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Intracellular ”in silico microscopes” - fully 3D spatial Hepatitis C virus replication model simulations

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Virus pandemics and endemics cause enormous pain and economic, political, and social costs and turmoil. While the Covid19 pandemics induced obvious damages, the “silent” Hepatitis C virus (HCV) infection induced liver destruction is the main reason for liver transplants. HCV virus replication sometimes serves as some sort of representative to study virus replication basics. HCV-generated virus genome replication factories are housed within virus-induced intracellular structures termed membranous webs (MW) which are derived from the Endoplasmatic Reticulum (ER). The ER is an interconnected intracellular membrane network and embedded within the cytosol. The interplay of virus components whose action is restricted to the 2D ER manifold and of other virus components which act in the 3D volume cytosol space is crucial for virus replication. Up to now, the very advanced experimental data such as highly spatially resolved fluorescence and electro-tomography data in many cases do not enter computational HCV viral RNA (vRNA) cycle models. Based upon diffusion-reaction partial differential equations (PDEs), we are developing fully 3D resolved “in silico microscopes”to mirror in vitro / in vivo experiments for the intracellular vRNA cycle dynamics. Our first models described the major components (vRNA, non-structural viral proteins - NSPs - and a host factor). The next steps incorporated additional parameters: Different aggregate states of vRNA and NSPs, and population dynamics inspired diffusion and reaction coefficients instead of multilinear ones. Our work in progress framework presently is merging effects restricted to the ER surface (e.g. NSP diffusion) with others taking place in the cytosol (e.g. host factor supply). Further we estimate and incorporate realistic parameters such as NSP diffusion constants. The simulations are performed upon experimental data based reconstructed cell geometries which indeed display a very complex porous medium structure. Our simulations help understanding the relation of form and function of intracellular virus replication mechanisms. In the long run, our framework might help to facilitate the systematic development of efficient direct antiviral agents and vaccines.

Participation

In-Person

References

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