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Modeling the mechanisms of acute hepatitis B virus infection

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Abstract

Mathematical models have been used to understand the factors that govern infectious disease progression in viral infections. Here we focus on hepatitis B virus (HBV) dynamics during the acute stages of the infection and analyze the immune mechanisms responsible for viral clearance. We start by presenting the basic model used to interpret HBV therapy studies conducted in chronically infected patients. We then introduce additional models to study acute infection where immune responses presumably play an important role in determining whether the infection will be cleared or become chronic. We add complexity incrementally and explain each step of the modeling process. Finally, we validate the model against experimental data to determine how well it represents the biological system and, consequently, how useful are its predictions. In particular, we find that a cell-mediated immune response plays an important role in controlling the virus after the peak in viral load.
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Keywords: Hepatitis B virus; Viral dynamics; Acute infection dynamics; Modeling viral infections; cccDNA; Immune response modeling

1. Introduction

Hepatitis B virus infects liver cells (hepatocytes) and can cause both acute and chronic disease. It is believed that host factors, in particular immune responses, are responsible for determining whether the infection is cleared or becomes chronic (Thimme et al., 2003). In Fig. 1 we show a typical profile of HBV viral load during acute infection.

Mathematical models have been used to help understand the dynamics of viral infections, such as human immunodeficiency virus and hepatitis C infection (see Perelson, 2002; Perelson et al., 2005 for reviews). Following these approaches, dynamic models were developed to analyze the changes in hepatitis B virus levels during drug therapy (Nowak et al., 1996; Tsiang et al., 1999; Lau et al., 2000; Lewin et al., 2001; Colombatto et al., 2006). These models typically considered uninfected (T) and infected (I) hepatocytes and free virus (V). They assumed that target cells, i.e., cells susceptible to infection, are produced at a constant rate λ, die at per capita rate d, and become infected at a rate kTV, proportional to both the target cell concentration and the virus concentration. Infected hepatocytes are thus produced at rate kTV and are assumed to die at constant rate δ per cell. Upon infection, hepatocytes produce virus at rate p per infected cell, and virus is cleared at rate c per virion. The dynamics of the system are governed by the following equations:

$$\begin{aligned}\frac{dT}{dt} &= \lambda - dT - kVT,\\ \frac{dI}{dt} &= kVT - \delta I,\\ \frac{dV}{dt} &= pI - cV.\end{aligned} \tag{1}$$

Several studies (Nowak et al., 1996; Tsiang et al., 1999; Lau et al., 2000; Lewin et al., 2001) have modified Eq. (1) to include antiviral therapy. The models introduced a therapy-induced block in virus production with efficacy ε, i.e., replaced the term pI with $(1-\varepsilon)pI$, and a block in viral infection with efficacy η, i.e., replaced the term kVT with $(1-\eta)kVT$. The models were then fit to viral load data

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