DEVELOPMENT OF OPTIMAL TREATMENT STRATEGIES FOR HIV INFECTION BY MATHEMATICAL METHODS

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HAART (Highly Active Antiretroviral Therapy)

HAART is a customized combination of different classes of medications that a physician prescribes based on such factors as the patient's viral load (how much virus is in the blood), the particular strain of the virus, the CD4+ cell count, and other considerations (e.g., disease symptoms). Because HAART cannot rid the body of HIV, it must be taken every day for life. HAART can control viral load, delaying or preventing the onset of symptoms or progression to AIDS, thereby prolonging survival in people infected with HIV. HAART has been in use since 1996 and has changed what was once a fatal diagnosis into a chronically managed disease.

Palella, F.J., Jr., et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med, 1998. 338(13): p. 853-60.

PROBLEMS for mathematical and computer modeling:

- 1. When to initiate the HAART?
- 2. At what viral load, i.e. amount of viral copies to begin treatment? At what number of infected lymphocytes CD4?
- 3. The need for the appointment of treatment regimens take into account the patient's individual characteristics.
- 4. The toxicity of drugs and their long-term consequences.
- 5. The need for drugs throughout a patient's life and arising in connection with the side effects that can cause severe, sometimes combined with a life and disease.
- 6. The choice of optimal treatment regimen of drugs, drug combinations.
- 7. Development and study of new, more effective antiviral drugs.

- 8. Effect of treatment failure patient treatment medication.
- 9. What happens when you opt-out of ART?
- 10. Development the therapeutic and preventive vaccines against HIV infection.
- 11. The presence of viral reservoirs, i.e. latently infected cells in which the virus persists, do not replicate. The problem is that the virus infects different cell types, including those with high life expectancy, for example, macrophages, and lymphatic tissue, tissue and intestinal mucosa, glands, CNS, thymus and testes.
- 12. The emergence of drug-resistant virus, its genetic variability, the emergence of new strains.
- 13. Identification of the HIV infection parameters.

When to initiate the HAART?

Time to hit HIV, early and hard!

or

Hit HIV hard, but only when necessary!

1. Ho D. (1995). Time to hit HIV, early and hard. N Engl J Med, 333: 450-451.

2. Harrington M., Carpenter C.C. (2000). Hit HIV-1 hard, but only when necessary. Lancet, 355: 2147-2152.

Jeffrey A.M., Xia X., Craig I.K. (2003). When to initiate therapy: A control theoretic approach. IEEE Transaction on Biomedical Engineering, 50(11): 1213-1219.

The very early acute infection stage (5th day) and the late advanced stages are the most difficult to control.

The acute infection stage (10th day), when the viral load is very high is the easiest stage to control.

Paci P., Carello R., Bernaschi M., D'Offizi G. and Castiglione F. (2009). Immune control of HIV-1 infection after therapy interruption: immediate versus deferred antiretroviral therapy. BMS Infections Diseases, 9(172): 1-13.

Simulations show that immediate therapy does not prolong the disease-free period and does not confer a survival benefit when compared to treatment started during the chronic infection phase. Hence, deferral of therapy should be preferred in order to minimize the risk of adverse effects, the occurrence of drug resistances and the costs of treatment.

Structured Treatment Interruption (STI) strategies for HIV infection

In the works of Banks, HT (Source Center for Research in Scientific Computation, North Carolina State University, Raleigh, USA) and colleagues have been studied the so-called STI strategy (Structured Treatment Interruption), i.e. discontinuation of a treatment regimen, as contrasted to continued exposure to that regimen. STIs are being evaluated as a means to reduce pill burden and drug toxicity. In areas with limited resources, such strategies offer the possibility of increasing access to antiretroviral therapy (ART).

1. Adams B.M., Banks H.T., Tran H.T., Kwon H. (2004). Dynamic multidrug therapies for HIV: Optimal and STI control approaches. Math. Biosci. Eng, 1(2): 223-241.
2. Adams B.M., Banks H.T., Davidian M., et al. (2005). HIV dynamics: Modeling, data analysis, and optimal treatment protocols. J. Comp. Appl. Math., 184(1): 10-49.
3. Adams B.M., Banks H.T., Davidian M., Rosenberg E.S. (2007). Model Fitting and Prediction with HIV Treatment Interruption Data. Bull. Math. Biol., 69: 563-584.
4. Rosenberg E.S., Davidian M., and Banks H.T. (2007). Using mathematical modeling and control to develop structured treatment interruption strategies for HIV infection. Drug and Alcohol Dependence special supplement issue on “Customizing treatment to the Patient: Adaptive Treatment Strategies” 88S, S41-S51.
5. Banks H.T., Davidian M., Hu S., Kepler G.M. and Rosenberg E.S. (2008). Modeling HIV immune response and validation with clinical data. J. Biol. Dyn., 2(4): 357-385.
6. Banks H.T., Cintron-Arias A., Kappel F. (2012). Parameter Selection Methods in Inverse Problem Formulation. In: Mathematical Modeling and Validation in Physiology, Series Lecture Notes in Mathematics, 2064:43-73.

