A complete categorization of multiscale models of infectious disease systems

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ABSTRACT

Modelling of infectious disease systems has entered a new era in which disease modellers are increasingly turning to multiscale modelling to extend traditional modelling frameworks into new application areas and to achieve higher levels of detail and accuracy in characterizing infectious disease systems. In this paper we present a categorization framework for categorizing multiscale models of infectious disease systems. The categorization framework consists of five integration frameworks and five criteria. We use the categorization framework to give a complete categorization of host-level immuno-epidemiological models (HL-IEMs). This categorization framework is also shown to be applicable in categorizing other types of multiscale models of infectious diseases beyond HL-IEMs through modifying the initial categorization framework presented in this study. Categorization of multiscale models of infectious disease systems in this way is useful in bringing some order to the discussion on the structure of these multiscale models.

1. Introduction

An important distinct property of infectious disease systems that set them apart from other diseases is that besides the fact that they are highly relevant and affecting large populations as they remain a leading source of human morbidity and mortality [124], they involve clear molecular targets pertaining to the life cycle of the pathogen and the host–pathogen interactions. We have to date witnessed major advances in the prevention and treatment of infectious disease systems (diagnostics, therapeutics, and vaccines), but they remain a significant public health challenge. The emergence of new infectious disease involving high-profile epidemics such as dengue fever in 1945, HIV/AIDS in 1981, hepatitis C in 1989, hepatitis E in 1990, SARS in 2002, H1N1 influenza strain in 2009 [24, 87] and re-emergence of some infectious disease around the world [85] such as tuberculosis [7] has compounded the problem of infectious diseases. To make things even worse, infectious agents are developing resistance to antimicrobials and antivirals [125]. However, molecular biology, which started in the 1950s [16], has now given us a comprehensive view of the basic components of living things and how they interact with each other (e.g. the cataloguing of
DNA sequences of human, animal and plant genomes), and has to date improved our ability to define the molecular identity and dynamics of infectious agents, their hosts and even vectors, and has greatly increased our understanding of the immune responses of their hosts. We also now understand better the machinery underlying the evolutionary dynamics of infectious diseases [19].

An understudied aspect of infectious disease systems is that their transmission is a result of complex, dynamic relationships that occur at varying spatial and temporal scales [9, 38, 42]. The dynamics of infectious diseases may therefore, require integration across several temporal and spatial scales associated with the cellular, tissue, organ, organism, community and ecosystems levels of biological organization. Insights from molecular biology, immunology, epidemiology and environmental health has stimulated some interest into multiscale modelling of these various aspects in an integrated manner especially if all these aspects pertain to a single infection in order to acquire more knowledge on the transmission dynamics of infectious disease systems. To date, infectious disease transmission dynamics at large and small scales is increasingly becoming well understood. Yet in general, we have no means of translating the detailed knowledge of the fundamental building blocks of infectious disease systems at these micro and macro scales into their effect on the transmission of an infectious disease system as a whole. Without the capability to bridge the scales of infectious disease systems the goal of One Health [65] (a strategy for interdisciplinary collaborations in all aspects of health for humans, animals and the environment, based on the understanding that the health of humans, animals and the environment are inextricably linked) will remain out of reach. Every day worldwide infectious disease systems research produce a huge amount of information. But this information is highly fragmented, and its integration is largely left to human actors, who find this more and more difficult as the breadth and depth of information produced continues to increase rapidly. To organize this detailed information and arrive at a better understanding of the transmission dynamics of infectious disease systems, we need to support the development of predictive multiscale models of infectious disease systems in order to address the policy needs and options of a One Health approach in our health systems, which makes possible the integration of information, and simplifies its transformation into integrated knowledge [65]. Infectious disease modellers are gradually recognizing that the methods for single scale modelling of infectious disease systems are not sufficient to address the problems encountered in this field [9, 38, 41, 42, 50, 81, 93, 98] and that the macroscale phenomenon cannot be fully understood even if the microscale mechanisms were fully revealed to the finest detail. In recognition of this challenge, infectious diseases modellers are increasing turning to multiscale modelling [2, 9–11, 21, 26, 30, 32, 35, 41, 43, 69, 72, 73, 75, 82, 117, 119, 126]. The result is that we now have a wide variety of multiscale models of infectious disease systems with different structure and mathematical representations which are associated with the different levels of biological organization of an infectious disease system. A complete categorization of these multiscale models will be useful in bringing some order to the discussion on the structure of multiscale models of infectious disease systems.

An in-depth understanding of the transmission of infectious disease systems requires knowledge of the processes at the various scales of infectious diseases and how these scales interact. The two most studied scales in the transmission of infectious disease systems are the between-host scale (associated with disease transmission within the host population where epidemiological processes take place) and the within-host scale (associated
with disease dynamics within a single-host where immunological processes take place).

This paper considers categorization of multiscale models of infectious disease systems that integrate the within-host scale and the between-host scale first and then extend the categorization to other types of multiscale models of infectious disease systems. Such multiscale models close a circle of mutual interaction between the within-host scale and between-host scale of infectious disease systems. Traditionally, immunology and the epidemiology of diseases have been separate disciplines. The growing knowledge in mathematical modelling, epidemiology, immunology, parasitology and molecular biology has improved our understanding of the infection and immune status of individuals. Together with newly developed techniques these advances help in the quantification of patterns of infection and immunity at both the within-host scale and the between-host scale. This has generated a new discipline, which studies the influence of immunity on epidemiological processes called immuno-epidemiology. By definition immuno-epidemiology is the study of the distribution of immune responses and infection in populations, and of the factors influencing this distribution [123]. This new biomedical discipline examines how inter-individual differences in immune responses affect the population dynamics of micro- and macro-parasites to produce the epidemiological patterns of infection observed in heterogeneous host populations [49] and it is an important part of the study of infectious disease systems. By integrating immunology with epidemiology, we study not only the distribution and frequency of infection and disease but we also unearth how types and levels of immunity vary over time in relation to exposure to infection or clinical presentation. At the within-host scale, this can reveal how factors such as frequency of infection or genetic variation affect levels of immunity and, at the between-host scale, this can also reveal how immune responses influence the prevalence of infection and the burden of disease. The new discipline of immuno-epidemiology integrates several disciplines that include, mathematical modelling, immunology, epidemiology, microbiology, genetics, population biology, statistics and even ecology.

For purposes of this paper, a multiscale of an infectious disease system is any representation of an infectious disease system that can be used to study or characterize an infectious disease system at more than one scale. In this case multiscale models of infectious disease systems can be empirical models (that is, those based on experimental systems, observational systems, surveillance systems, clinical trials, animal model systems, etc.) which characterize infectious disease systems at more than one scale or they can be quantitative models (that is, those based on mathematical, statistical, computational concepts) that also characterize infectious disease systems at more than one scale. However, only quantitative multiscale models can be used as predictive tools. In this paper we categorize quantitative multiscale models of infectious disease systems. These are multiscale models which use mathematical and statistical equations as well as computational algorithms to quantitatively represent and simulate an infectious disease system at more than one scale while functionally integrating the models across these scales. In this study, ‘categorization’, ‘classification’ and ‘type’ are words used to identify different groups of multiscale models of infectious disease systems. We explicitly define categorization of multiscale models as ‘the process of defining different categories of multiscale models’ and classification of multiscale models as ‘the process of allocating particular multiscale models to the different categories of multiscale models’ while type of multiscale models refers to ‘multiscale models that integrate different sets of scales’. Further, we also define a
framework for categorizing multiscale models' as an instrument or a tool which specifies how categorization of multiscale models should be done.

The rest of this paper is organized as follows. In Section 2 we discuss the various spatial and temporal scales associated with infectious disease systems. In particular, we describe an infectious disease system in terms of its organizational levels and the spatial-temporal scales and indicate the possible levels and scales which can be integrated to develop multiscale models of infectious disease systems, which include the host level which is associated with the within-host scale and between-host scale, the cell level which is also associated with the within-cell and between-cell scales and the tissue level which is associated with the within-tissue and the between-tissue scales. We present the categorization framework for multiscale models of infectious disease systems that integrate the within-host scale and the between-host scale in Section 3. Based on this categorization framework we categorize and classify multiscale models of infectious disease systems that integrate the within-host and between-host scales in Section 4. The categorization framework in Section 3 is progressively modified to categorize multiscale models of infectious disease systems that integrate within-cell and between-cell scales in Section 5, multiscale models that integrate within-tissue and between-tissue scales in Section 6, and multiscale models that integrate several scales of infection in Section 7. We conclude the paper in Section 8 with a discussion and summary of the work presented.

