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Deterministic and Stochastic Multi-level Modeling of Hepatitis C Viral Kinetics and Resistance Evolution

Mathematical models of viral dynamics and resistance evolution have brought important insights for understanding the treatment of HIV, HBV and HCV viral infections. However, current models of in vivo anti-viral therapy (CI models) consider only cell to cell infection dynamics, disregarding the impact of intra-cellular replication dynamics. This class of models shows either viral decline with non-resistant viral strains or a permanent viral rebound once a phenotypically resistant strain evolves. Indeed, these are the patterns observed for HIV, where intra-cellular replication has less of an impact because integrated viral DNA is a static replication unit and the various resistance events occur at the time scale of cell infection. However, other patterns of viral evolution kinetics, which are contradictory to the current models, were observed during direct anti-viral therapy against HCV, where intra-cellular dynamics play an important role.

We have therefore developed a novel model (Guedj and Neumann, 2010) for resistance evolution, which includes viral dynamics and evolution in both the intra-cellular replication level and the cell-infection level (ICCI model). As a consequence of the complex interaction between the two levels of viral dynamics, the ICCI model predicts a rich repertoire of viral kinetics and resistance evolution patterns. In particular, we predict that continuous viral decline is possible even if a phenotypically resistant strain has emerged. Furthermore, we show that a resistance related viral breakthrough could be merely transient and nevertheless resolved. In both cases, counter-intuitively to our experience with HIV, viral eradication may be achieved even with a phenotypically resistant virus.

In addition, the ICCI model allows for rapid emergence of resistance evolution without the need for rapid turnover of infected cells, i.e. new cells are not needed to be available for infection by resistance virus. This is due to the fact that the intra-cellular replication space can be freed for evolution to resistant virus within the cells that are already infected. This theoretical possibility was verified also by stochastic modeling of the intra-cellular resistance evolution with a fixed population of infected cells. Furthermore, stochastic simulation of the ICCI model shows how different patterns of resistance evolution occur as function of the intra-cellular parameters. These results elucidate what the important parameters to measure empirically in order to understand what kind of resistance patterns will occur during treatment.