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Computational methods for hybrid stochastic multiscale modelling of virus infection dynamics

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Motivation and Aim: The dynamics of virus infections are governed by a variety of processes at multiple scales: at the whole organism level (systemic transport of immune cells, cytokines and viruses between lymphoid and target organs via blood and lymphatic systems), at the tissue level (immune cell locomotion, virus and cytokine spread in lymphoid and virus sensitive tissues, cell-to-cell virus transmission), and at the intracellular level (intracellular virus replication and molecular signalling determining the immune cell states). Certain processes at several scales are stochastic, and the resulting randomness influences other scales. By adopting an integrative approach, we have developed computational methods for studying virus infections through hybrid stochastic multi-scale multi-compartment modelling [1, 2].

Methods and Algorithms: Transport of viruses, cells and molecules between infection sites, lymphoid tissues and blood is modelled using a multi-compartment approach. Reaction-diffusion equations are used to model diffusion of free virions in the lymphoid tissue with moving sources, which are determined by the positions of the infected cells (immune cell motility model) and the rate of virion secretion from these cells (intracellular model). These transport equations are solved numerically using the finite element method on the unstructured tetrahedral meshes over the generalized lymph node geometry adaptively refined to the spherical sub-domains occupied by the productively infected cells [1]. Immune and target cells are treated as individual agents, with their positions determined by the cell motility model that parametrises the intercellular interaction forces, friction and the stochastic forces of active cellular motility [3]. The equations of cell motion are integrated numerically using the symplectic Euler method. Intracellular models describe the production of the virus replication intermediates during the virus life cycle, which are calibrated as continuous deterministic ordinary differential equation-based models [4]. After calibration, these models are transformed into the discrete stochastic Markov chain-based models with time-inhomogeneous propensities that depend on the extracellular virus concentrations [1]. Stochastic intracellular models are simulated using the integral- or uniformization-based Monte Carlo algorithms, as well as the hybrid discrete-continuous stochastic-deterministic approximation methods [1, 2, 5, 6].

Results: The immune cell motility model calibrated to reproduce the lymphocyte movement patterns in lymphoid tissues was used to estimate the numbers of HIV-specific cytotoxic T cells required for effective control over the local bursts of HIV

infection in the lymph nodes [3]. The detailed models of intracellular virus replication were developed and calibrated for HIV-1, SARS-CoV-2 and LCMV [4–6]. Local and global sensitivity analysis was performed for deterministic intracellular models and for their discrete stochastic counterparts to identify the potential targets for antiviral drug development among the processes that regulate the virus life cycles. Markov chain-based models were used for quantifying the stochastic heterogeneity of intracellular virus replication and progeny production, depending on the multiplicity of cell infection. A multiscale model was developed to study the dynamics of the local bursts of HIV-infection in lymph nodes, integrating the intracellular, tissue, and systemic levels [1, 2]. The hybrid discrete-continuous stochastic-deterministic computational algorithm which is based on the uniformization Monte Carlo method was implemented to perform multiscale simulations of virus infection dynamics [1].

Conclusion: The essential element of the proposed multi-scale modelling approach is the use of hybrid discrete-continuous stochastic Markov chain-based formulations and simulation algorithms. This allows for prediction of intracellular heterogeneity or virus replication dynamics of the infected cells. Since target and immune cells are treated as individual agents and their positions are determined by the stochastic cell motility model, the associated stochasticity extends to the other scales. The developed computational tool provides a way to study virus infection dynamics at multiple scales of the immune system organization.

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