2. The levels and scales of infectious disease systems

In multiscale modelling, like any other modelling effort, it is important to first of all, define and describe the specific system to be modelled and the purpose of modelling. In particular, for multiscale modelling, it is important to first of all describe the system to be modelled in terms of its organizational levels and the spatial and temporal scales of observation associated with the structural organization of the system. However, since multiscale models (like all other models) are produced to serve a specific purpose or answer a specific question, they do not necessarily need to include all the scales of the system, but only those scales that are relevant to the purpose of the multiscale modelling effort. In the context of the current study where the purpose is to categorize multiscale models of infectious disease systems, we first of all identify some of the levels and scales of an infectious system. The hierarchical multi-level and multiscale structure is the inherent nature of infectious disease systems. In this study, the four terms ‘system’, ‘level’, ‘scale’ and ‘component’ are commonly used for the partitioning of infectious disease systems. In particular ‘system’ here is used to emphasize the systems analysis approach to the study of infectious diseases as complex systems [31]. It emphasizes the integrated structural and functional organization of the components of an infectious disease as being multilevel and multiscale. Therefore, a system is considered a layer above a level and is used to describe the integrated nature of the functioning of different levels of organization of an infectious disease in the hierarchy. Similarly a level is considered a layer above a scale and is used for the sub-partitioning of a system to describe its functional organization in the hierarchy while a scale is considered a layer below a level and is used for the sub-partitioning of a level to describe its structural organization in the hierarchy. Any level or scale associated with the sub-partitioning of an infectious disease system is a component of that infectious disease system. While both levels and scales are used to sub-partition infectious disease systems, levels are considered
loosely coupled while scales are considered strongly coupled. Within levels, the strong interactions between the spatio-temporal multiscale structures usually give rise to the emergent properties of an infectious disease system (colonization of host by the pathogen, establishment of pathogen within the host while evading immune system responses, transmission to new hosts, altered host behaviour, use of host as transport and/or reservoir, castration of host, etc.). Therefore, reductionism is not sufficient even for interpreting an infectious disease system within a level. Therefore, in spite of the human need to reduce to parts in order to understand, infectious diseases are the result of intricate systemic interactions between many components at radically different levels and spatio-temporal scales.

The multilevel and multiscale nature of infectious disease systems comes from the fact that they are complex systems. The complexity of infectious disease systems and the different answers that single scale modelling provides remind of the popular tale ‘The Blind Men and the Elephant’ by John Godfrey Saxe (1816–1887) [80]. The author writes about a group of blind men who touch an elephant. Each person feels one part, such as the trunk, the ear and the legs; so when they describe to each other what they found they were in complete disagreement because each had felt one part of many of a complex system. A complex systems-type of thinking of an infectious disease as a human health issue is more informative for research activities on infectious disease systems [31]. In this regard we propose that a full multiscale model of an infectious disease system can be conceptualized as a complex system model incorporating many interacting components which are associated with the four main levels of organization of an infectious disease system, which are (i) the host/organismic level (human, animal, vector, plant), (ii) the pathogen level (virus, prion, helminth, protozoan, bacteria, fungus), (iii) the health interventions level (medical and public health interventions) and (iv) the environment level (inside-host or biological environment and outside-host environment with all its various domains which include physical, geographical, social, economic, etc.). Based on their structural organization, each of these four levels of organization of an infectious disease system can be resolved into a variety of scales (see Table 1 for a list of some of the scales). However, as the scales of each of the four levels of an infectious disease system increases in number, they tend to converge towards two extreme scales comprising of a lower scale and an upper scale. For the host we have the within-host scale and between-host scale, for the pathogen we have within-pathogen species scale and between-pathogen species scale, for the environment we have inside-host scale (biological environment) and outside-host scale (geographical environment), while for the health interventions we have the medical interventions scale and public health interventions scale. Because each of these components constituting the four different levels of organization of an infectious disease suggests its own implicit temporal and spatial scales through the duration of stages/states and associated processes and the spatial domains in which these stages/states and associated process occur, each of the four levels of organization of an infectious disease system is also a complex system on its own with its own levels of organization and scales. Examples of temporal and spatial scales associated with each of these four levels of organization of an infectious disease system include the following.

(i) **The pathogen level:** The pathogen level of organization of an infectious disease system can be any of the six different types (virus, prion, helminth, protozoan, bacteria,
fungus) or more than one of these in the case of multiple pathogens infectious disease systems. The variety of scales associated with each of these pathogen types is determined by the complexity of its structural organization. The complexity of interaction with other levels of an infectious disease system is determined in part by the complexity of its life cycle. Depending on its life cycle, the pathogen may have a life in host organs such as the blood or liver or lung or gut, a life in cells, such as in the case of malaria where the plasmodium parasite multiplies inside the liver and red blood cells, a life in the vector and a life in the geographical environment’s physical entities (water, air, soil, food, formites, etc.), such as the case of schistosomiasis where the infective stages of schistome parasite survive in water. Each of these different levels and their associated spatial scales can interact with the pathogen during different infectious disease processes which are also associated with different time scales [83]. For example, pathogen development and the population growth may take hours to days to months depending on the type of pathogen and the spatial domain in which this growth and development takes place. This implies interaction of the different scales associated with the life of the pathogen alone [105]. Therefore pathogen stages/states are driven by their epidemiological dynamics (transmissions) within and among hosts. Thus pathogens in infectious disease may progress to different developmental stages upon successful completion of the life cycle in vectors, human and animals hosts and the environment [92]. Several other spatial and temporal scales associated with the pathogen include those associated with pathogen replication in organs and cells, persistence of pathogen within a vector, and evolution of pathogen as well as competition between pathogens (if the infection involves co-infection with multiple strains or involves co-infection with multiple pathogens) as well as pathogen resistance to health interventions such as resistance to treatment with drugs [83].

(ii) The host level: This could be animals or human hosts or plants or vectors or a combination of any two or three of these in the case of multi-host infections. The host level of an infectious disease system, which is associated with the within-host scale and the between-host scale encompass various other levels of biological organization which include the cell level which is associated with the within-cell scale and between-cell scale, the tissue level which is also associated with the within-tissue scale and between-tissue scale, the organ level which is associated with the within-organ scale and between-organ scale, the community level which is associated with the within-community scale and between-community scale, and the ecosystem level which is associated with the within-ecosystem scale and between-ecosystem scale. Thus, the host/organism level incorporates the biological, epidemiological and demographic scales. Disease specific states/stages of hosts (human or animals) are known to be susceptible to alteration by the pathogens they carry [67]. Disease conditions may take years to eradicate at between-host scale (e.g chronic disease). At the same time disease progression and healing/cure/recovery at within-host scale requires days or even years. The time scale associated with healing/recovery/cure at within-host scale may depend on processes associated with levels of biological organization of immune response at the site of infection which may include molecular level which is associated with the different ‘omics’ (e.g. proteomics, genomics, metabolomics, etc.), cellular level which is associated with the various immune cells, aspects of host history
and immune memory, environmental level, which incorporate the various environmental domains which include biological social, political, economic, geographical, behavioural etc. factors that alter risks of exposure to infection and the health interventions scale which include the effect of applied drugs as well as compliance with health interventions [92]. The vector development states/stages takes place at different time scales varying from days to weeks. In addition, apart from being altered by environmental level conditions, disease vectors have been shown to be susceptible to alteration in their survival, development and fecundity rates by the microbes and pathogens they carry [63]. In particular, characteristics of vector life cycle also affect disease processes at within-vector scale which is associated with persistence and development of the pathogen to infectious stages [92].

(iii) The Environmental level: The cells, tissues and organs constitute the inside-host environmental level (biological environmental level) for infectious diseases where pathogens may grow and reproduce. The geographical environmental level (village level, district level, town level, province/state level, country level, continent, whole world, etc.) and the associated physical environments (soil, water, air, formites, etc.) also constitute the outside-host environmental levels where both pathogens and hosts may also grow and reproduce inside these environments. A variety of infectious disease systems are modified by environmental domains which include the biological environmental levels (cell level, tissue level, organ level, organism level, etc.), the geographical environmental level's physical entities such as soil, air, water, food, contact surfaces and objects where exposure to pathogens or vectors takes place in the geographical, economic, social and political environment which determines the nature of the health infrastructure and technologies available (treatments, vaccines, toilets, clean water, etc) [83]. In particular the physical environment is in turn modified by a host of other factors which include climate change or variability (temperature, rainfall, and humidity), ecosystem and land-use change, agriculture and other economic practices, urbanization, human migration, host demographic and behaviour changes etc. The spatial scales associated with each infectious disease system at the outside-host environmental level include within-village and between-village scales, within-district and between-district scales, within-town and between-town scales, within-province/state scale and between-province/state, within-country and between-country scales etc. and each of these environmental scales is associated with other environmental domains which modify it which include the economic, political, social, behavioural etc. environments [92]. The different environmental domains largely define the context of an infectious disease system.

(iv) The health interventions level: This includes both public health and medical interventions levels. Medical interventions are those intended for the inside-host (biological) environmental scale while public health interventions are those intended for the outside-host environmental scale. In general, for infectious diseases, there is always a reciprocal influence between public health interventions to control disease systems which are focused on communities and populations (outside-host environmental scale) on one hand, and medical interventions to treat diseases which are focused on the well-being of the individual (inside-host environmental scale) on the other hand. This implies that in the context of infectious disease systems, there are important medical planning consequences to consider during the process of epidemiological
(public health scale) planning and vice-versa in that treatment that cures a patient from an infectious disease is equally good for both the patient and the public because this patient no longer poses a transmission risk of the disease to the public [32]. While these interventions are implemented at different spatial scales (inside-host and outside-host environmental scales), they also occur at different time scales. For example, health interventions such as vaccination programmes may vary from days to weeks to months. These different time scales may also dependent on the spatial scale associated with vaccine programme coverage which many vary from a small community or village to a town or the whole country. This is also associated with diagnostics and case detection. Healing, curing and preventive aspects of the intervention depend on its efficacy.

