INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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Thesis Title: A Theoretical Study of Recycling Effects of rcDNA-containing Capsids on Hepatitis B Virus Infection

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SHORT ABSTRACT

In this thesis, the dynamics of hepatitis B virus (HBV) infection are studied by incorporating several aspects, such as recycling of capsids, the effects of fractional-order derivative, the impacts of proliferation, the roles of sub-viral particles and antibodies. This dissertation begins by investigating the roles of cytoplasmic recycling of rcDNA-containing capsids in HBV infection. To this purpose, a novel four-compartmental (uninfected and infected hepatocyte, rcDNA-containing capsids and virus) ODE model is proposed to better understand this viral infection. This model demonstrates excellent agreement with the experimental data of two chimpanzees. The effects of three key parameters (recycling rate, virus production rate, and volume fraction of newly produced capsids in favor of virus production) are analyzed via numerical experiments. Furthermore, a comprehensive global sensitivity analysis is conducted using the widely-used technique Latin hypercube sampling–partial rank correlation coefficient. As a result, this study shows that the accumulation of rcDNA-containing capsids within the infected hepatocyte is a key factor contributing to the exacerbation of the disease. In other words, the cytoplasmic recycling of newly produced rcDNA-containing capsids acts as a positive feedback loop in the viral infection.

Next, the proposed model is extended by replacing the ordinary derivative with a fractional derivative, resulting in two nonlinear fractional-order HBV infection models based on the Caputo derivative. In the first model, the order of fractional derivatives is commensurate across all compartments, whereas in the second model, the orders are incommensurate. The existence and uniqueness of solutions for both models are established. The modified models are validated with experimental data. We numerically solve both fractional-order models using the predictor–corrector Adams–Bashforth–Moulton method (for commensurate order) and implicit product integration of trapezoidal type method (for incommensurate order) with various choices of fractional orders and initial conditions. Stability analyses are conducted for both models. Additionally, the impacts of individual component of fractional derivatives in incommensurate-

order model on infection dynamics are also explored. All the results are presented graphically, and it is observed that with the decrease in the order of fractional derivative, the peak level of infection or severity of the infection decreases, however, disease takes longer time to be cured.

Later, the temporal dynamics of this viral infection are investigated through two more intercellular mathematical models that incorporate the proliferation of both uninfected and infected hepatocytes, as well as the recycling of capsids. One model examines continuous proliferation, while the other one deals with discontinuous proliferation based on cellular volume of the liver. Both models are formulated on the basis of the following biological findings reported in the literature: mitosis of an infected hepatocytes yields in two uninfected progenies. After showing the identifiability of the model parameters, the values of the parameters are estimated based on the experimental data. The results of this study suggest that if the infected hepatocytes proliferate at a different rate that of uninfected hepatocytes, the proliferation of uninfected hepatocytes contributes to an increase in infection, but the proliferation of infected hepatocytes acts to reduce the infection from the long-term perspective. The global sensitivity analysis also corroborates these findings. Furthermore, it is also observed that the differences between the outcomes of continuous and discontinuous proliferations are significant and noteworthy.

The subsequent work presents an updated mathematical model that incorporates the roles of sub-viral particles (SVPs) and roles of immune system, specifically antibodies. This model also accounts for the spatial mobility of capsids, viruses, SVPs, antibodies, and offers unique characteristics in the context of this viral infection. The study examines the changes in the infection dynamics considering both single-point and multi-point initial conditions. The findings suggest that SVPs significantly enhance the intracellular viral replication and gene expression by reducing the neutralization of virus particles by antibodies. Furthermore, the recycling of capsids substantially increases the concentration of SVPs. Experiments conducted with single-point and multi-point infection initial conditions show that if the liver is infected at multiple points, the infection spreads more rapidly.

The final work focuses on a comprehensive analysis of the intracellular dynamics of this viral infection. Considering the intracellular processes observed in the viral life cycle and can be targeted by the antiviral therapy, an intracellular HBV infection dynamics model is proposed. The well-known fourth-order highly accurate Runge-Kutta method is employed to numerically solve the proposed model. In order to identify the most influencing parameters, a global sensitivity analysis of the parameters is performed using partial rank correlation coefficients based on Latin hypercube sampling method. The effects of initial concentrations of cccDNAs, the roles of HBx proteins, dslDNA-containing intermediates and intracellular delay are explicitly discussed. Results indicate that HBx proteins show considerable influence on the course of infection, whereas intracellular delay and dslDNA-containing intermediates have negligible impacts on the disease dynamics. Furthermore, the study reveals that SVPs have potential to augment the infection.