Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Theoretical Biology 238 (2006) 368–382
Journal of Theoretical Biology
www.elsevier.com/locate/yjtbi

A model predictive control based scheduling method for HIV therapy ☆

Ryan Zurakowski[a,*], Andrew R. Teel[b]

[a]Department of Ecology and Evolutionary Biology, 321 Steinhaus Hall, University of California, Irvine, CA 92697, USA
[b]Department of Electrical and Computer Engineering, University of California, Santa Barbara, CA 93106, USA

Received 11 July 2004; received in revised form 23 May 2005; accepted 24 May 2005
Available online 5 july 2005

Abstract

Recently developed models of the interaction of the human immune system and the human immunodeficiency virus (HIV) suggest the possibility of using interruptions of highly active anti-retroviral therapy (HAART) to simulate a therapeutic vaccine and induce cytotoxic lymphocyte (CTL) mediated control of HIV infection. We have developed a model predictive control (MPC) based method for determining optimal treatment interruption schedules for this purpose. This method provides a clinically implementable framework for calculating interruption schedules that are robust to errors due to measurement and patient variations. In this paper, we discuss the medical motivation for this work, introduce the MPC-based method, show simulation results, and discuss future work necessary to implement the method.

Keywords: Viral dynamics; Antiretroviral therapy; Nonlinear control

1. Introduction

In the majority of cases of untreated human immunodeficiency virus (HIV) infection, the patient undergoes a short (2–10 weeks) period of acute infection, which may be accompanied by symptoms similar to those found in most viral infections. During this period, there is a sharp drop in the concentration of circulating helper-T cells, and a large spike in the level of circulating free virus (to an average of 10^7/ml). During this period, a humoral (antibody) response and a cellular (cytotoxic-T cell) response are established (Koup et al., 1994). After this period, the level of circulating helper-T cells returns to near-normal (1000 cells/ml), and the viral load drops dramatically (to an average of about 50 000/ml). During the next phase of infection, which can last as long as 10 years, the patient remains asymptomatic, but the level of circulating helper-T cells slowly declines. When the number of helper-T cells drops below a critical threshold (200/ml), the patients adaptive immune system is no longer able to control infections, and a number of so-called opportunistic infections cause a rapid deterioration of health and a total collapse of the adaptive immune system. The slow rate of helper-T cell decline during the long, asymptomatic chronic infection phase once led people to believe that the virus was relatively inactive during this period, but it is now known that vigorous viral replication and helper-T cell turnover occurs during this time (Ho et al., 1995; Perelson et al., 1996; Perelson and Nelson, 1999). In fact, the total viral production during this phase is on the order of 10^{10} virions per day, and the turnover rate of helper-T cells on the order of 2×10^9 cells per day. The dynamics of HIV infection are

☆ Research supported in part by NIH grant number R21 AI057071.
*Corresponding author. Tel.: +1 949 824 0154; fax: +1 949 824 2181.
E-mail addresses: ryanz@uci.edu (R. Zurakowski), teel@ece.ucsb.edu (A.R. Teel).

0022-5193/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jtbi.2005.05.004

obviously quite fast, but the immune response is able to maintain a near-homeostasis for a number of years.