A summary of the scales associated with each of the four main levels of organization of an infectious disease system is given in Table 1. This table shows the hierarchical nature of levels and scales of an infectious disease system. It shows that within each level, there are other levels and that within each scale, there are also other scales. For example, at the health interventions level, we have only listed two levels within this level (medical health interventions level and public health interventions level) and the two limiting scales associated with each of these levels: within-medical interventions scale and between-medical interventions scale (for medical health interventions level) and within-public health interventions scale and between-public health interventions scale (for public health interventions level). However, within for example, public health interventions level, there is also the institutional level which also has its own levels (e.g. clinic level and hospital level) and with each of these levels being associated with their own scales. For instance, the clinic level has the within-clinic and between-clinic scales while the hospital level has the within-hospital and between-hospital scales. Thus, necessarily the list of levels and scales of an infectious disease system listed in Table 1 is not complete. Further, we highlight that models that integrate two or more levels of organization are called multi-level models while those that integrate two or more scales are called multiscale models. However, unlike multiscale models whose mathematical representation can be done using different formalisms (ordinary differential equations (ODEs), delay differential equations, stochastic differential equations, partial differential equations (PDEs), agent-based models (ABMs), cellular automata (CA) models, network models, Integro-differential equations, statistical models and petri nets, etc.), multi-level models are mainly represented by regression-based statistical models (multi-stage sampling multi-level models, multiple response multi-level models, cross-classified multi-level models, multiple membership multi-level models, correlated cross-classified multi-level models, and others such as survival multi-level models, time series multi-level models, spatial multi-level models, meta-analysis multi-level models (Random effect meta-analysis), factor analysis, latent class and structural equation multi-level models) [96,112]. Therefore, a complete systems understanding of infectious disease systems requires integrated, multi-level and multiscale modelling of the hierarchical layers of regulation and control.

From the discussion of different levels and scales of infectious disease systems, we note that the spatial and temporal dynamics of scale hierarchies of infectious disease systems comprising hosts, pathogens, health interventions and the environment, linked through processes of indirect, top-down and bottom-up effects, are concepts that can only be fully
considered through systems-type thinking of infectious disease systems and multiscale modelling. In the next section, we present the categorization framework for categorizing multiscale models of infectious disease systems that integrate the within-host scale and the between-host scale.

Table 1. Summary of some of the scales associated with structural organization of each of the four main levels of organization of an infectious disease system.
3. The categorization framework for multiscale models of infectious disease systems

A useful starting point for systematically placing the development and analysis of multiscale models on sound theoretical foundations in any application area is to define the integration frameworks that are used in linking the submodels at the different scales. In the context of multiscale modelling applied to chemical engineering, we have, to date witnessed the development of five multiscale integration frameworks that organize and inform the research that lead to development of multiscale models [52]. Although these multiscale integration frameworks were developed in a chemical engineering context, in this paper we adapt them to an infectious disease system context and then use them to categorize multiscale models of infectious disease systems. These integration frameworks are further summarized and analysed in [53]. The integration frameworks are described for linking two adjacent scales at a time: the lower scale (microscale) and an upper scale (macroscale) submodels in the development of multiscale models. Therefore, when applied to an infectious disease context this implies that the entire infectious disease system multiscale model domain is considered to comprise of the microscale sub-domain and the macroscale sub-domain. Briefly, the five integration frameworks previously designed for chemical engineering applications, and now adapted here for an infectious disease context, for linking submodels in the development of multiscale models of infectious disease systems are:

(a) **Simultaneous integration framework**: The microscale submodel describes the entire infectious disease system multiscale model domain as shown in Figure 1(a). No macroscale submodel is written. In order to describe the macroscopic scale, the microscale results are converted by summing, averaging or performing some detailed statistical analysis of them and aggregate the information into macroscopic variables for interpretation at that scale.

(b) **Serial integration framework**: The microscale and the macroscale submodels operate sequentially as shown in Figure 1(b). First, the microscale submodel is solved and its results are then used to build the macroscale submodel. As a result the macroscale submodel describes the entire infectious disease system multiscale model domain. A wide range of techniques are used to incorporate the microscale submodel into the macroscale submodel. This gives rise to different classes of multiscale models of infectious disease systems when using the serial integration framework.

(c) **Multi-domain integration framework**: The microscale and the macroscale occupy adjacent but non-overlapping parts of the infectious disease system multiscale model domain as illustrated in Figure 1(c). Information is exchanged between the microscale and the macroscale using a common interface between these scales.

(d) **Embedded integration framework**: The macroscale occupies the whole infectious disease system multiscale model domain while the microscale occupies part of it. Therefore the microscale submodel domain is embedded within the macroscale submodel domain as shown in Figure 1(d). Information is exchanged between the two submodels that describe these two scales directly.

(e) **Parallel integration framework**: Several multiscale models are coupled to form a single multiscale model for the infectious disease system. Each multiscale model which is
Figure 1. A conceptual diagram of the integration frameworks for multiscale modelling adapted for describing the time evolution of an infectious disease system when linking two scales at a time: the microscale and the macroscale: (a) simultaneous integration framework, (b) serial integration framework, (c) multi-domain integration framework, (d) embedded integration framework and (e) parallel integration framework.
used as a submodel in the coupled multiscale model describes phenomena occurring over a range of scales with some of these scales overlapping with those associated with other multiscale models in the coupled multiscale model. Therefore, as illustrated in Figure 1(e), both multiscale models shown in this figure, labelled Multiscale 1 and Multiscale 2 span the entire infectious disease system multiscale model domain.

Figure 1 shows a conceptual diagram of the five integration frameworks adapted for describing the time evolution of an infectious disease system when linking two scales at a time: the microscale and the macroscale. The five multiscale integration frameworks as represented in Figure 1 are: Figure 1(a) represents the simultaneous integration framework, Figure 1(b) represents the serial integration framework, Figure 1(c) represents the multi-domain integration framework, Figure 1(d) represents the embedded integration framework and Figure 1(e) represents the parallel integration framework. Details of the definitions and analysis of these five integration frameworks are given in [53]. An attractive feature of these multiscale integration frameworks is that even though they describe linking two submodels at a time, they can be applied pairwise to form more complex multiscale models integrating several scales [53].

The integration frameworks of multiscale models of infectious disease systems in Figure 1 can be applied to categorizing multiscale models at host level of biological organization. In this case the microscale and macroscale incorporated into the multiscale correspond to the within-host scale and between-host scale. In order to give a complete categorization of multiscale models of infectious disease systems that integrate the within-host scale and the between-host scale, we propose that the integration frameworks in Figure 1 must be used in conjunction with the following five criteria:

**Criterion I:** The nature of inter-scale information flow: which is also directly related to the nature of coupling between the scales which can be bidirectional (essential coupling [82]) or unidirectional (inessential coupling [82]) so that information can propagate across multiple levels and scales within one multiscale model.

**Criterion II:** The relationship between the scales associated with the submodels of the multiscale model: which is related to the hierarchy that these scales may be organized into in which one scale may be ‘contained’ or nested or embedded into another scale.

**Criterion III:** The order in which the different scales are incorporated into the multiscale model: e.g. bottom-up, top-down, concurrent, etc.

**Criterion IV:** The level of biodiversity involved in the transmission of the infectious disease system which may include the simplest situation where only a single-pathogen and single-host population species are considered or the more complex situations where the diversity among host species (multi-host infections) and/or diversity among pathogen species (multi-pathogen infections) and/or diversity within a single-pathogen species (multi-strain infections) and/or diversity within a single-host species (multi-host group infections) are considered: which determines the type of infectious disease system which may be multi-host or multi-pathogen or multi-strain or multi-group or combination of these infectious disease system.

**Criterion V:** The nature or formalism of the different submodels that constitute the multiscale model: This refers to the form of the mathematical representation of the different
single scale submodels which can be different depending on the nature of variation of
time scale (discrete or continuous time), the nature of variation of the state variables
(stochastic or deterministic), the nature of variation of the spatial scale (homogeneous
and associated with use of ODEs or heterogeneous and associated with PDEs), etc.

These five criteria for categorizing multiscale models of infectious disease systems are also
an attempt to align the interpretation of the integration frameworks to an infectious dis-
 ease context (since these integration frameworks were originally formulated for a chemical
engineering context) and to a particular level of biological organization of the infectious
disease system (see Table 1 for details of the different levels of organization of an infectious
disease system) considered in the multiscale model.

