

A Stage Structured Hybrid Model for Disease Dynamics and Modelling of Complex Systems

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Abstract: Stochasticity and spatial distribution of the pathogen play a critical role in determining the outcome of an infection. 1 in a million immune system cells are specific to a particular pathogen. The serendipitous encounter of such a rare immune system cell with its fated antigen can determine the mortality of the infected animal. Moreover pathogens may remain initially localized in a small volume of tissue. Hence stochastic and spatial aspects play an important role in pathogenesis, especially early on in the infection. Current efforts at investigating the effect of stochasticity and space in modeling of host immune response and pathogens use agent based models (ABMs). However these are computationally expensive. Population level approaches like ordinary differential equations (ODEs) are computationally tractable. However they make simplifying assumptions that are unlikely to be true early on in the infection. We proposed a *stage-structured hybrid model* that aims to strike a balance between the detail of representation of an ABM and the computational tractability of an ODE model. It uses a spatially explicit ABM in the initial stage of infection, and a coarse-grained but computationally tractable ODE model in the latter stages of infection. Such an approach might hold promise in: 1) modeling of other pathogens where the initial stochasticity of the pathogen dictates the trajectory of pathogenesis, and 2) lead to insights into immune system inspired strategies and architectures for distributed systems of computers.

Introduction

Stochasticity and spatial distribution of the pathogen play a very critical role in determining the outcome of an infection. 1 in 10^6 B-cells are specific to a particular pathogen [1]. The serendipitous encounter of such a rare cognate B-cell with its fated antigen can determine host mortality. Mosquito vectors inject an average of 10^5 PFU of West Nile Virus (WNV) into an animal [2]. However there is a lot of variation around this mean. If a mosquito injects into a vein, the pathogen can spread systemically instead of being localized in tissue, leading to faster progression disease progression but possibly faster recognition by immune system cells. If a mosquito only injects into tissue, the pathogen may remain initially localized in a small volume of tissue.

Such stochastic and spatial aspects of pathogenesis likely play a role in other diseases also. For example, macaques experimentally inoculated with a low dose of Simian Immunodeficiency virus became infected with a very low probability in a dose dependent manner suggesting the role of initial stochastic events in shaping the trajectory of pathogenesis [3].

Current efforts at investigating the effect of stochasticity and space in modeling of host immune response and pathogens use agent based models (ABMs). An ABM represents each entity or agent (each cell or virion in our case) explicitly, and a computer program encodes each rule or behavior for interacting with other agents. The agents move about in space and interact with other agents in their neighborhood according to the encoded rules. ABMs emphasize local interactions based on first principles, and these interactions give rise to the complex high-level phenomena of interest.

Due to the level of detail at which individual components are represented, ABMs can be computationally expensive and sometimes intractable. Population level approaches like ordinary differential equations (ODEs) are computationally tractable [4] and can scale up to simulate host pathogen dynamics in large organisms [4]. However they make simplifying assumptions. For example they subsume individuals into a homogeneous compartment. They also assume that populations are homogeneously mixed. For example, the implicit assumption is that at initialization, a population of injected virions and normal cells would be “well-mixed”. This is unlikely to be satisfied during the initial stage of infection, when inoculated virions localize at the site of infection. Such spatial effects assume more importance during the onset of infection, when the number of virions is low, and we need an ABM to address this.

We proposed an approach that aims to strike a balance between the detail of representation of an ABM and the computational tractability of an ODE model. We call this a stage-structured hybrid model [4]. It uses a detailed and spatially explicit, but computationally intensive ABM in the initial stage of infection, and a coarse-grained but computationally tractable ODE model in the latter stages of infection (when the assumptions of homogeneous mixture of population are likely to be satisfied and spatial effects can be ignored). Such an approach might hold promise in modeling of other pathogens where the initial stochasticity of the pathogen and host response dictates the trajectory of pathogenesis. A general schematic of the approach in Fig. 1.

The scheme involves running simulations of within-host viral dynamics in two distinct phases. The first phase involves running a spatially explicit ABM till well-mixed assumptions are likely to be true. In the second phase, parameters of the ABM simulation are transferred (after modification if necessary) to an ODE model, which is then run for the remainder of the simulation.

