173e Optimal Medication Strategies for the Early Stages of HIV Infection

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Human immunodeficiency virus (HIV) infection has received a lot of attention because of its wide spread, way of contraction, and fatal effect. Drug development is an active research topic with the objective of prolonging life expectancy of patients. However, such drugs have a number of side effects on vital human functions, thus creating the need to quantify their toxicity and compute dosage strategies that are optimal with respect to prolonging life. Mathematical models may become an important tool in this quest for optimal dosage strategies because of their ability to predict the response of the average patient to medication. In order to describe the dynamics of the disease, numerous mathematical models have been proposed in the open literature to capture different aspects of disease progression. These models have also been used to schedule optimal treatments to increase life expectancy [1], focusing on the later stages of the infection, since, in general, HIV infection is diagnosed after some time (due to flu-like symptoms at the early stages), when the viral load has reached high concentration, and the body immune system has weakened. However a few groups of people (e.g., hospital personnel) may know that they might have been infected immediately after. The initial stage of HIV infection (first two to three months) is of vital importance. If medication starts immediately after infection, when the viral load is low, there is a chance to cure an otherwise fatal disease. Consequently, there is strong motivation to model the early stages of the infection; the infection dynamics at that early stage are different from the subsequent quasi steady-state stage and knowledge of the events that take place during the initial infection stage can be beneficial to the development of an accurate model.

The purpose of this work is scheduling the optimal therapy for patients in the primary stage of HIV infection. To achieve this, initially a detailed mathematical model (based on [2], [3]) is derived which describes the intracellular dynamics of the initial stage of infection. Several discrete events should take place in the T cell for a successful infection. In addition, at the early stage of infection, the number of virus particles is considerably low and the body immune response in combination with medication may be able to eradicate infection thoroughly. Other factors (e.g., chance infections in the body at the time or the patient immune system strength) also play a role for a successful infection. Considering these factors, random fluctuations that might affect the dynamics of primary infection are important. Consequently, a stochastic model should describe the infection more accurately at this stage. Contrary, deterministic methods are reliable when large populations are studied and fluctuation effects are negligible. In this work, both stochastic and deterministic models were employed. Subsequently, dynamic optimization problems were formulated, based on these models, that employed the dose prescription as a control variable, with objective to reduce the patient viral load over a finite-time horizon, also accounting (through appropriate weight functions) for the effects of drug toxicity. With respect to medication scheduling, drug toxicity prevents physicians from prescribing high dosages of medication for patients since it may cause further problems for the patient in the long run. Consequently, we were seeking a dosage high enough to ensure a high probability of virus eradication and simultaneously as low as possible to be less harmful. Another issue is the mutation of virus and consequently, production of new virus strains which are resistant to an individual drug. As a result, combination therapy based on different type of drugs (i.e., RT inhibitor and protease inhibitor) has been suggested to sustain a more reliable response. Different strategies are thus possible for combination therapy (e.g., prescribing drugs simultaneously or sequentially). In this work, different strategies of therapy were considered and optimal dose schedules were identified independently for each strategy. Sensitivity of the identified schedules to toxicity was also investigated.

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