REVIEW FOR PEERJ PAPER

Multi-scale Models and Data for Infectious Diseases: A Systematic Review (#33906)

by

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Summary:

The authors conducted a systematic review of the published literature on multiscale mathematical models of infectious disease dynamics to determine the extent to which mathematical models are being used to understand across-scale dynamics at host level, and the extent to which these models are being confronted with data. They followed PRISMA guidelines for systematic reviews. The focus was on multiscale models that integrate the within-host and between-host scales. The review identified 19 of 139 qualifying papers across 30 years that include both linked within-host and between-host sub-models. They analyzed traits of the19 papers focusing on which species are modeled, which pathogens are modeled, which types of models are used, how the within-host and between-host dynamics are linked, and at what level data has been used. The main findings are that it was most common for these multiscale models to describe a human population, to model a viral disease, to use a deterministic modeling at either scale, to link the pathogen load at the within-host scale, to link the transmission rate at the between-host scale, and to use data at the within-host scale.

General comments:

1. The title of paper and even the way the whole manuscript is written seems to imply that multiscale modelling of infectious diseases means developing multiscale models only at host level of organization of an infectious disease system, that is, only integrating within-host scale and between-host scale. That is not true. There are also other levels of organization of an infectious disease system at which multiscale models can be developed to describe disease dynamics (see [3] below for other levels of organization of an infectious disease system at which multiscale models can be developed). If the authors would like to keep

the title of the paper as it is, they should acknowledge the existence of other levels of organization of an infectious disease system at which multiscale models can be developed and indicate why they chose the host level if the objective was to establish the state of multiscale modelling of infectious disease systems in general as implied by the title and the writing of throughout the paper.

2. The authors indicate that in their search for papers on multiscale models of infectious disease dynamics, they identified papers which were of review nature which they excluded in the analysis. However, since their paper is also of review nature, they should indicate how those other review papers are different from their current review paper.

3. In the manuscript, the submodels used in the multiscale were categorized into four groups (i.e. types of modeling framework): deterministic, statistical, individual-based, and stochastic for purposes of analysis. The authors did not give the criteria used to make this grouping of submodels in the multiscale models. The problem is that there is conflicting literature on what is an individual based model as some authors do not make distinction between individual-based models, stochastic models and statistical models (see for example [4] below which treats any model which does not describe disease variables as averaged quantities as individual-based model). Based on this criteria some individual based models can be statistical models, while some stochastic models can be individual based models. Therefore, the authors should clarify their grouping of the types of submodels into the four groups (deterministic, statistical, individual-based, and stochastic).

4. The authors identified two linking mechanisms which they categorized either as a state or a trait. Integrating the scales is one of the main scientific challenges in multiscale modelling of infectious disease systems. The authors identified that most of the submodels were linked through the pathogen load while pathogen growth rate was the second most used trait to link submodels. In general, the scales of an infectious disease system are linked through disease processes (see [3] below for a detailed discussion of some of the linkages between scales through disease processes). However, the challenge is to convert an actual disease processes that represents exchange of information

between scales (e.g. exchange of pathogen between within-host scale and between-host scale) into a mathematical linking mechanism. But is there any scientific/biological basis to support the existence of the linkage of scales through any of the following traits: pathogen death rate, pathogen growth rate, host death rate, host recovery rate, pathogen frequency, pathogen virulence. The authors should explain how these traits represent exchange of information between scales of an infectious disease system and which scales exchange information through these traits. Otherwise such linkages are unrealistic and may not be representing any linkage of scales in an actual disease system. Equally, it is not clear how host immune response at the site of infection can be thought of constituting a linking mechanism between scales of an infectious disease. What is clear is that the immune response system at the site of infection is a complex system, with its own scales as explained in [2] and its own multiscale modelling approaches [1]. An infectious disease system is also another complex system made up of three components (host, pathogen, environment) , with its own scales and its own multiscale modelling approaches (Garira, 2017). The two different complex systems (infectious disease system and immune response system at the site of infection) are linked during infection. The authors should explain how immune response system at the site of infection represent exchange of information between scales of an infectious disease system. There is possibility of confusion if this aspect is not explained and scientifically justified. One possible source of confusion is that models of infectious disease dynamics which are single scale in representing infectious disease dynamics (e.g. within-host scale model alone), but which are multiscale in modelling immune response at the site of infection (e.g. those integrating molecular scale and cellular scale of immune response) may end up being considered as multiscale models of infectious disease systems. Yet they are not multiscale models of infectious disease.

5. The way the authors presented the results of the traits of the 19 papers does not allow for easy independent verification of the results by readers. Since the papers are few (only 19), the authors should indicate which papers or give some examples of papers that have specific traits as presented in the analysis in the results section to allow for easy independent verification of the results by readers. For example, the authors indicated that pathogen growth rate was the

second most used trait to link the within- to between-host model (4/19 papers). It would be better if the authors could give examples of papers with such a trait.

Specific comments/typos:

1. Page 1, lines 40-41. The authors indicated that biological systems do not exhibit clear separation of temporal or spatial scales. Its not clear what the authors want to say. It appears as if they want to say there are no clear boundaries between scales. If that is the case I do not think its true. The authors need to clarify what exactly do they mean by ``… do not exhibit clear separation of temporal or spatial scale, ….".
2. Page 4, Figure 2. In the caption of this figure it appears as if the meaning of gray colour and blue colour are exchanged.
3. Page 5, line 160. The author wrote: *In a multi-scale model, the within-host component and between-host component are both modeled explicitly*. First, this statement seems to imply that every multiscale of an infectious disease system integrates within-host scale and between-host. This is not true. Some multiscale model integrate within-cell and between-cell scales while others may integrate within-tissue and between-tissue scales (see [3] below). Second, it is not always the case that in a multiscale model that integrates the within-host scale and the between-host scale both scales are modelled explicitly. Some individual-based multiscale models (Garira, 2017) do not have explicit representation of both scales. I also think that the survey identified such papers, but excluded them from the analysis.
4. Page 5, line 170. The Figure is not correctly specified.
5. Page 7, lines 208 – 217. The authors should replace the word **level** with the word **scale** throughout this paragraph. In multiscale modelling of complex systems the these words often have different meanings and may not be used interchangeably.
6. Page 7, line 245. Unless the authors can present some justification of how host immunity represents exchange of information between scales of an infectious disease system, they should not propose it as an alternative linking mechanism of scales of an infectious disease system. The point is that before we start talking about mathematical linking mechanism, we should first talk about a biological or disease process linking mechanism.

References

[1.] Cappuccio, A., Tieri, P., & Castiglione, F. (2015). Multiscale modelling in immunology: a review. *Briefings in bioinformatics*, *17*(3), 408-418.

[2.] Eftimie, R., Gillard, J. J., & Cantrell, D. A. (2016). Mathematical models for immunology: current state of the art and future research directions. *Bulletin of mathematical biology*, *78*(10), 2091-2134..

[3.] Garira, W. (2018). A primer on multiscale modelling of infectious disease systems. *Infectious Disease Modelling*, *3*, 176-191.

[4.] Tian, Y., & Osgood, N. (2011). Comparison between Individual-based and Aggregate Models in the context of Tuberculosis Transmission. In *Proceedings, the 29th International Conference of the System Dynamics Society* (pp. 1-29).