Overall, the five integration frameworks and the five criteria constitute the catego-
 rization framework for categorizing multiscale models of infectious disease systems that
integrate the within-host scale and the between-host scale. Later on in this study, we
shall show that by modifying criterion IV, this categorization framework becomes appli-
cable in categorizing other types of multiscale models of infectious disease systems that
integrate two scales at a time. In addition, we also propose a categorization framework
for categorizing multiscale models of infectious disease systems that integrate several
scales of infection by simplifying the categorization framework for categorizing host-level
immuno-epidemiological models (HL-IEMs) in this section. However, we note that this
categorization framework for categorizing multiscale models that integrate the within-host
scale and the between-host scale and the other categorization frameworks derived from
modifying it are for categorizing multiscale models of infectious disease systems that arise
largely because infectious agents can survive, grow and multiply in habitats which are at
multiple hierarchical levels of biological organization (cell level, tissue level, organ level,
host/organism level, environmental level, etc.) with different spatial and temporal scales
associated within each of these different levels of biological organization. Table 1 shows
some of these levels of biological organization and the associated scales that can be con-
sidered when developing multiscale models of infectious disease systems. In the context
of Table 1, the host/organism (human, animal, vector, plant) is considered as the highest
basic level of biological organization at which infection by the pathogen can be consid-
ered. However, care must be taken in the application of the categorization framework in
categorizing multiscale models of infectious disease systems particularly in relation to cri-
terion V. In the context of the categorization frameworks for categorizing multiscale models
of infectious disease systems presented in this study, we do not consider models of infec-
tious disease systems which are single scale in pathogen habitat, but multi-level in immune
response as multiscale models of infectious disease systems. For example, the model in [12]
for malaria parasite dynamics at between-cell scale only, which is therefore single scale in
pathogen habitat, but multi-level in immune response (molecular and cellular levels) can-
not be categorized as a multiscale model of a malaria disease system in the context of the
categorization frameworks presented in this study for categorizing multiscale models of
infectious disease systems.

The main potential problem in using the categorization framework in categorizing
multiscale models of infectious disease arises because immune response at the site of infec-
tion has three main levels of biological organization: molecular level, cellular level and
tissue level [22]. In some cases these three levels of biological organization of the immune
response at the site of infection may be considered as three different scales, leading to some models of infectious disease systems which are multi-level in immune response but singe-scale in pathogen habitat being categorized as multiscale models of infectious disease systems. Further, the two adjacent scales (microscale/lower scale and macroscale/upper scale) considered in the integration frameworks which are part of the categorization framework correspond to possible different pathogen habitats in the transmission of an infectious disease system. A potential problem that can arise is in the interpretation of criterion V when one is expected to determine the form of mathematical representation of the two submodels associated with the two adjacent scales (microscale/lower scale and macroscale/upper scale) especially when within a single scale (e.g. when the microscale corresponds to within-host scale) and the different levels of immune response at the site of infection (molecular, cellular and tissue) are described using different mathematical representations within that single scale (within-host scale). In that case we recommend that only the mathematical representation of the highest level of immune response at the site of infection should be considered in the categorization of the multiscale model. In the following section we now apply the categorization framework to categorize multiscale models of infectious disease systems that integrate within-host scale and between-host scale.

4. Categorization of multiscale models of infectious disease systems that integrate within-host and between-host scales

In this section, we categorize multiscale models of infectious disease systems when the microscale and the macroscale of an infectious disease system are the within-host scale and the between-host scale. These multiscale models are sometimes called immuno-epidemiological models of infectious disease systems. However, because in this study we also consider categorization of other types of immuno-epidemiological models associated with other lower levels of biological organization of the host in Sections 5 (the cell level), 6 (the tissue level) and 7 (multiple levels), we will in this study call this type of multiscale models host-level immune-epidemiological models (HL-IEMs). This type of multiscale models consider host–pathogen interactions at the whole organism level of biological organization. These host–pathogen interactions are partly responsible for the observed incidence and abundance of the disease inducing pathogen and the epidemiological characteristics of the disease within the host population. The pathogen's survival hinges on these interactions because during these interactions the pathogen enters the host and replicates, then it further transmits its progeny to other hosts within the host population before the pathogen is cleared or before the host is killed. This interaction depends on a number of factors which include host density, pathogen density, movement patterns and transmission mechanism which may be vector-borne, environmental transmission (food borne, air borne, soil borne, water borne, formite borne) or direct transmission (from host to host). These factors determine the pathogen's ability to maintain circulation in the host population. There has been little attempt to categorize multiscale models of infectious disease systems that integrate the within-host scale and between-host scale despite the fact that these are the most studied multiscale models. To the best of our knowledge we know of only one attempt to categorize multiscale models of infectious disease systems that integrate the within-host scale and between-host scale submodels (see [77]). In [77] the categorization of such multiscale models is based on the nature of the between-host scale submodel
We think that this kind of categorization makes it difficult to distinguish between multiscale models and single scale models since single scale models are also sometimes categorized using the same criteria. Further, this categorization treats different classes of hybrid multiscale models of infectious disease systems as different categories (see [114] for a complete classification of hybrid multiscale models). Using the categorization framework presented in Section 3, we categorize multiscale models of infectious disease systems that integrate the within-host and between-host scales into five categories, with each integration framework in the categorization framework corresponding to a different category of multiscale models.

We identify five categories of multiscale models of infectious disease systems that integrate the within-host scale and between-host scale of infectious disease systems. The five identified categories of multiscale models of infectious disease systems are: individual-based multiscale models (IMSMs), nested multiscale models (NMSMs), embedded multiscale models (EMSMs), hybrid multiscale models (HMSMs) and coupled multiscale models (CMSMs). In what follows we briefly describe each of these five categories.

**Category I: IMSMs:** This category of multiscale models is formed based on simultaneous integration framework (see Figure 1(a)). For these individual-based multiscale models, the within-host submodel is used to describe the entire infectious disease system across both the within-host scale and between-host scale. No explicit between-host scale submodel is used in this approach. There is also no information flow from the between-host scale submodel to within-host scale submodel. However, any within-host scale information may be transferred to the between-host scale. The within-host scale submodel results are converted by summing up, averaging, or performing some statistical analysis of them into between-host scale variables for interpretation at that scale. In this case the between-host scale results are observed as an emergent behaviour of the within-host scale submodel which considers individual variability. This is a bottom-up type of multiscale modelling. Based on identifying the different formalisms that can be used to formulate individual-based multiscale models, we identify four main classes of multiscale models in this category which we name and describe as follows.

**Class 1: Network modelling individual-based multiscale models (NETW-IMSMs):** These are multiscale models which are developed using graph theoretic or network modelling techniques. Several types of network-based techniques can be used to develop multiscale models in this class which include lattice network models, small-world network models, random network models, scale-free network models and spatial network models [57]. The first NETW-IMSM of the host level immuno-epidemiology of infectious diseases was contributed by Tuckell et al. [116]. In [116] a NETW-IMSM was developed to characterise the spread of viral diseases taking into account both the dynamics of viral growth at within-host scale and the interactions between individuals at between-host scale. Using this model, the authors studied nearest-neighbour interaction and transmission which was shown to decline exponentially with distance between the individuals. The distribution of the final size of an epidemic was determined in the cases of extreme clustering and dispersion of infected individuals. This work was followed by that of Kostova [58], who used a NETW-IMSM to identify that even if
the immune response clears the infection in each individual when isolated, while these individuals are in a network, the pathogen persists in each one of them and at between-host scale. Further work on developing NETW-IMSMs to study the host level immuno-epidemiology of infectious disease systems was contributed in [119, 120].

Class 2: Empirical data modelling individual-based multiscale models (EMPI-IMSMs): These are HL-IEMs of infectious disease systems which are developed using a range of statistical modelling techniques to model hierarchical empirical data from a range of sources including experimental systems, observational systems, animal model systems, surveillance systems, clinical trials, etc. The papers [5, 33, 102] provide some of the generalized approaches to developing the multiscale models in this class. A good example of statistical modelling approaches that result in the development of EMPI-IMSMs are those which use regression-based approaches where the assumption that the outcomes of infection at within-host scale for the units of analysis (i.e. the individual hosts) are independent is violated because they share the same between-host scale characteristics and are therefore influenced by the same measured between-host 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.). This class of multiscale models are sometimes called multi-level models. In this case the within-host scale and the between-host scale are the levels of organization of the infectious disease system that are considered. The variation in infection outcomes for the units of analysis (individual hosts) include those associated with within-host pathogen load, levels of immune response, levels of pathogen species diversity, levels of pathogen strain diversity, levels of treatment response and treatment uptake. The empirical data individual-based modelling multiscale model (EMPI-MSM) by Elfaki et al. [23] provides an example of an EMPI-IMSM. The model describes immuno-epidemiological profiles of individuals infected with Schistosoma mansoni in Sudan. The study established that epidemiological factors and immune responses to schistosomes depend on the actual infection status (patent versus pre-patent/low egg producing). This is a crucial finding which facilitates our understanding of the biology of the disease which may improve the development of techniques to identify early stages of pathology (fibrosis) which could help prevent further damage and morbidity.

