Fitting viral dynamic models to longitudinal data using a population based approach

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Summary

Viral dynamic analyses of HIV-infected patients under treatment have shed light into many details and rates of the viral infection process. Here we will present this approach, with specific examples of analyzing longitudinal viral load data for subjects starting antiretroviral treatment. We will discuss the relevance of statistical models (mixed-effects) together with a mechanistic interpretation of the infection process to shed light on the biology of HIV.

Keyword: Drug treatment, HIV, Mixed-effects, Viral dynamics.

Introduction

Viral infectious diseases represent a huge burden for public health, with important implications for mortality, morbidity and health care costs [1]. Quantitative studies of viral load kinetics under antiviral treatment have allowed the definition of viral turnover and infected cell turnover in many different infections. Analyses of human infections as diverse as human immunodeficiency virus (HIV) [2; 3] or hepatitis C virus (HCV) [4] have demonstrated how quickly circulating virus is produced and cleared, even in long-term chronic infections, when the infection seems to be in clinical latency and the patient remains (mostly) asymptomatic.

Results

The standard model of HIV infection includes target cells, T, infected cells, I and free virus, V [2; 3]. Cells are infected at rate βTV, proportional to the availability of target cells and free virus, generating productively infected cells, I, which die at rate δ. In turn, virus, V, is produced by cells I at rate p per cell and is cleared from the circulation at rate c per virion. These infection processes are modified by the effect of drug treatment, which depending on the mode of action can affect infectivity (β), production of virus (p), or other processes. This model can be written as a system of ordinary differential equations, which can be solved under appropriate assumptions. We will present the development of these models and analyze a specific application to HIV-infected individuals treated with a combination of antiretrovirals. To fit the model to the data, we used a mixed-effects approach, with subject as the random effect. The covariates and the random effect covariance structure were chosen based on likelihood ratio tests. The objective was to estimate the parameters governing the dynamics of viral infection, and the efficacy of the drugs in reducing infection.

In Figure 1, we present the model prediction for the decline in viral load under therapy. Adjusting these curves to the data, we can estimate under various circumstances the death rate of infected cells, the clearance rate of free virus, and the efficacy of the drugs in blocking specific steps of the viral lifecyle. Using mixed-effects models to analyze this longitudinal data is a natural and powerful approach that allows simultaneous fitting of all the data, and analyses of important covariate factors with influence on the parameters estimated.

This approach showed that during clinical latency of HIV the viral turnover is huge. The half-life of free virus was estimated at ~45 minutes, implying total production and clearance of over 10^{10} virions per day. The half-life of productively infected cells was estimated at ~1 day, implying that about 10^7 cells are infected and killed every day by the virus [3]. These estimates have important clinical implications. For example, given the mutation rate of the virus, one understands the large diversity of the viral quasi-species and why drug resistance leads to treatment failure, or why it is so difficult to find an effective vaccine for this virus. One clinical corollary is that HIV must be treated with combination therapy (multiple drugs) [5].

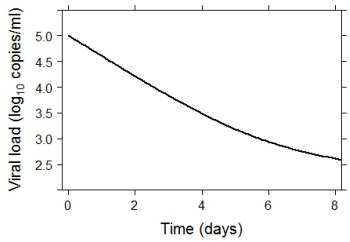

Figure 1. Predicted plasma HIV RNA decay under therapy

Conclusions

Modeling the dynamics of viral infections is a new field [6]. Matching these mechanistic models with mixed-effects fitting of data from individuals under treatment (and indeed other cases) has proven to be very successful in providing biological and clinical insight into the lifecycle of these viruses.

References

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