Abstract

Title: HIV temporal patterns in clinical practice: a case report with real data

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The clinical follow-up of the HIV progression in a patient consists of monitoring clinical markers such as the viral load and the $CD4^+$ cell count. It is well accepted that high viral load values indicate high viremia in the system and constitute a significant risk factor of morbidity and of mortality [2], while reduced CD4 values reflect an impairment of the patient's immune system [1]. The CD4 value is also used in clinical practice to define the beginning of the antiretroviral treatment, that (hopefully) will prevent the progression of the disease. The antiretroviral treatment enables a decrease in the viral load as well as the reproduction and increase of CD4 values which, in turn, increases the ability of the immune system to fight the HIV and other infections.

A typical HIV infection without treatment is characterized by three phases: the acute phase, the chronic phase and the phase of acquired immunodeficiency syndrome. The acute phase starts after the HIV infection and is characterized by an accentuated decay of the number of $CD4^+$ cells since these are the HIV preferred target. Then, the immune system tries to fight back the virus by producing antibodies. The chronic phase starts with body recovery and a slight increase in the number of $CD4^+$cells is observed. Finally, succeeding the chronic phase, the acquired immune deficiency syndrome (AIDS) is the final and most serious HIV phase, which causes severe damage to the immune system and, if left untreated, will lead to the death of the patient. When the patient is under treatment, there are only two phases in the HIV infection: the acute phase (before treatment) and the chronic phase (after treatment). In the large majority of the cases, a patient is diagnosed when symptoms start to be visible and, thus, the typical HIV clinical follow-up usually starts after the accentuated $CD4$ decay in the acute phase.

The above mentioned acute and chronic phases can be described with individual HIV models that are based on systems of ordinary differential equations. These systems

consider physiological knowledge and known-relations between the viral load and the $CD4^+$cells count of a patient since these variables are those observed in a common clinical follow-up [1]. In this way, the parameters of the model have a clear physiological and clinical interpretation, e.g. one parameter represents the "effectiveness of therapy". Our previous work dealt with the development of different statistical methods for the estimation of the model's parameters from a set of temporal observations of a patient [4,5]. By another hand, the optimal parameters of the model are obtained as the solution minimizing the error between a solution of the model and the experimental data, subject to constraints and physiological bounds [4]. The optimal solution allows the representation of the optimal trajectory for the patient and makes possible to characterize the state of the patient e.g. before the beginning of the therapy (before HIV infection and during the acute phase) and after the last known observation (e.g. with utmost importance for prediction purposes). By another hand, we considered a Bayesian approach based on Markov chain Monte Carlo strategy to obtain the posteriori distributions associated with the model's parameters [5]. The same way as for the optimal solution, each *a posteriori* solution allows the representation of one temporal trajectory. This approach makes possible the characterization of the variability in the temporal trajectory by constructing a temporal variation band containing the trajectories with the lowest error to the experimental data of one patient. The methods developed in both studies [4,5] were validated with simulated data that mimic experimental temporal trajectories of several patients and incorporates laboratory measurement errors of the clinical markers.

Our present work aims to illustrate the application of the previously developed methods in real data [3]. As mentioned before, individual real data refers to the viral load and the number of $CD4^+$ cells during the chronic phase as a typical HIV patient is not observed before evident symptoms (i.e. before and during the accentuated $CD4$ decay in the acute phase). Therefore, the validated methods have to be adapted in order to proceed with the estimation of the parameters in real data, e.g. by including the estimation of the initial state of the subject, before HIV infection, which is not observed in the real data. Also, the estimated trajectories allow the prediction of the patient evolution after its last observation, with potential repercussion on better individual adjustment in treatment and inherent health care improvement.

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