Class 3: Simulation modelling individual-based multiscale models (SIMU-IMSMs): No mathematical equations are used to model the host level immuno-epidemiology of an infectious disease system in this class of multiscale models. Instead, infectious disease systems are modelled using computational algorithms. A wide variety of such computational algorithm-based approaches have been applied to modelling the host level immuno-epidemiology of infectious disease taking into account individual variation at within-host scale and at between-host scale. Examples of such computational algorithm-based models include agent-based model (ABM), CA and petri-nets (PN) (e.g. coloured PNs, stochastic PNs and timed PNs). The most widely used simulation modelling approach in this class of multiscale models to study infectious diseases by integrating within-host
immunity and between-host transmission are agent-based models. The review by Bauer et al. [3] gives some generalized approach to developing agent-based models to study infectious diseases. A typical example of SIMU-IMSM in this class is given in the paper by Ogunjimi et al. [91] where an agent-based model was used to investigate the impact of varicella vaccination on zoster. This SIMU-IMSM was used to estimate currently unknown pivotal biomedical parameters, including the duration of exogenous boosting at 2 years, with a peak threefold to fourfold increase of varicella-zoster virus (VZV) cellular mediated immunity (CMI); the VZV weekly reactivation probability at 5% and VZV subclinical reactivation having no effect on VZV-CMI. The model also predicted that a 100% effective chickenpox vaccine given to 1 year olds would cause a 1.75 times peak increase in HZ 31 years after implementation. This increase was predicted to occur mainly in younger age groups than is currently assumed. In general, because SIMU-IMSMs do not model immuno-epidemiology of infectious disease using equation-based techniques, they have an advantage over the other two classes of multiscale models in this category of multiscale models (NETW-IMSMs and EMPI-IMSMs) because they require less mathematical ability to develop than NETW-IMSMs and EMPI-IMSMs.

Class 4: Hybrid individual-based multiscale models (BRID-IMSMs): These are individual-based multiscale models where the individual entities are represented using different formalisms. For example, some entities in an ABM may be described by continuous time variables while others are described by discrete time variables. The use of hybrid PNs will also result in BRID-MSMs. However, unlike the category of HMSMs (see description for category IV) which is based on describing the different scales of an infectious disease system using different formalisms, the HMSMs in this class are based on describing the entities of a single scale of an infectious disease system using different formalisms. This is because in individual-based multiscale models, the within-host submodel is used to describe the entire infectious disease system across both the within-host scale and between-host scale.

Individual-based multiscale models are the only category of multiscale models that exclusively incorporate individual-level heterogeneity in the development of multiscale models. For multiscale models that integrate within-host scale and between-host scale, such individual-level heterogeneity would include variation in infectiousness or individual variation in immune response which arise due to heterogeneity in properties of the host, pathogen and the environment. However, IMSMs require more computational resources to implement than the other categories of multiscale models of infectious diseases.

Category II: NMSMs: In this category, multiscale models are formed based on the serial integration framework (see Figure 1(b)). Therefore, in this category of HL-IEMs, there is only unidirectional flow of information in NMSMs (only from within-host scale submodel to between-host scale submodel). There is never, any reciprocal feedback from the between-host scale submodel back down to the within-host scale submodel in nested multiscale models. This category of multiscale models integrates within-host scale and between-host scale while allowing the between-host scale to be dependent on the within-host processes, they assume that the within-host scale dynamics is
independent of the between-host scale. A key requirement of this class of multiscale models is that both the within-host scale submodel and the between-host scale submodel must be described by the same formalism. In this type of multiscale models, the between-host scale submodel is used to describe the entire disease system across the within-host scale and between-host scale. No explicit within-host scale submodel features in this type of multiscale models, and when it does, it will be independent from the between-host scale submodel. This is because within this category of multiscale models, there are three main different methods for linking the within-host and the between-host submodels. They are the transformation method, unidirectional coupling method and simplification method [53]. As a result, we identify three main classes of multiscale models in this category which we briefly describe as follows.

Class 1: Transformation based nested multiscale models (TRAN-NMSMs): In this class of HL-IEMs the within-host scale submodel is formally transformed into a between-host scale model. This type of multiscale models is formulated through developing physiologically structured between-host scale submodels. In most cases, this task is accomplished by subdividing the entire host population into various sub-classes corresponding to the different levels of immune protection: naive or completely susceptible, completely or partially immune, vaccinated, immune compromised or protected from infection due to certain genetic factors. The paper by Yang [126] provides a good example of TRAN-NMSM. This paper investigates the transmission of malaria using a TRAN-NMSM where the human hosts are distributed over seven compartments in which three different compartments of immune protection were incorporated (immune, partially immune, non-immune but with immunologic memory). The author noted that although the three types of immunity loss rates do not appear in the basic reproduction ratio formula, the effects can be measured indirectly on the malaria transmission. The effect of the three types of human immune responses against malaria delay the recurrence of the individuals, who already have had contact with parasite, to the susceptible category and that the immunity boosting also avoids the flow into the susceptible compartment. Another example of developing TRAN-NMSM is given in the paper by Chiyaka et al. [11] where a malaria transmission model of malaria in a partially immune population is presented where the duration of partial immunity was modelled by a discrete time delay. The authors deduced that an increase in the period within which partial immunity is lost increases the spread of the disease. Other examples of this modelling approach where the within-host immunological properties are incorporated at between-host level include [62, 117].

Class 2: Unidirectional coupling based nested multiscale models (UNID-NMSMs): In this class of immuno-epidemiological models, the nature of the multiscale model is such that there is strictly one-way inter-scale information flow among the two submodels: the within-host submodel and the between-host submodel. There has been little progress in developing multiscale models of the host level immuno-epidemiology of infectious disease systems in this class. To the best of our knowledge, we are only aware of one publication [34], which addresses the development of UNID-NMSMs in a general way. But we are not aware of
any specific application of this modelling framework to a specific infectious disease system in the context of unidirectional coupled nested multiscale models. However, we note that some multiscale models in this class can be developed as a transitional stage towards the development of the third class of immunoepidemiological models (class 3 of UNID-NMSMs which we discuss next). This is achieved by making some simplifications as described in the third class of multiscale models in this category.

Class 3: Simplification-based nested multiscale models (SIMP-NMSMs): In the development of HL-IEMs models in this class, the order of the within-host submodel is reduced and then it is used in formulating the between-host scale submodel. The approach here is to integrate the within-host scale submodel and the between-host scale submodel by expressing the parameters of the between-host scale submodel as functions of the dependent variables of the within-host scale submodel. For example, transmission rate may be assumed to be a function of the pathogen load, or disease-induced mortality rate may be assumed to be a function of the pathogen load and the immune system [41]. One way of doing this is by simplifying a UNID-NMSM. In general, the simplification is usually achieved by some dimension reduction methods to simplify multiscale models characterized by high-dimensional state or input parameter space to their essential dimensions, with significantly reduced number of degrees of freedom. Dimensional reduction of the multiscale model of the infectious disease system is important for three reasons: (i) to reduce the computational needs for simulating the multiscale model, (ii) to identify the most fundamental components with respect to the drivers of the multiscale model behaviour, and (iii) to simplify the process of analysis of the multiscale model. To date, several dimensional reduction methods have been developed which include the following: slow and fast time scale analysis [10, 27, 28], response surface modelling [86], statistical methods such as principal component analysis [55], response and statistical surrogate modelling [29] as well as dynamical systems based methods such as centre manifold theory [8]. In the context of slow and fast time scale analysis, the simplification is usually achieved by separation of time scales, by making the following assumptions:

(i) Very slow processes (between-host scale submodel) are essentially constant at a fast scale.

(ii) Very fast processes (within-host submodel) are essentially always in steady state at a slow time scale.

A consequence of these assumptions is that the within-host submodel equations are reduced to algebraic equations which can be solved to get some values which feed into the parameters of the between-host scale submodel. The result of this modelling framework are multiscale models in which the within-host model is represented phenomenologically as parameter(s) of the between-host model. Despite their simplicity and a clear description of how such multiscale models may be formulated, there has been no single SIMP-NNSM developed to date in this class.

A major weakness of this category (although they are simple to analyse) is that the assumption that the within-host does not depend or is not influenced by the between-host scale may not be a realistic assumption.
Category III: EMSMs: These are HL-IEMs of infectious disease systems where both the within-host scale submodel and the between-host submodel influence each other. Therefore, this is both a top-down and bottom-up modelling approach. As the name implies, this category of multiscale models is formed based on the embedded integration framework (see Figure 1(d)). In this category of multiscale models, the within-host scale submodel and the between-host scale submodel feature in the multiscale model. Therefore, unlike in [82] where NMSMs and EMSMs are considered the same, this study makes distinction between nested multiscale models and EMSMs. We recognize that the distinction between EMSMs and NMSMs is somewhat ambiguous because both words 'embedded' and 'nested' imply 'something inside something else'. In the case of EMSMs and NMSMs as different categories of multiscale models, the within-host spatial scale (inside-host environmental scale) and between-host spatial scale (outside-host environmental scale) form a hierarchy in which the within-host spatial scale is contained in the between-host spatial scale. However, it is the nature of information flow between the within-host scale submodel and between-host scale submodel that makes the distinction between embedded multiscale models and NMSMs. There is bidirectional flow of information between the within-host scale submodel and between-host scale submodel in EMSMs while there is only unidirectional flow of information in NMSMs (only from within-host scale submodel to between-host scale submodel). There is never, any reciprocal feedback from the between-host scale submodel back down to the within-host scale submodel in nested multiscale models. We identify two main classes of EMSMs in this category of multiscale models of infectious disease systems. In what follows we briefly describe the two classes.

