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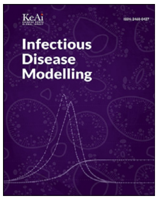

A primer on multiscale modelling of infectious disease systems

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ABSTRACT

The development of multiscale models of infectious disease systems is a scientific endeavour whose progress depends on advances on three main frontiers: (a) the conceptual framework frontier, (b) the mathematical technology or technical frontier, and (c) the scientific applications frontier. The objective of this primer is to introduce foundational concepts in multiscale modelling of infectious disease systems focused on these three main frontiers. On the conceptual framework frontier we propose a three-level hierarchical framework as a foundational idea which enables the discussion of the structure of multiscale models of infectious disease systems in a general way. On the scientific applications frontier we suggest ways in which the different structures of multiscale models can serve as infrastructure to provide new knowledge on the control, elimination and even eradication of infectious disease systems, while on the mathematical technology or technical frontier we present some challenges that modelers face in developing appropriate multiscale models of infectious disease systems. We anticipate that the foundational concepts presented in this primer will be central in articulating an integrated and more refined disease control theory based on multiscale modelling - the all-encompassing quantitative representation of an infectious disease system.

1. Introduction

Infectious diseases continue to pose a major threat to human health. Although advances in medicine and public health have helped control many endemic diseases, World Health Organization (WHO) study on the global burden of diseases indicates that by 2002, infectious diseases were the cause for more than one quarter of approximately 57 million deaths worldwide (World Health Organization (WHO), 2004). In addition, approximately two thirds of all deaths in developing countries among children younger than 5 years of age are due to infectious diseases (World Health Organization (WHO), 2005). In order to respond effectively to the growing health threats of infectious diseases such as HIV/AIDS, tuberculosis, malaria and the transfer of these health risks we need to identify and implement high-impact health interventions. Therefore, there is need to develop appropriate mathematical modelling techniques to evaluate the effectiveness and value of health interventions in the control, elimination and eradication of infectious diseases to complement clinical trial studies, systematic

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reviews, innovative research strategies, and clinical registries. However, there is limited use of appropriate mathematical modelling techniques to achieve this. Since disease dynamics is strongly scale-dependent, mathematical models of mechanisms underlying health interventions, especially multiscale models that synthesize information from at least two scales describing variation in disease mechanisms in the patient population, are useful tools for health intervention research.

The past few years have witnessed a dramatic increase in our awareness and the need to understand the multiscale nature of infectious disease dynamics (see (Cen, Feng, & Zhao, 2014; Feng et al., 2013; Feng et al., 2015; Garira et al., 2014; Netshikweta and Garira, 2017) and references therein). Despite the recognition of the importance of multiscale analysis of infectious disease dynamics, a large number of published papers focused on modelling the dynamics of infectious diseases to date still do not address the multi-spatial and/or the multi-temporal scales of these disease systems. This may be largely attributed to the absence of a powerful foundational knowledge to support the development of multiscale modelling of infectious disease systems on three main frontiers: (a) the conceptual framework frontier, (b) the scientific applications frontier, and (c) the mathematical technology frontier. The objective of this primer is to introduce foundational concepts in multiscale modelling of infectious disease systems focusing on these three main frontiers. The conceptual framework frontier is introduced by proposing a three-level hierarchical framework of an infectious disease system. This is achieved by conceptualizing an infectious disease system as being organized into three main fundamental hierarchical levels which are: (i) the cell level, (ii) the tissue level, and (iii) the host level which serve as the units of multiscale analysis. Each of these three levels can be resolved into two adjacent scales which are the individual/lower/micro scale and population/upper/macro scale. For the cell level we have the within-cell scale and the between-cell scale, for the tissue level we have the within-tissue scale and the between-tissue scale, and for the host level we have the within-host scale and the between-host scale. At each of these three hierarchical levels (the cell level, the tissue level, and the host level) five different categories of multiscale models of an infectious disease system can be developed that integrate the individual/lower/micro scale (within-cell scale, within-tissue scale, within-host scale) and population/upper/macro scale (between-cell scale, between-tissue scale, between-host scale) (Garira, 2017). In what follows, we briefly describe each of these five categories of multiscale models of an infectious disease system.

Category I - individual based multiscale models (IMSMs)

In this category of multiscale models of infectious disease systems the individual/lower/micro scale (within-cell scale, within-tissue scale, within-host scale) submodel is used to describe the entire infectious disease system across both the individual/lower/micro scale and population/upper/macro scale (between-cell scale, between-tissue scale, between-host scale). There is no information flow from the population/upper/macro scale submodel to the individual/lower/micro scale submodel. The population/upper/macro scale is observed as emergent behaviour of the individual/lower/micro scale entities. The four main classes of multiscale models in this category are (Garira, 2017):

- *Class 1:* Network modelling individual-based multiscale models (NETW-IMSMs): These are multiscale models which are developed using graph theoretic or network modelling techniques.
- *Class 2:* Empirical data modelling individual-based multiscale models (EMPI-IMSMs): These are multiscale models of infectious disease systems which are developed using statistical modelling techniques to model hierarchical empirical data. For example those which use regression-based approaches where the assumption that the outcomes of infection at individual/lower/micro scale for the units of analysis (i.e. the individual hosts) are independent is violated because they share the same population/upper/macro scale characteristics and are therefore influenced by the same measured population/upper/macro scale factors (e.g. access to health services, demographic factors, environmental factors, economic factors, etc.) or unmeasured factors (e.g. cultural factors, religious factors, behavioural factors, etc.).
- *Class 3:* Simulation modelling individual-based multiscale models (SIMU-IMSMs): No mathematical equations are used to model the infectious disease system in this class of multiscale models. Instead, infectious disease systems are modelled using computational algorithms such computational algorithm-based models which include agent-based models (ABM), cellular automata (CA) and petri-nets (PN). If mathematical equations appear in this class, they are only used to describe specific entities with a particular scale, rather than to describe the dynamics of a whole scale.
- *Class 4:* Hybrid individual-based multiscale models (BRID-IMSMs): These are individual-based multiscale models where the individual entities within a single scale are represented using different formalisms or mathematical representations. For example, some entities in an agent-based model (ABM) my be described by ODEs while others are described by PDEs. The use of hybrid petri nets will also result in BRID-MSMs.

Category II - nested multiscale models (NMSMs)

These are multiscale models of infectious diseases in which there is only unidirectional flow of information (only from individual/lower/micro scale submodel to the population/upper/macro submodel). Therefore, in this category of multiscale models the individual/lower/micro scale dynamics is independent of the population/upper/macro scale. The individual/