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Intracellular ”in silico microscopes” - fully 3D spatio-temporal virus replication model simulations

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Despite being small and simple structured in comparison to their victims, virus particles have the potential to harm severly and even kill highly developed species such as humans. To face upcoming virus pandemics, detailed quantitative biophysical understanding of intracellular virus replication mechanisms is crucial. Unveiling the relationship of form and function will allow to determine putative attack points relevant for the systematic development of direct antiviral agents (DAA) and potent vaccines. Biophysical investigations of spatio-temporal dynamics of intracellular virus replication so far are rare.
We are developing a framework to allow for fully spatio-temporally resolved virus replication dynamics simulations based on partial differential equation models (PDE) and evaluated with advanced numerical methods on large supercomputers. This study presents an advanced highly nonlinear model of the genome replication cycle of a specific RNA virus, the Hepatitis C virus (HCV). The diffusion-reaction model mimics the interplay of the major components of the viral RNA (VRNA) cycle, namely non structural viral proteins (NSP), VRNA and a generic host factor (energy supply etc.). Technically, we couple surface PDEs (sufPDEs) on the 3D embedded 2D Endoplasmatic Reticulum (ER) manifold with PDEs in the 3D membranous web (MW) and cytosol volume. (The MWs are the replication factories growing on the ER induced by NSPs.) The sufPDE/PDE model is evaluated at realistic reconstructed cell geometries which are based on experimental data. The simulations couple the effects of NSPs which are restricted to the ER surface with effects appearing in the volume. The volume effects include the host factor supply from the cytosol and the MW dynamics. Special emphasis is put to the exchange of components between ER surface, MWs and cytosol volume. As the vRNA spatial properties are not fully understood so far in experiment, the model allows for vRNA both restricted to the ER and moving in the cytosol. The visualization of the simulation resembles a look into some sort of fully 3D resolved “in silico microscopes” to mirror and complement in vitro /in vivo experiments for the intracellular VRNA cycle dynamics. The output data are quantitatively consistent with experimental data and provoke advanced experimental studies to validate the model.

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References

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