Class 1: Bidirectionally Coupled Embedded Multiscale Models (BIDI-EMSMs): These are HL-IEMs of infectious disease systems which are such that there is strictly two-way inter-scale information flow between the within-host scale submodel and the between-host scale submodel. These BIDI-EMSMs are homogeneously described by the same formalism and are also bidirectionally coupled. There has been little progress in developing HL-IEMs of infectious disease systems of the BIDI-EMSM type. Only a few BIDI-EMSMs have been developed and of these few the majority of them have been restricted to modelling the host level immuno-epidemiology of environmentally transmitted infectious disease systems. In the case of environmentally transmitted infectious disease systems, the within-host submodel and the between-host submodel are linked through the pathogen load in the environment. To the best of our knowledge only one BIDI-EMSM for directly transmitted infectious disease systems has been developed to date [26] in the context of a general viral infectious disease system. The model allows the two dynamic processes at both the within-host scale and the between-host scale to explicitly depend on each other. From the analysis of this BIDI-EMSM it is shown that new properties can emerge from the coupled system such as multiple endemic equilibria and bistability. A typical example of EMSMs arising from modelling the host level immuno-epidemiology of environmentally transmitted infectious disease systems is provided in [32] in the context of schistosomiasis infectious disease system. Using results from the analysis of the endemic equilibrium expression, the disease reproductive number $R_0$, and numerical simulations of the full model, the authors were able
to adequately account for the reciprocal influence of the linked within-host and between-host submodels. In particular, the authors illustrated that for human schistosomiasis, the outcome of infection at the individual level determines if, when and how much the individual host will further transmit the infectious agent into the environment, eventually affecting the spread of the infection in the host population [32]. In [10, 27, 28], BIDI-EMSMs for *Toxoplasma gondii* (another environmentally transmitted infectious disease system) were developed and analysed using different modifications where the within-host submodel and the between-host submodel are coupled through the pathogen load in the environment. The main findings from these studies is that infection may persist at population level even if the isolated between-host reproduction number is less than one. Another good example of a BIDI-EMSM is given in [121] in the context of cholera transmission with both environmental and direct transmission.

Class 2: *SIMP-EMSMs*: To date, little progress has been registered in developing SIMP-EMSMs. Like in the case of BIDI-EMSMs, the few SIMP-EMSMs that have been developed have been restricted to modelling the host level immunoepidemiology of environmentally transmitted infectious disease systems. In the development of HL-IEMS in this class the approach has been to develop a BIDI-EMSM first. Then assumptions are identified that lead to the decoupling of the within-host scale and the between-host scale submodels, effectively allowing solutions of the within-host scale submodel and between-host scale submodel to be determined independently. Therefore, EMSMs of this type consists of two models that employ the same formalism which are independent or decoupled submodels. These two submodels describe the within-host scale and the between-host scale using the same formalism. Although the two submodels are independent and can be analysed independently, their synergy gives an added value to the overall multiscale description of the infectious disease system. The simplification can sometimes be achieved as in UNID-NMSM by performing a slow-fast time scale analysis. A classic example of this modelling approach to develop SIMP-EMSMs which integrate the within-host scale and the between-host scale is given in [121]. In the SIMP in [121], a BIDI-EMSM was developed first in the context of a HL-IEM to concurrently study the within-host scale and between-host scale dynamics of cholera. The explicit linkage between within-host scale and between-host scale submodels was formulated by presuming a general representation for both the direct transmission and the pathogen shedding, and the interaction between environmental vibrios at between-host scale and human vibrios at within-host scale. The BIDI-EMSM was subsequently simplified using slow and fast time scale analysis into a SIMP-EMSM composed of two submodels with one of them describing the within-host scale parasite dynamics (fast system) and the other describing the between-host scale disease dynamics (slow system). Using this SIMP-EMSM, the authors carefully analysed the within-host and between-host dynamics of the disease. The results show that dynamics of the integrated system can be recovered by those of the slow and fast systems obtained by the fast-slow analysis. The authors illustrated that the fast system exhibits a unique equilibrium, either infection-free or endemic, and it is globally asymptotically stable. Further, they also illustrated that in contrast, the
slow system that captures between-host scale dynamics is much more complex. This subsystem was shown to undergo a backward bifurcation, and the precise condition for the occurrence of a backward bifurcation was derived. The results of backward bifurcation analysis indicate that reducing the type reproduction number of infectious persons (or the basic reproduction number) below one is not sufficient for eradicating the disease. This finding is different from all previous mathematical cholera studies, in which the models only exhibit a forward bifurcation and reducing a disease threshold (e.g. the basic reproduction number) below one leads to disease extinction. Thus, the authors attributed the occurrence of the backward bifurcation in the submodel to be a direct result of coupling the within-host scale and between-host scale cholera dynamics. Furthermore, BIDI-EMSM for *Toxoplasma gondii* transmission dynamics in [27] was simplified into SIMP-EMSM. The simplification was achieved by using a singular perturbation argument, which allows for decoupling of the full model by separating the fast- and slow-systems. Thus, the SIMP-EMSM consists of two independent single scale models: one for the within-host scale and the other one for the between-host scale. The authors defined new reproductive numbers for the within-host and between-host dynamics for the isolated systems. They established that, the reproduction number for the between-host (slow) system dependent on the parameters associated with the within-host (fast) system in a very natural way. Further, the authors illustrated that these reproduction numbers determine the stability of the infection-free and the endemic equilibrium points. Further analysis of the SIMP-EMSM in [27] was done in [10, 28]. However, although there will be significant reduction in analytical and computational expense associated with the independent submodels in a SIMP-EMSM, the decoupling restricts the behaviours that can be modelled using these independent submodels.

A major attractive property of EMSMs is that both the within-host submodel and the between-host submodel influence each other. However, an interesting question that arises in developing EMSMs is how to capture and model the feedback between the within-host submodel and between-host submodel and develop EMSMs where both the within-host and between-host dynamics influence each other.

**Category IV: HMSMs:** These are multiscale models which are formed based on multi-domain integration framework (see Figure 1(c)). In the context of developing multiscale models that integrate the within-host submodel and the between-host submodel, the use of this integration framework implies that the within-host scale and the between-host scale belong to different domains. This implies that unlike in all the other three categories of multiscale models (category I, II and III where the within-host scale and the between-host scale belonged to the same domain and were therefore modelled in a homogeneous way using the same formalism), here the within-host scale and the between-host scale may no longer be modelled in a homogeneous way. In short, each domain may now be described by a submodel of a different formalism leading to coexistence of heterogeneous modelling techniques for the within-host scale and the between-host scale leading to a methodologically hybrid modelling approach for developing multiscale models of the host level immuno-epidemiology of infectious disease systems. In its most general definition, a HMSM is any multiscale model composed of at least two scales in which at least one of the scales is described by a
submodel whose formalism is different from that of the rest of submodels constituting the multiscale model. In the context of integrating the within-host scale and between-host scale of an infectious disease system, the submodels for the within-host scale and between-host scale will be based on different formalisms. Examples of the different paired formalisms that can be used to establish multiscale models integrating the within-host scale and the between-host scale are deterministic/stochastic, discrete time/continuous time, mechanistic/phenomenological, ODE/PDE, ODE/ABM, ODE/CA, etc. Based on the different ways in which the two submodels may be linked to establish a HMSM, we identify three classes of multiscale models in this category. We now further describe these three classes.

Class 1: Unidirectionally coupled hybrid multiscale models (UNID-HMSMs): The nature of the multiscale model is such that there is strictly one-way inter-scale information flow between the within-host scale submodel and the between-host scale submodel. Therefore, these are multiscale models which are similar to NMSMs except that in this case the within-host scale and the between-host scale are described by different formalisms but are still unidirectionally coupled as in UNID-NMSM. There are two main ways in which these UNID-HMSM can be established. One of them, and also the most widely used is the time-since-infection approach. This approach was suggested for the first time by Gilchrist and Sasaki [35] where an explicit within-host scale submodel is linked to the between-host scale submodel through a structural variable of the between-host scale submodel. Here the integration of the within-host scale submodel to the between-host scale submodel is implemented through a structural variable of the between-host scale submodel. The between-host model must be structured through time-since-infection. The time-since-infection is then used as an independent variable in the within-host scale submodel, which is valid only in the infected compartment of the between-host scale submodel. The result is a HMSM in which the within-host submodel is typically an ODE model adopted from literature while between-host model incorporates age-since-infection described by a system of integro-differential equations. The UNID-HMSM in [35] was used to analyse a simple host-parasite system. The authors found out that the co-evolutionary equilibrium is always stable and that host survivorship and parasite fitness vary greatly with the cost of the immune response and parasite growth. This modelling approach is reviewed in [82]. However, since this pioneering work, several authors have used this approach to develop unidirectionally coupled HMSMs for studying the host level immuno-epidemiology of infectious disease systems (see for example [6, 43, 68, 75, 76, 118] and references therein) using the time-since-infection approach. Another approach for developing unidirectionally coupled hybrid multiscale is the size-structured approach. This approach was first introduced in [74]. In this approach the between-host scale submodel consists of physiological structured integro-differential equations in which the structural independent variables are the dynamical variables of the ODE within-host submodel describing the evolution of the immune system. Using the UNID-HMSM in [74], the authors established that the possibility of reinfection of recovered individuals results in sub-threshold endemic equilibria and that the differential immunity of the infectious individuals leads to multiple
nontrivial equilibria in the superthreshold case. Further extensions to this work was contributed in [30] to incorporate a situation where the between-host scale density of infected individuals is structured by both the viral load and the immune response. Other variations of the size-structured approach can be found in the following works [2, 21, 84].

