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Research paper

Threshold dynamics of HCV model with cell-to-cell transmission and a non-cytolytic cure in the presence of humoral immunity

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ABSTRACT

A mathematical model for HCV infection, which incorporates both the routes of infection spread, namely, virus-to-cell and cell-to-cell transmission along with a cure rate of infected cells through the non-cytolytic process, is presented. In addition, the model also includes the effect of humoral immune response using a nonlinear activation rate. To the best of our knowledge, this is the first model for HCV dynamics which incorporates both the cell-free and cell-to-cell transmission as well as cure rate within the same model, in addition to antibody being a part of the model setup. The non-negativity and boundedness of solutions of the model system are established and the basic as well as viral reproduction number is determined. The local and global stability analysis of the three equilibria, namely, disease-free, immune response free and infected equilibrium with humoral immune response are investigated theoretically as well as numerically in terms of conditions on the basic reproduction number and viral reproduction number. Comparison of four different HCV models is carried out numerically. The numerical results indicate that the consideration of cell-to-cell infection increases the concentration of infected cells, while the humoral immune response neutralizes the virus density effectively and it has a less significant effect in reducing the infection. The inclusion of the non-cytolytic cure increases the level of uninfected cells. The effects of both the modes of infection spread and cure in infected cells, on the basic reproduction number and the subsequent impact on the dynamical behavior of the system are illustrated.

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1. Introduction

Hepatitis C virus (HCV) infection is a hepatological condition, with an estimated global burden of 130–150 million [1]. HCV is a blood-borne disease where the human-to-human transmission can be attributed to factors like injecting drug use and ineffective screening of potentially HCV infected blood donors [2,3]. Different long-term prognosis has been reported for HCV infected patients. Neumann et al. [4] noted that 20 – 30% of the individuals with chronic HCV infection may develop liver cirrhosis and 1 – 3% may develop liver cancer. Roe and Hall [5] noted that 50 – 80% of HCV infected cases begin as chronic, out of which about 20 – 30% may develop liver cirrhosis, of which hepatocellular carcinoma could occur in 5%

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of the cases. HCV which is an enveloped flavivirus with the positive-stranded viral RNA encoding a polyprotein precursor amino acids, followed by entry of HCV into the cell after binding to its surface [6].

One of the earlier models for HCV dynamics due to Neumann et al. [4] was on the in-vivo dynamics of HCV progression and the efficacy of anti-viral treatment using interferon-α (IFN-α). The basic mathematical model used for this study involved the production of target cells (uninfected hepatocytes) at a constant rate, with the resulting analysis indicating that IFN played a more effective role in the blocking of production as well as the release of HCV virions, in comparison to its effectiveness in blocking the HCV infection itself. An extension of the basic model in [4] incorporating the combination anti-viral therapy of pegylated interferon and ribavirin appeared in [7]. The model was based on clinical observations that the administration of ribavirin results in the decrease of HCV infectivity. While administration of ribavirin alone has limited therapeutic effect in terms of decline in viral load, a combination of ribavirin with interferon results in substantially improved long-term prognosis for the patients. The long-term dynamics predicted by the model was observed to be in agreement with the HCV RNA decline in patients administered with the combination therapy. The models in [4] and [7] was extended by Dahari et al. [8] and was based on the argument that the liver is an organ that can regenerate itself, and included a logistic term for the homeostatic mechanism of the liver. The model was able to explain several clinical observations, namely, biphasic and triphasic decline patterns in the viral load, cases of partial responders and the relapse to baseline value after discontinuation of the combination treatment. Further, the model established a critical level of combination drug efficacy, above which the HCV will undergo eventual clearance and below which one could expect a partial response and a chronic steady state is reached. A further generalized model, with the efficacy of ribavirin (in rendering a fraction of the virions as non-infectious) being considered a function of time was analyzed by Dahari et al. [9]. The model predicted that the observed triphasic decline in HCV RNA happened only in case of patients who had a majority of their hepatocytes being infected even before the initiation of therapy. The pharmacokinetics of HCV therapy with the drug efficacy as a function of drug concentration and the resulting HCV RNA decay profile is reviewed in [10]. The apparent discrepancy resulting from the model based long-term results (such as sustained virological response (SVR)) and clinical observations, was addressed by the introduction of extinction threshold in [11]. However, Debroy et al. [12] showed that bistability in the HCV models, which happens under certain physiological conditions, could lead to SVR, even without the inclusion of extinction threshold. Delay dynamics observed in the biological phenomenon, was studied for HCV dynamics, though the latent period of infected hepatocytes in [13], wherein stability switches in the model are demonstrated. Further, they illustrated how bubbles and chaos can be induced by an intracellular delay.