CD4+ T-cell-guided structured treatment interruptions for HIV infection

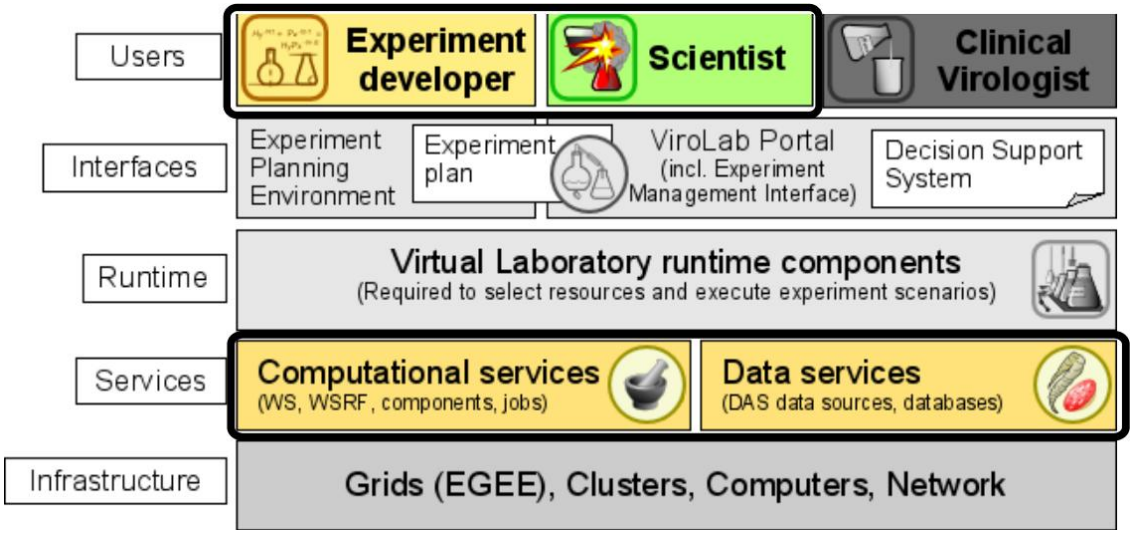
International trials (SMART) have shown that CD4+ T-cell-guided structured treatment interruptions of antiretroviral therapy lead to worse outcomes than continuous treatment. In [Yazdanpanah, et al., 2010] found the conditions (start ART earlier, interrupt/reintroduce treatment at very high CD4+ T-cell thresholds and use first-line medications with higher resistance barrier), when STI can be applied.

Yazdanpanah Y., Wolf L.L., Anglaret X., et al. (2010). CEPAC-International Investigators. CD4+ T-cell-guided structured treatment interruptions of antiretroviral therapy in HIV disease: projecting beyond clinical trials. Antivir. Ther., 15(3), 351-361. doi:10.3851/IMP1542.

COMPUTER TOOLS

ViroLab: A Virtual Laboratory for Decision Support in Viral Disease Treatment

http://www.virolab.org/



The main objective of the ViroLab project is to develop a Virtual Laboratory for Infectious Diseases that facilitates medical knowledge discovery and decision support for, e.g., HIV drug resistance. Large, high quality in-vitro and clinical patient databases have become available which can be used to relate genotype to drug-susceptibility phenotype. Relevant data has two main characteristics: it spans all temporal and spatial scales from the genome up to the clinical data, and it is inherently distributed over various sources (virological-, clinical- and drugs-databases) that change dynamically over time.

1. Slot P.M.A., Boukhanovsky A.V., Keulen W., Tirado-Ramos A., Boucher C. (2005). A grid-based HIV expert system. J. Clinical Monitoring and Computing, 19: 263-278.
2. Slot P.M.A., Tirado-Ramos A., Altintas I., Bubak M., Boucher C. (2006). From molecular to man: decision support in individualized e-health. IEEE Computer Society.
3. Slot P.M.A., Coveney P.V., Ertaylan G., Mller V., Boucher C.A.B. and Bubak M.T. (2009). HIV decision support: From molecular to man. Philosophical Transactions of the Royal Society, 367: 2691-2703.

