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HIV dynamics: Modeling, data analysis, and optimal treatment protocols

B.M. Adams[a], H.T. Banks[a,*], M. Davidian[a], Hee-Dae Kwon[a,1], H.T. Tran[a], S.N. Wynne[a], E.S. Rosenberg[b]

[a] *Center for Research in Scientific Computation, Box 8205, North Carolina State University, Raleigh, NC 27695-8205, USA*
[b] *Massachusetts General Hospital and Harvard Medical School, I.D. Unit-Gray 5, Fruit Street, Boston, MA 02114, USA*

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Abstract

We present an overview of some concepts and methodologies we believe useful in modeling HIV pathogenesis. After a brief discussion of motivation for and previous efforts in the development of mathematical models for progression of HIV infection and treatment, we discuss mathematical and statistical ideas relevant to Structured Treatment Interruptions (STI). Among these are model development and validation procedures including parameter estimation, data reduction and representation, and optimal control relative to STI. Results from initial attempts in each of these areas by an interdisciplinary team of applied mathematicians, statisticians and clinicians are presented.

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1. Introduction—HIV modeling and STI

Although the correlates of immune protection in HIV infection remain largely unknown, our knowledge of viral replication dynamics and virus-specific immune responses has grown. Concurrent with these

* Corresponding author.
E-mail addresses: bmadams3@unity.ncsu.edu (B.M. Adams), htbanks@unity.ncsu.edu (H.T. Banks), davidian@unity.ncsu.edu (M. Davidian), tran@math.ncsu.edu (H.T. Tran), snwynne@unity.ncsu.edu (S.N. Wynne), erosenberg1@partners.org (E.S. Rosenberg).
[1] Department of Mathematics, Inha University, Inchon, South Korea.

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advances, there has been an abundance of mathematical models that attempt to describe these phenomena. The models proposed have principally involved linear and nonlinear ordinary differential equations, both with and without delay terms. While data fitting problems motivated the development of some models, others have been proposed in a more abstract sense to suggest new experiments or possibilities for ways in which the body interacts with this pathogen. 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. In any discussions of mathematical modeling of complex systems, it is appropriate to point out that while complex models may be needed to provide accurate descriptions of the underlying dynamics, the models are most useful when they can be compared to clinical and/or experimental data. In developing models for HIV infection and treatment, this requires that a balance be struck between complexity and utility.

We begin this paper with a brief summary of issues that have arisen in the development of models for HIV infection and motivate the model fitting problem. We also offer an introduction to STIs as a potentially improved treatment strategy and indicate how mathematical control theory can be helpful in finding treatment schemes. This background will set the stage for the model- and data-based examples that follow.

1.1. Models for HIV infection

Numerous factors have been considered in modeling HIV infection as one must typically choose only a critical subset of the many possible biological compartments and interactions. Moreover, scale is important in that one must decide whether to model at the micro level of viral RNA or more at the systemic level. Our focus is on compartmental models in which compartments each typically correspond to a type of cell population throughout the body. We do not attempt to provide a comprehensive survey of the extensive collection of mathematical models used with HIV infection. Rather, we refer the reader to one of the excellent survey articles already published; see, for example, [15,55]. We provide a brief overview of some important developments here.

Investigations of the kinetics of virus and CD4+ T-cell populations using mathematical models with data from patients undergoing highly active anti-retroviral therapy (HAART) support the theory of very rapid and constant turnover of the viral and infected cell populations in all individuals studied; see, for example [30,66,56]. This contrasts with researchers' previous assumptions that the stable viral and CD4+ T-cell concentrations seen during the period of clinical latency of chronic HIV infection were due to the absence of any significant viral replication. The studies by Ho, Wei and Perelson indicate that both the viral and infected cell populations are turning over rapidly and continuously. Further work in [54] revealed a second population of longer lived infected cells contributing to the population of viral RNA. Since these reports, numerous groups have used mathematical models to estimate decay rates for infected cell populations [42,44,46,47,70]. In Section 2 we present a model that can predict the observed persistent low-level replication of virus and includes multiple infected cell populations.

The early linear models developed in [66,30,56,54] are approximations to more realistic nonlinear models for viral and infected cell decay, and thus are applicable only over short periods of time, most likely on the order of days. While these linear models have been extremely useful in characterizing short-term dynamics of HIV infection after therapy, several researchers have attempted to use these models to