Class 2: SIMP-HMSMs: In the development of HL-IEMs in this class, the order of the within-host submodel is reduced and then it is used in formulating the between-host submodel. This class of hybrid multiscale is established by finding simplified versions of the UNID-HMSM. One way of developing multiscale models in this class is by making simplified versions of the UNID-HMSM which simplify to hybrid multiscale of the mechanistic/phenomenological nature. The simplification can be achieved as in UNID-NMSM by performing a slow-fast time scale analysis so that the parameters of the between-host model are expressed as functions of the dependent variables of the within-host model as in UNID-NMSM. An alternative to forming such type of multiscale models is to use model other dimensional reduction methods in [8, 29, 55, 86] instead of just performing slow and fast time scale analysis. A typical example of simplification-based HMSM is presented in [69] where an ordinary differential equation at within-host scale was coupled to an agent-based model at between-host scale. Using an equation-based, within-host scale model of influenza A virus (IAV) infection, they developed a function that expresses the dependence of infectivity and symptoms of an infected individual on initial viral load, age and other within-host variables. They also incorporated this response function in a population-scale agent-based model of influenza A epidemic to create a hybrid multiscale modelling framework that reflects both population dynamics and individualized host response to infection. The HMSM (ABM/ODE) was able to replicate results of simulated epidemics with simpler within-host assumptions, and provides additional flexibility to explore questions relevant to host heterogeneity at no extra computational cost. The simplification part in this work arise from use of response surface analysis to simplify the computation of output trajectories of the equation-based within-host model, which makes the immuno-epidemiological model just as efficient and scalable as the underlying population-level ABM (see [69] for more details). For an additional example of the SIMP-HSM see the paper by Steinmeyer et al. [113].

Class 3: Bidirectionally Coupled Hybrid Multiscale Models (BIDI-HMSMs): These are HL-IEMs of infectious disease systems which are such that there is strictly two-way inter-scale information flow between the within-host scale submodel and the between-host scale submodel. Therefore, these are multiscale models which are similar to EMSM except that in this case the within-host scale and the between-host scale are described by different formalisms but are still bidirectionally coupled as in EMSMs. There has been little progress in developing immuno-epidemiological models of infectious disease systems of the BIDI-EMSM type.

Category V: CMSMs: This category of multiscale models is formed based on parallel integration framework (see Figure 1(e)). The category takes an ecosystem view to multiscale modelling of the host level immuno-epidemiolgy of infectious disease
systems and considers the overlap of biodiversity and drivers of infectious disease systems. In this multiscale modelling category, the other four categories of multiscale models (NMSMs, IMSMs, EMSMs, HMSMs) are used as submodels to describe the host level immuno-epidemiology of infectious disease systems that includes the full within-host and between-host and pathogen species diversity implicated in the transmission of the infectious disease system. Unlike the other four categories of multiscale models (IMSMs, NMSMs, EMSMs, HMSMs) which investigate infectious disease systems focusing on specific one-host-one-pathogen relationships, this category of multiscale models, takes into account the effect of within-pathogen species diversity (multi-strain infections), between-pathogen species diversity (multi-pathogen infections), within-host species diversity (multi-group infections) and between-host species diversity (multi-host infections) on the transmission of infectious disease systems. It also takes into account the diversity within a single-host species (multi-group infections) and diversity within a single-pathogen species (multi-strain infections). There is no restriction on the formalism of each of the multiscale models that are used as submodels in the coupled multiscale model. They can be any of the four categories of multiscale models (IMSM, NMSM, EMSM, HMSM). Such multiscale models are central to the research that informs the ecological, evolutionary and socio-ecological principles and processes that regulate the transmission of infectious disease systems. Based on the different levels of within and between-host and pathogen species diversity implicated in the transmission of infections, we identify three main different classes of multiscale models in this category. However, the application of criterion V results in these CMSMs being further classified as either homogeneous or hybrid CMSMs. We describe them one by one as follows.

Class 1: Single-host multi-pathogen coupled multiscale models (SHMP-CMSMs): These are multiscale models of the host level immuno-epidemiology of infectious disease systems for either multi-pathogen infections or multi-strain infections or multi-group infections. We classify together into a single class multiscale models of the host level immuno-epidemiology of all the three different types of infectious diseases systems (multi-pathogen, multi-strain and multi-group) because for all of them the infection outcomes at within-host scale for the units of analysis (i.e. individual hosts) vary in a discrete way so that several compartments of infected hosts can be identified in the multiscale model. In this class of multiscale models, a multiscale model that integrates the within-host and the between-host submodels is developed first for each pathogen (for multi-pathogen infections) or for each strain (for multi-strain infections) or for each different class of infected hosts (for multi-group infections). Then these different multiscale models covering the entire within-host and between-host and pathogen species diversity implicated in the transmission of the infectious disease system are coupled together to form a single multiscale model. We define SHMP-CMSM as those multiscale models in which at least two of the multiscale models that are used as submodels integrate the within-host scale and the between-host scale for at least two of the pathogens/strains/infected classes that are implicated in the transmission of the infectious disease system. A typical example of the SHMP-CMSM for modelling the host level immuno-epidemiology of infectious diseases is given in the paper by Legros and Bonhoeffer [64] in the form of a
multi-strain model for malaria infection using a stochastic modelling approach. Each submodel (for the between-host and for the within-host) was first presented as a deterministic set of ODEs. The final, stochastic model was then obtained by translating each deterministic component into the corresponding stochastic model, using Gillespie tau-leap algorithms [36]. Thus, this multiscale model is further classified as a SHMP-CMSM of homogeneous type. The coupled multiscale model was used to investigate the evolution of drug resistance during malaria infection. The authors established that the spread of resistance is generally less likely in areas of intense transmission, and therefore of increased competition between strains, an effect exacerbated when costs of resistance are higher. Further, they also used the SHMP-CMSM to illustrate how treatment influences the spread of resistance, with a trade-off between slowing resistance and curbing disease incidence. The authors established that treatment coverage has a stronger impact on disease prevalence, whereas treatment efficacy primarily affects resistance spread, suggesting that coverage should constitute the primary focus of control efforts. Another typical example of a SHMP-CMSM for studying the immuno-epidemiology of infectious disease systems is presented in [90] in the context of a multi-group HIV/AIDS infection model. A multi-group coupled multiscale model composed within-host model of ODEs and between-host model of ODE and first-order PDEs was formulated together with the optimal control problem subject to fusion inhibitors (FIs) and protease inhibitors (PIs). Therefore, this multiscale model is further classified as a SHMP-CMSM of hybrid type. The optimality system was solved numerically. The numerical simulations obtained suggest that the combination of fusion and PIs reduces viral load at the within-host level and the disease-induced mortality at the population level, but results in an increase in the number of infectious individuals at the population level since infectious individuals live longer in the presence of drugs. For further examples of this multiscale modelling approach see [18, 72, 73, 79] (for modelling multi-strain infections) and [110] (for modelling multi-group infections).

Class 2: Multi-host single-pathogen coupled multiscale models (MHSP-CMSMs): These are multiscale models of the host level immuno-epidemiology of infectious disease systems arising from infection of multiple host species by a single pathogen. Such infectious disease systems arise because either the pathogen has a complex life cycle so that there is a sequence of hosts necessary to complete the pathogen’s life cycle or because of its generalist nature. A good example of such multi-host single-pathogen infectious disease systems is that caused by Schistosoma japonicum, which causes human schistosomiasis in Asia, which can infect up to 120 different species of mammals [103]. In this class of multiscale models, a multiscale model that integrates the within-host and the between-host submodels is developed first for each of the host species that is implicated in the transmission of the infectious disease system. Then these different multiscale models covering the entire diversity of host species implicated in the transmission of the infectious disease system are coupled together to form a single multiscale model. Therefore, we define MHSP-CMSM as multiscale models in which at least two of the multiscale models that are used as submodels integrate the within-host scale and the
between-host scale scale for at least two of the hosts that are implicated in the transmission of the infectious disease system. This modelling approach was proposed in [78] in the context of a two-host single-pathogen infectious disease. The model involves two coupled UNID-HMSM which use the time-since-infection approach resulting in ODE/PDE hybrid HL-IEMs where the ODE within-host submodel and the integro-partial differential equation between-host submodel are unidirectionally coupled. Therefore, we further classify this multiscale model as a SHMP-CMSM of hybrid type. The model was used to investigate the principle for host evolution, when the host is subjected to a fatal disease. The authors found that the minimization of the case fatality proportion is an evolutionary stable strategy for the host. For a further example of modelling the host level immuno-epidemiology of infectious disease systems using MHSP-CMSM see the paper by Heizzmann [46].

