Mechanistic dynamics of Hepatitis C virus replication in single liver cells

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Infection with hepatitis C virus (HCV) causes chronic liver diseases. HCV-related liver damage is the main reason for liver transplantations in the western world. Spatial resolution is an aspect that has not yet been appreciated in current modeling simulations despite strong biological evidence that suggests intracellular spatial dependence is a crucial factor in the process the virus uses to replicate its RNA genome. HCV replication is believed to occur in specialized compartments within virus-infected cells, termed replication complexes, which are derived from altered regions (called the membranous web) of the endoplasmic reticulum (ER - the ER is a central structure of each cell). Trafficking of both replication complexes, and their components, is likely a dynamic process occurring in three dimensions that is both difficult to capture experimentally and conceptually visualize. Therefore, we are developing a spatially-resolved biophysical model of HCV replication dynamics in single liver cells. We used data derived from 3D confocal microscopy of HCV-infected human hepatoma cells labeled for the ER membrane in order to reconstruct 3D geometries of single hepatocytes using NeuRA2. On top of these geometries, we developed a model using (surface) partial differential equation of viral RNA replication dynamics with particular emphasis upon RNA movement, viral protein production, cleavage and movement, and viral RNA replication within the membranous web. The arising (s)pde s on the ER surface are solved using the simulation platform UG4 within a Finite Volume framework combined with multigrid techniques. Our approach is based on two columns which are intended to grow together in the middle run: On the one hand side, we are doing parameter estimations of single components of viral replication based on the Gauss-Newton algorithm in order for extracting e.g. the diffusion constant of basic viral proteins on the surface of the ER using experimental FRAP time series. On the other hand side, we are developing the model which mimics the interplay of all important component of virus replication, e.g. viral RNA and various states of viral proteins. The estimated parameters are entering the model step by step. Therefore, the presented work is a practical application of the powerful tool UG4 and its multigrid techiques for the case of a huge number of DoFs (about 10^6) already at base level and demonstrates the excellent usability (and scalability) of UG4 in the context of modern biophysical research.

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