Lior Strauss
Bar-Ilan University, Ramat-Gan, Israel
e-mail: liorstr1@gmail.com
Avidan U. Neumann
Bar-Ilan University, Ramat-Gan, Israel

Distributed Intra-Cellular Model of Hepatitis C Viral Replication and Resistance Evolution

The new generation of direct acting anti-viral (DAA) drugs for HCV led to the need for mathematical models that take in consideration the intra-cellular drug effects within clinical virology data. We have recently introduced the ICCI model that integrated the intra-cellular level of replication and resistance evolution processes with the cellular infection level (Guedj and Neumann, 2010). However, the ICCI model used a mean-field approach to treat all infected cell as the same dynamics, which we know is not accurate. Here, we present a new model (DIC) that describes the intra-cellular level dynamics integrated into the cell infection level whle taking into consideration the distribution of infected cells as function of the number of replication complexes in each cell. The DIC model shows that main novel findings of the ICCI model hold even when the mean-field assumption is released. Most importantly, the model allows for 2 modes of viral decline: either the delta model, where long term viral decline slope is governed by the loss of infected cells, or the gamma mode, where the viral decline is more rapid and related to the intra-cellular loss of replication complexes. Furthermore, the DIC model shows that while on the delta mode the distribution of cells with different number of replication complexes is held stable, on the gamma mode the distribution of cells is shifting towards intra-cellular clearance. We have also established the properties of the infected cell distribution at steady state. The model was able to show a good fit for a wide range of results observed in real patients treated either with IFN based therapy or DAA combination therapy. In a second part of the work we have established the various resistance evolution patterns observed with the ICCI model hold also without the mean-field assumption. Furthermore, we show how the distribution of cells with different number and identity, wild-type versus resistant, of replication complexes follows specific patterns during evolution of resistance. These results are important for our understanding of the DAA therapy effect and allowing us to optimize treatment and prevent resistance evolution.