173f The Role of Mathematical Modeling on the Optimal Control of HIV-1 Pathogenesis

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The human immune system is complex and not fully understood, and no model, mathematical or otherwise, can capture every facet of its phenomenology. Nevertheless, mathematical modeling of HIV-1 infection has proven to be instrumental for the current understanding of the AIDS pathogenesis [Ho et al. (1995) Nature, 373(12), 123-126; Wei et al. (1995) Nature, 373(12), 117-122], since it offers the unique means to adequately pose hypotheses concerning AIDS dynamics and treatment protocols.

Focusing on the HIV-1 subtype-B epidemic, it is the purpose of this paper to delve into this complicated combination of mathematics and immunology in order to provide a comprehensive and unified overview of the main features directly involved in the development of mathematical models aimed at the optimal management of HIV-1 infection through highly active antiretroviral therapy (HAART) schemes. Based on recent results, this paper targets the cellular and molecular biology levels and addresses key-issues concerned with the natural history of AIDS, the basic human anatomic model, the host cell entry of HIV-1, the quantification the HIV-1 infectivity in terms of viral coreceptor specificity as well as regulation and expression of CCR5 and CXCR4 molecules on the target cell, the T-lymphocyte generation and infection models and the immune response model.

The major contributions of this work are as follows: a) a unified comparison of the major mathematical developments in the area emphasizing main potentials and limitations that characterizes past work; b) several issues related to mathematics and immunology and a biology-oriented discussion that focuses on novel mechanisms recently identified that affect the course of HIV-1 infection; c) development of a more comprehensive biological basis that addresses the complex and integrated human immunology for development of phenomenological mathematical models, which may serve to study the dynamics of other viral pathogenesis, as hepatitis-C. In particular, these concern the development of biological models that incorporate a multi-compartment human body model, which considers the peripheral blood, the lymphoid tissues and the central nervous system; a cellular apoptotic model that may contribute to T-cell depletion throughout the infection course; a comprehensive CD4+ T-cell infection model that considers distinct cellular phenotypes and infection routes other than virus-cell, and an integrated model for the CD8+ T-cell pool dynamics that regards its immunologic interactions with the monocyte-macrophage cell lineage d) the foundations for the development of a realistic HIV-1 drug chemotherapy model that must be incorporated into the human immunology model in order to compose an integrated tool that is able to define the optimal drug chemotherapy short-term schedule for AIDS infection as function of patient status at a given time.