Article

A stage structured hybrid model for within-host emerging infectious disease modelling

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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 emerging 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.

Keywords stage structured hybrid model; immune system modeling; viral dynamics modeling; agent based models; ordinary differential equation models.

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1 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 (Soderberg, 2005). 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 plaque forming units (PFU: a measure of infectious virus) of West Nile Virus (WNV) into an animal (Styer et al., 2007). 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 (Keele et al., 2009).

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 and can scale up to simulate host pathogen dynamics in large organisms (Banerjee and Moses, 2009). 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 (Banerjee and Moses, 2009). 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 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 is illustrated 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.

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.

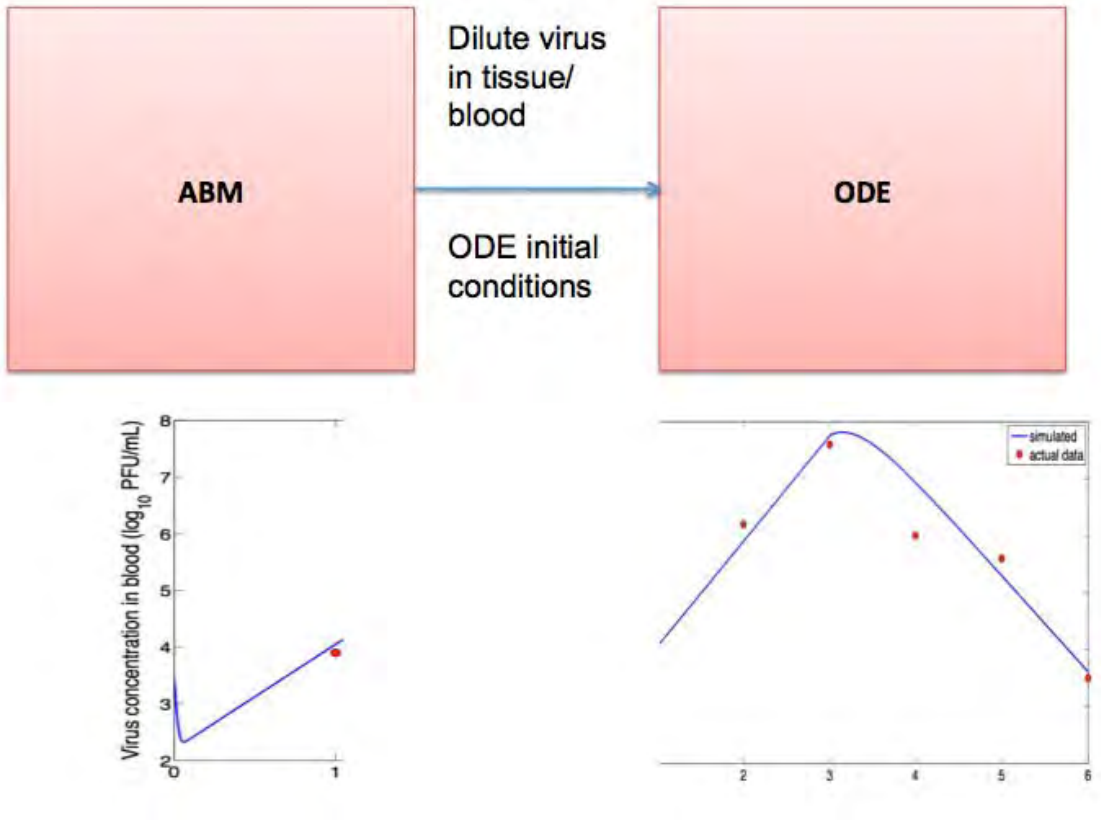

Fig. 1 A general schematic of stage-structured hybrid model approach. The ABM is run till well-mixed assumptions are met (say till day 1 post-infection), after which the simulation is transitioned to an ODE model.

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 (Banerjee, 2013; Banerjee and Moses, 2010a; Banerjee et al., 2016).

