sup>
$k$	0.075
$q_l$	0.05
$q_a$	0.55
$r_T$	2000 cell <sup>-1</sup> day <sup>-1</sup>
$c$	5 day <sup>-1</sup>
[84, 85, 50, 46]	

Table A.2: Parameter estimates for the latently infected model : Set 2.

Parameter	Value
$s_T$	$10 \text{ mm}^{-3} \text{ day}^{-1}$
$p$	$0.03 \text{ day}^{-1}$
$T_{max}$	$1000 \text{ mm}^{-3}$
$d_T$	$0.01 \text{ day}^{-1}$
$\beta_T$	$4 \times 10^{-5} \text{ mm}^3 \text{ day}^{-1}$
$\delta_l$	$0.01 \text{ day}^{-1}$
$\delta_a$	$0.5 \text{ day}^{-1}$
$k$	0.025
$q_l$	0.005
$q_a$	0.55
$r_T$	$240 \text{ cell}^{-1} \text{ day}^{-1}$
$c$	$5 \text{ day}^{-1}$

Table A.3: Parameter estimates for the latently infected model : Set 3.

Parameter	Value
$s_T$	$10 \text{ mm}^{-3} \text{ day}^{-1}$
$d_T$	$0.01 \text{ day}^{-1}$
$\beta_T$	$7.5 \times 10^{-6} \text{ mm}^3 \text{ day}^{-1}$
$q_l$	0.05
$q_a$	0.8
$\delta_l$	$0.01 \text{ day}^{-1}$
$\delta_a$	$0.5 \text{ day}^{-1}$
$k$	0.075
$r_T$	$2000 \text{ virions cell}^{-1} \text{ day}^{-1}$
$c$	$5 \text{ day}^{-1}$

[85, 50, 84, 7, 90].

Table A.4: Typical parameters estimates for the extended model.

Parameter	Typical Value
$T(0)$	$10^6 \text{ mL}^{-1}$
$M(0)$	$3 \times 10^4 \text{ mL}^{-1}$
$V(0)$	$10 \text{ mL}^{-1}$
$s_T$	$10^4 \text{ mL}^{-1}\text{day}^{-1}$
$d_T$	$0.01 \text{ day}^{-1}$
$\beta_T$	$4.5 \times 10^{-8} \text{ mL day}^{-1}$
$p$	$0.02 \text{ day}^{-1}$
$T_m$	$10^6 \text{ mL}^{-1}$
$q_l$	0.005
$q_a$	0.55
$\delta_l$	$0.01 \text{ day}^{-1}$
$\delta_a$	$0.5 \text{ day}^{-1}$
$k$	$0.025 \text{ day}^{-1}$
$s_M$	$150 \text{ mL}^{-1}\text{day}^{-1}$
$d_M$	$0.005 \text{ day}^{-1}$
$\beta_M$	$1.75 \times 10^{-8} \text{ mL day}^{-1}$
$q_M$	1
$\mu$	$0.05 \text{ day}^{-1}$
$r_T$	$240 \text{ cell}^{-1}\text{day}^{-1}$
$r_M$	$35 \text{ cell}^{-1}\text{day}^{-1}$
$c$	$5 \text{ day}^{-1}$
$\eta_{rt}$	$[0, 1)$
$\eta_{pi}$	$[0, 1)$
$\alpha_{rt}$	$(0, 1]$
$\alpha_{pi}$	$(0, 1]$
$\eta_{ps}$	$[0, 1)$
$\eta_{da}$	$[0, 1]$

[46, 71, 78, 84, 176]