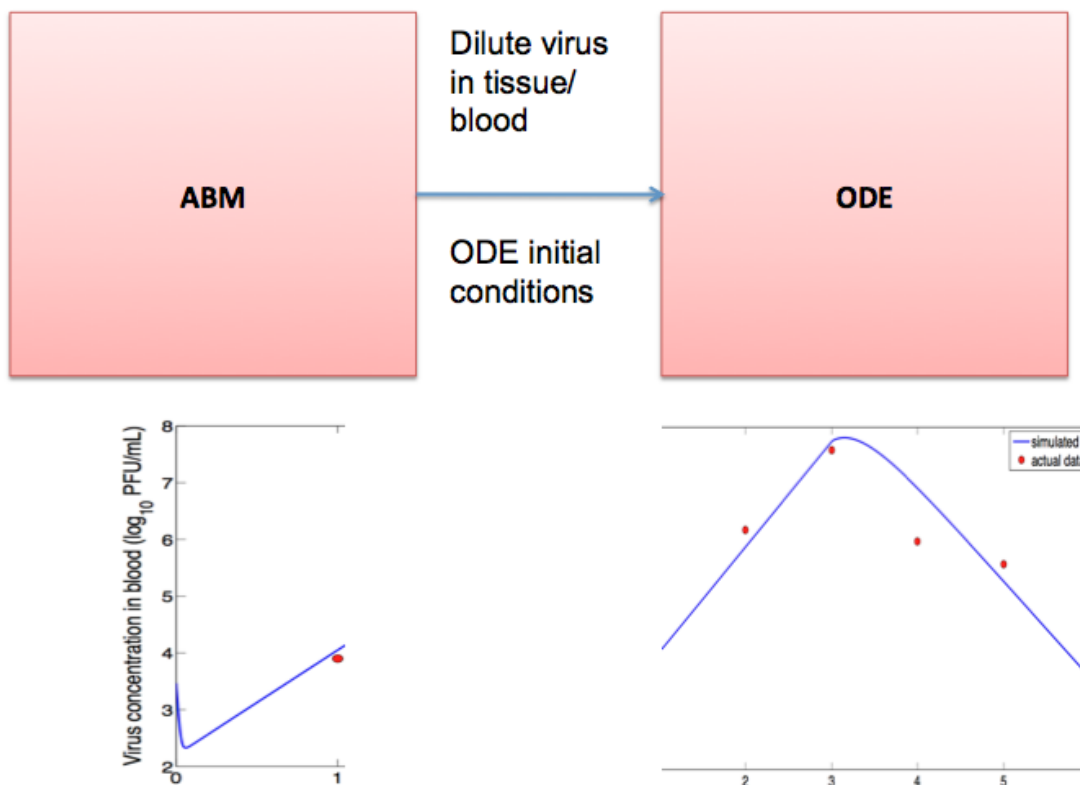


Fig. 1. A general schematic of stage-structured hybrid model approach. The ABM is run till well-mixed assumptions are met (say till day 1 post-infection), after which the simulation is transitioned to an ODE model.

We note the caveat that in practice it may be hard to determine when well-mixed assumptions are met. As a first approximation, we suggest that well-mixed assumptions are likely to be satisfied when a pathogen has spread systemically throughout the host.

There are several advantages to exploiting tradeoffs between modeling fidelity and computational complexity:

- 1) The stage-structured hybrid modeling approach can help estimate parameters of infection much faster (since many methods of estimating parameters rely on running the simulations multiple times with different values of parameters to gauge goodness of fit to experimental data).
- 2) The stage-structured hybrid modeling approach can also be extended to modeling disease transmission between hosts. Mediating computational costs while modeling at both the level of within-host and between-host infection may help modeling at multiple scales and help in translating results of within-host modeling to make predictions for between-host disease spread [5,7].
- 3) Hybrid approaches can also help in simulations of disease dynamics across different scales ranging from dynamics within cells (intra-cellular regulatory networks) [16] to interactions between cells [15].
- 4) Such a hybrid approach may also lead to more insights into immune system inspired strategies and architectures for distributed systems of computers [5-12].
- 5) Finally, hybrid approaches such as the ones proposed here may also be used in modelling socio-economic and socio-technological systems [13,14].

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