The EuResist Project: Integration of viral genomics with clinical data to predict response to anti-HIV therapy

http://www.euresist.org/web/guest/home

The EuResist Integrated Data Base (EIDB), among the largest available databases of HIV genotypes and clinical response to antiretroviral therapy, with more than 65.000 patients.

The EuResist Satellite DB (EsaDB), a tool for management of HIV patients data running locally on a PC.

The EuResist treatment response prediction engine. The EuResist prediction engine is a data-driven system which predicts the response to combination drug therapy for a patient with a given viral genotype. The engine has an overall accuracy of around 77% which compares favourably with existing rules-based state-of-the-art systems such as HIVdb, ANRS, REGA.

Internet-project "Mathematical Analysis of the HIV infection" allows to perform parameter identification for HIV infection models of individual patients.

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Université de Pretoria

Ouattara D.A., Mhawej M.J., Moog C.H. (2007). IRCCyN web software for the computation of HIV infection parameters. Available at http://vih.irccyn.ec-nantes.fr

C-ImmSim: IMMUNE SYSTEM SIMULATOR

The C-ImmSim model describes both the humoral and the cellular response of a mammalian immune system to the presence of antigens (virus, bacteria, etc.), at the cellular level (mesoscopic scale).

One or more cubic millimeters of a secondary lymphoid organ (or, at convenience, micro litres of peripheral blood) of a vertebrate animal is mapped onto a three-dimensional lattice with periodic boundary conditions.

Recently C-ImmSim has been enriched to simulate HIV infection and cancer immunotherapy.

Castiglione F., Pappalardo F., Bernaschi M. and Motta S. (2007). Optimization of HAART with genetic algorithms and agent-based models of HIV infection. Bioinformatics, 23(24): 3359-3355.

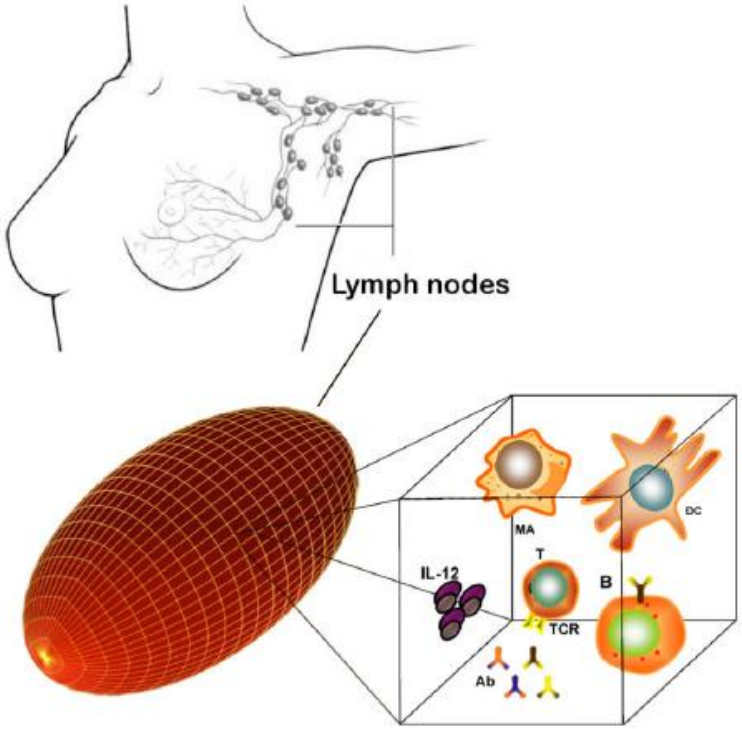

Figure 6
Simulation space. The space modeled consists in a 3D-ellipsoid lattice that resembles the typical shape of a lymph node. Each lattice point corresponds to a certain volume unit where interactions take place. Some entities are sketched: lymphocytes (T and B), antibodies (Ab), macrophages (MA), dendritic cells (DC) and the interleukins IL-12.

"Mathematical models alone cannot answer questions about the pathogenesis of HIV infection or similar biological processes. But when used in conjunction with data as part of designed experiments, models can be a powerful tool in understanding mechanisms in complex systems. Moreover, data-oriented mathematical models can also stimulate further clinical and laboratory research."

Adams B.M., Banks H.T., Davidian M., et al. (2005). HIV dynamics: Modeling, data analysis, and optimal treatment protocols. J. Comp. Appl. Math., 184(1): 10-49.

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