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Non-linear dynamics models characterizing long-term virological data from AIDS clinical trials. (English) Zbl 1015.92022

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Summary: Human immunodeficiency virus (HIV) dynamics represent a complicated variant of the textbook case of nonlinear dynamics: predator-prey interaction. The interaction can be described as naturally reproducing T-cells (prey) hunted and killed by virus (predator). Viruses reproduce and increase in number as a consequence of successful predation; this is countered by the production of T-cells and the reaction of the immune system. Multi-drug anti-HIV therapy attempts to alter the natural dynamics of the predator-prey interaction by decreasing the reproductive capability of the virus and hence predation. These dynamics are further complicated by varying compliance to treatment and insurgence of resistance to treatment. When following the temporal progression of viral load in plasma during therapy one observes a short-term ($1-12$ weeks) decrease in viral load. In the long-term (more than 12 weeks from the beginning of therapy) the reduction in viral load is either sustained, or it is followed by a rebound, oscillations and a new (generally lower than at the beginning of therapy) viral load level.

Biomathematicians have investigated these dynamics by means of simulations. However the estimation of the parameters associated with the dynamics from real data has been mostly limited to the case of simplified, in particular linearized, models. Linearized models can only describe the short-term changes of viral load during therapy and can only predict (apparent) suppression.

In this paper we put forward relatively simple models to characterize long-term virus dynamics which can incorporate different factors associated with resurgence: (F1) the intrinsic nonlinear HIV-1 dynamics, (F2) drug exposure and in particular compliance to treatment, and (F3) insurgence of resistant HIV-1 strains. The main goal is to obtain models which are mathematically identifiable given only measurements of viral load, while retaining the most crucial features of HIV dynamics. For the purpose of illustration we demonstrate an application of the models using real AIDS clinical trial data involving patients treated with a combination of anti-retroviral agents using a model which incorporates compliance data.

MSC:

92C50 Medical applications (general)
62P10 Applications of statistics to biology and medical sciences; meta analysis
92D25 Population dynamics (general)

Keywords:

HIV dynamics; nonlinear models; linearized models; mixed effects; anti-retroviral drug therapy

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NONMEM

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