The investigation into the kinetics of viral infection progression in presence of immune response is essential since the entry of pathogens and consequent infection triggers the immune system. Nowak and Bangham [14] explored, through a mathematical model, the relation between immune response and virus characteristics, namely, virus load and diversity, and involved an additional term for the magnitude of the cytotoxic T lymphocytes (CTLs) in a basic viral dynamics model. The model predictions were compared with the data from patients with human T cell leukemia virus (HTLV-1) and human immunodeficiency virus (HIV-1). Wodarz [15] proposed an extended model for examining the role of both CTL and antibody responses in HCV patients. The dynamics in case of both acute and chronic patients were examined in order to study the evolution of the virus and the disease progression. The model highlights the key role being played by the immune response in ascertaining the prognosis for the patient, namely, whether the patient remains asymptomatic or shows signs of pathology. The model shows that CTL responses play an essential role in the infection being cleared out. Failure to do so could lead to CTL induced liver pathology, at which point the antibodies, which otherwise are unable to clear the infection, could prevent this CTL induced liver pathology thereby keeping the patient in an asymptomatic state. This model [15] was later analyzed in detail from a mathematical perspective by Yousfi et al. [16] and with the inclusion of therapeutic efficacy by Meskaf et al. [17]. The significance of lytic and non-lytic immune response in patients with viral infections is reviewed in detail in [18]. While the former involves the killing of the infected cells, the latter acts by preventing the viral replication process itself without affecting the infected cells. The complex interplay of both these responses and the consequent impact on whether the patient is asymptomatic or pathological is dwelled upon in detail in the context of HCV. Li et al. [19] considered a model to include the role of antigen-presenting cells (APCs), namely, dendritic cells (DC) with CTLs in case of HCV infection, in which they assumed that CTL expands through cross-presentation of activated DC and gets removed by the direct presentation of infected cells. They observed that the immune response would be more effective upon activation of the non-activated DCs and a reduced CTL clearance rate. Further, it was observed that initial DC and CTL levels have a role in the immune response outcome.

The understanding of mechanism and dynamics of virus-host interplay during primary infection is somewhat limited [20]. The quantitative analysis of this aspect was carried out in [20] for a mathematical model which accounted for the HCV RNA levels and alanine aminotransferase (ALT) kinetics. The analysis resulted in the observation that endogenous type I interferon somewhat inhibits the rate of early-stage production of the virions. The control of viral replication was also observed to be aided by the half-life of the infected cells. The dynamics of post-therapeutic progression of HCV RNA, that realistically encapsulated the large set of clinical observations, was mathematically modeled and analyzed by Reluga et al. [21]. Leon [22] modeled the cure rate of the infected hepatocytes along with intracellular delay caused by the delay in the virions becoming infectious in nature. The term “cure” in the context of this model meant the inclusion of the rate at which the uninfected hepatocytes are created from the infected hepatocytes as a result of being cured. This reversion from the infected to the uninfected state was modeled in [23]. This term reflected the cytokine-induced cure observed in acute hepatitis B (HBV) patients as a result of loss of covalently closed circular DNA (cccDNA) from their nucleus, which caused a

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