1.1. Long-term non-progressors

While the majority of untreated HIV-infected patients exhibit the pattern of disease progression described above, a small number of untreated patients show no progressive decline in helper-T cell counts, and never develop AIDS. These patients are termed long-term non-progressors (LTNP). These patients exhibit extremely low viral loads, frequently below the threshold for measurement. Compared to patients with progressive infections, these patients exhibit strong HIV-specific helper-T cell responses (Rosenberg et al., 1997,1999; Rosenberg and Walker, 1998; Gloster et al., 2004; Moss et al., 2000). Levels of HIV-specific cytotoxic-T cells are similar in both cases (Rodes et al., 2004), but in the case of LTNPs, their HIV-specific cytotoxic-T cell counts are maintained at low levels of viral load (Harrer et al., 1996a,b; Migueles et al., 2002), where patients with progressive infections see corresponding decreases in the level of HIV-specific cytotoxic-T cell activity if the viral load is suppressed by therapy (McMichael and Rowland-Jones, 2001; Mollet et al., 2000; Kalams et al., 1999b; Appay et al., 2002). This is also seen in animal model experiments such as Schmitz et al. (1999) and Jin et al. (1999). Longitudinal studies of LTNPs have shown that the control of the virus sometimes fails (Rodes et al., 2004), probably due to mutational escape (Yang et al., 2003). Also, even in patients with exceptionally broad specificity in their CTL response to HIV, escape due to super-infection has been shown to occur (Altfeld et al., 2002a). Long-term non-progressors are widely studied as a model for potential therapeutic vaccines, as they apparently have naturally developed an immune response that successfully contains the virus.

1.2. Highly-active anti-retroviral therapy

Prior to 1995, anti-retroviral drugs were applied one or two at a time. Work done by Ho and colleagues (Ho et al., 1995) showed that the replication and mutation rates of HIV in vivo were so high as to make the emergence of strains resistant to any one drug inevitable. The solution was to use three or more drugs that target separate components of the HIV replication cycle. This multi-drug therapy regime is known as highly active anti-retroviral therapy (HAART). This technique is highly effective at reducing viral load and restoring immune function (Gray et al., 2000), 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. HAART is expensive, costing as much as $10 000 per patient per year, and it must be continued for the life of the patient. Even though it can suppress the viral load below the measurement threshold, various viral reservoirs cause re-emergence of the virus upon cessation of therapy, even after many years of suppression (Finzi et al., 1999). Finally, the drugs used in HAART cause a number of adverse side effects in almost all patients, ranging from the mild to life-threatening (Gegeny, 2000; Manegold et al., 2001). While HAART is an effective therapy that prolongs the life of HIV-infected individuals, the associated costs keep us searching for a better solution. An excellent review of the available drugs, their usage, and their side effects can be found in Hoffmann and Kamps (2003).

1.3. Treatment interruptions

A significant amount of effort has been put into the use of interrupted schedules of HAART (Gulick, 2002). Interrupting HAART has been done for a number of reasons, usually to manage side effects or allow treatment of a secondary infection with which the drugs in HAART would interfere, such as hepatitis-A (Montaner, 2001; Dybul et al., 2001; Fischer et al., 2003). However the case of the "Berlin patient" began a series of investigations into the use of treatment interruptions as a way of boosting the immune response to HIV, and potentially controlling the virus (Autran and Carcelain, 2000). In the case of the Berlin patient, HAART was begun during acute infection, discontinued due to poor adherence, re-initiated, discontinued again due to hepatitis-A infection, re-initiated, then discontinued permanently, following which there was no measurable viral rebound (Lisziewicz et al., 1999). Follow-up with this patient showed measurable virus in the lymph nodes, but no viral rebound for several years after discontinuation of therapy. Obviously, the treatment schedule had somehow induced an immune response capable of controlling the HIV infection.

Further studies on patients who initiated HAART during acute infection, followed by a pattern of structured treatment interruptions (STI), showed varying degrees of success in inducing at least a transient control of viral replication in the absence of continued therapy (Lori et al., 2000; Ortiz et al., 1999; Papasavvas et al., 2000; Ruiz et al., 2001; Rosenberg et al., 2000). In all of the successful cases, viral control was associated with increased HIV-specific helper-T responses and strong HIV-specific CTL responses that were maintained even at low viral load, which suggested an immune response profile similar to that seen in LTNPs. However, a follow-up study that tracked some of those patients that successfully controlled the virus in the absence of continued therapy showed a disappointing lack of durability in the immune response; among 14 patients who successfully controlled viral replication for up to 3 years following cessation of therapy, all except