3) Hybrid approaches can also help in simulations of disease dynamics across different scales ranging from dynamics within cells (intra-cellular regulatory networks) (Liu et al., 2014) to interactions between cells (Banerjee, 2015).

4) Such a hybrid approach may also lead to more insights into immune system inspired strategies and architectures for distributed systems of computers (Banerjee, 2009; Banerjee and Moses, 2010a, 2010b; Banerjee et al., 2011; Moses and Banerjee, 2011; Banerjee, 2013; Banerjee and Hecker, 2015).

5) Finally, hybrid approaches such as the ones proposed here may also be used in modelling socio-economic and socio-technological systems (Banerjee et al, 2015; Banerjee, 2015b, 2015c).

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References

Banerjee S. 2009. An immune system inspired approach to automated program verification. arXiv preprint arXiv:0905.2649

Banerjee S. 2013. Scaling in the Immune System, PhD Thesis. University of New Mexico, USA

Banerjee S. 2015b. Analysis of a planetary scale scientific collaboration dataset reveals novel patterns. arXiv preprint arXiv:1509.07313

Banerjee S. 2015c. Optimal strategies for virus propagation. arXiv preprint arXiv: 1512.00844

Banerjee S, Guedj J, Ribeiro RM, Moses M, Perelson AS. 2016. Estimating biologically relevant parameters under uncertainty for experimental within-host murine West Nile virus infection. Journal of the Royal Society Interface, 13(117): 20160130

Banerjee S, Hecker J. 2015. A multi-agent system approach to load-balancing and resource allocation for distributed computing. arXiv preprint arXiv:1509.06420

Banerjee S, Levin D, Moses M, Koster F, Forrest S. 2011. The Value of Inflammatory Signals in Adaptive Immune Responses. The 10th International Conference on Artificial Immune Systems (ICARIS). Cambridge, UK

Banerjee S, Moses M. 2009. A hybrid agent based and differential equation model of body size effects on pathogen replication and immune system response. In: Lecture Notes in Computer Science: Vol. 5666. Artificial Immune Systems (Andrews PS et al., eds). 8th International Conference, ICARIS 2009. 14-18, Springer, Berlin, Germany

Banerjee S, Moses M. 2010a. Scale invariance of immune system response rates and times: Perspectives on immune system architecture and implications for artificial immune systems. Swarm Intelligence, 4(4): 301-308

Banerjee S, Moses M. 2010b. Modular RADAR: An immune system inspired search and response strategy for distributed systems. In: Lecture Notes in Computer Science: Vol. 6209. Artificial Immune Systems (Hart E et al, eds). 9th International Conference, ICARIS 2010. 116-129, Springer, Berlin, Germany

Banerjee S, van Hentenryck P, Cebrian M. 2015. Competitive dynamics between criminals and law enforcement explains the super-linear scaling of crime in cities. Palgrave Communications, 1: 15022

Keele, BF, Brocca-Cofano E, Guan YJ, et al. 2009. Low-dose rectal inoculation of rhesus macaques by SIVsmE660 or SIVmac251 recapitulates human mucosal infection by HIV-1. Journal of Experimental Medicine, 206: 1117-1134

Liu P, Calderon A, Konstantinidis G, Hou J, et al. 2014. A bioorthogonal small molecule switch system for controlling protein function in cells. Angewandte Chemie, 53(38): 10049-10055

Moses M, Banerjee S. 2011. Biologically inspired design principles for scalable, robust, adaptive, decentralized search and automated response (RADAR). In: Proceedings of Artificial Life (ALIFE). IEEE, 30-37, Paris, France

Soderberg A, Payne G, Sato A, Medzhitov R, Segal S, Iwasaki. 2005. A innate control of adaptive immunity via remodeling of lymph node feed arteriole. Proceedings of the National Academy of Sciences of USA, 102(45): 16315-16320

Styer LM, Kent KA, Albright RG, Bennett CJ, Kramer LD, et al. 2007. Mosquitoes inoculate high doses of West Nile virus as they probe and feed on live hosts. PLoS Pathogens, 3(9): e132