Class 3: Multi-host multi-pathogen coupled multiscale models (MHMP-CMSMs): These are multiscale models for infectious disease systems in which a wide range of host and pathogen species are implicated in the transmission of the infectious disease system. These are the most complex of all the other classes of multiscale models in this category. These multiscale models arise from modelling multi-host, multi-pathogen, multi-strain and multi-group infectious disease systems and are useful in accounting for the joint effect of the within and between-host and pathogen diversity in the transmission of infectious disease systems. We define MHMP-CMSMs as multiscale models of the host level immuno-epidemiology of infectious disease systems in which at least two pathogen species/pathogen strains/classes of infected hosts and at least two-host species are implicated in the transmission of an infectious disease system and at least one of the multiscale models that integrate the within-host scale and the between-host scale and is used as a submodel in the CMSM is a MPSH-CMSM, that is, at least two of the hosts are co-infected with the two pathogens. Based on criterion V, these multiscale models are also further classified as CMSMs of either homogeneous or hybrid type.

Table 2 shows a summary of categorization of HL-IEMs.

We presented in this section the proposed categorization of multiscale models of the host level immuno-epidemiology of infectious disease systems. We used a set of five criteria to categorize the multiscale models, which are based on the interpretation of the integration frameworks. However, we note that within each category of multiscale models, there is a variety of ways of linking the within-host and between-host submodels of infectious disease systems. As a result, we have presented some of the different classes of multiscale models that belong to some of the categories of multiscale models of infectious disease systems. However, this categorization of multiscale models of infectious disease systems offers no guidance on which category of multiscale models is best for a given application. In the following two sections (Sections 5 and 6), we consider categorization and classification of other types of multiscale models outside host level immuno-epidemiology involving two scales of infection for infectious disease systems by modifying criterion IV.
| Name of category | Acronym | Brief definition | Some key features of the category | Name of class | Acronym | Some key features of the class | References | Comments |
|------------------|---------|------------------|-----------------------------------|---------------|---------|--------------------------------|------------|----------|
| Individual-based Multiscale Models (Category 1) | IMSMs | Host level immunoepidemiological models in which within-host scale influences between-host scale without any reciprocal feedback taking into account individual variability | ▶ Uses simultaneous integration framework ▶ Bottom-up multiscale modelling ▶ Unidirectional flow of information from within-host scale to between-host scale ▶ Submodels may be described homogeneously or in a hybrid way | Network modelling individual-based multiscale models | NETW-IMSMs | Developed using graph theoretic or network modelling techniques | [58, 116, 119, 120] | ▶ Requires less mathematical skills but needs more computational resources ▶ Takes into account individual variability. ▶ Between-host scale results are observed as emergent behaviour of within-host scale submodel |
| Nested Multiscale Models (Category 2) | NMSMs | HL-IEMs in which within-host scale influences between-host scale without any reciprocal feedback | ▶ Uses serial integration framework ▶ Unidirectional flow of information from within-scale submodel to between-host scale submodel ▶ Top-down multiscale modelling ▶ Submodels described homogeneously | Transformation based NMSMs | TRAN-NMSMs | Models subdivide the entire host population into various sub-classes corresponding to the different levels of immune protection Submodels are unidirectionally coupled | [11, 117, 126] | ▶ Potentially the simplest multiscale models to develop and analyse although little work has been done in this category. ▶ Methods to develop SIMP-NMSMs have now been described. |
|                   |         |                  |                                   | Unidirectional coupled nested multiscale models | UNID-NMSMs |                                    | [34] |          |
|                   |         |                  |                                   | Simplification-based nested multiscale models | SIMP-NMSMs | Within-host submodel is simplified, for example, reduced into a composed parameter that appears feeds into between-host submodel | – |          |
| Embedded Multiscale Models (Category 3) | EMSMs | HL-IEMs in which within-host scale and between-host scale influence each other with reciprocal feedback |
|----------------------------------------|-------|------------------------------------------------------------------------------------------------------------------|
|                                        |       | ▶ Uses embedded integration framework ▶ Bidirectional flow of information between the scales ▶ Top-down & bottom-up multiscale modelling ▶ Submodels described homogeneously |
| Bidirectionally coupled BIDI-EMSMs     |       | within-host and between-submodels are coupled into unified multiscale model with reciprocal influence on each other |
| [10, 26–28, 32, 121]                   |       | ▶ Difficult to capture and model the reciprocal feedback between the within-host submodel and between-host submodel |
| Simplification-based SIMP-EMSMs        |       | Within-host submodel and between-host submodel are decoupled into separate and independent submodels |
| [10, 27, 28, 121]                      |       | ▶ Simplification-based EMSMs |

| Hybrid Multiscale models (Category 4) | HMSMs | HL-IEMs in which within-host scale and between-host scale influence each other with or without reciprocal feedback |
|--------------------------------------|-------|------------------------------------------------------------------------------------------------------------------|
|                                      |       | ▶ Uses multi-domain integration framework ▶ Bi-directional or uni-directional flow of information or both ▶ Bottom-up or both bottom-up and top-down ▶ Submodels described in hybrid way |
| HMSCs                                |       | Unidirectionally coupled submodels described in hybrid way |
| [2, 6, 21, 30, 35, 43, 68, 74–76, 82, 84, 118] |       | ▶ Most difficult to simulate since one has to simulate separately their different components using specific methods for each of these components. |
| Simplification-based SIMP-HMSCs      |       | Unidirectionally coupled submodels described in hybrid way in the mechanistic/phenomenological form |
| [69, 113]                            |       | ▶ Bidirectionally coupled HMSMs |
| Bidirectionally coupled BIDI-HMSCs    |       | Bidirectionally coupled submodels and described in hybrid way |
| –                                    |       | ▶ Bidirectionally coupled HMSMs |

(continued)
| Name of category                      | Acronym | Brief definition                                                                 | Some key features of the category                                                                 | Name of class | Acronym | Some key features of the class                                                                 | References | Comments                                                                 |
|--------------------------------------|---------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|---------------|---------|-------------------------------------------------------------------------------------------------|------------|--------------------------------------------------------------------------|
| Coupled Multiscale Models (Category 5) | CMSMs   | HL-IEMs which take into account the diversity of pathogen and host species composition | ▶ Uses parallel integration framework  
▶ HL-IEMs are described homogeneously or in hybrid way  
▶ Takes into account host and pathogen species diversity  
▶ Top-down or bottom-up multiscale modelling or both | Single-host multi-pathogen coupled multiscale models | SHMP-CMSMs | These multi-pathogen/multi-strain/multi-group immune-epidemiological models | [18, 36, 64, 73, 79, 90, 110] | ▶ This is most useful in the ‘one-health’ approach to public health  
▶ Useful in the study of the spread of antimicrobial resistance in host population |
|                                      |         |                                                                                  |                                                                                                   |               |         | Multi-host single-pathogen coupled multiscale models                                           |            |                                                                         |
|                                      |         |                                                                                  |                                                                                                   |               |         | MHSP-CMSMs                                                                                     | [46, 78]   |                                                                          |
|                                      |         |                                                                                  |                                                                                                   |               |         | These multi-host immune-epidemiological models                                                 |            |                                                                         |
|                                      |         |                                                                                  |                                                                                                   |               |         | MHMP-CMSMs                                                                                     |            |                                                                         |
|                                      |         |                                                                                  |                                                                                                   |               |         | Involve combination of multi-host and multi-pathogen/multi-strain/multi-group immune-epidemiological models |            |                                                                         |
5. Categorization of multiscale models of infectious disease systems that integrate within-cell and between-cell scales

In developing multiscale models of infectious disease systems, the cell is a lower level of biological organization associated with transmission of intracellular pathogens (which include viruses, some bacteria, certain protozoa and certain fungi) at which infection by a pathogen can be considered. This implies that infection by a pathogen in an infectious disease system can be considered at the cell level of biological organization. This level of biological organization (the cell level) has two limiting scales of infection which are the within-cell scale and the between-cell scale. Further, these two adjacent limiting scales give rise to a different type of multiscale models of infectious disease systems. So far we have only considered the categorization of multiscale models of infectious disease systems of one type of multiscale models, that is, those which arise when the two adjacent scales of infection incorporated into the multiscale model are the within-host scale and the between-host scale. In this section we consider categorization of multiscale models of infectious disease systems that integrate within-cell and between-cell scales. In the context of this study we call such multiscale models cell level immuno-epidemiological models (CL-IEMs). We also alternatively call this type of multiscale models cytoimmuno-epidemiological models. Thus, we name this type of multiscale models after a sub-discipline of biology addressing the study of the cell level of biological organization called cytology where the word ‘epidemiological’ in ‘cytoimmuno-epidemiological’ is used to imply the study of distribution of infection among cell populations. Therefore, cytoimmuno-epidemiology becomes the study of the distribution of immune responses and infection in cell populations, and of the factors influencing this distribution.

However, the condition for applying the five integration frameworks given in the categorization framework in Section 3 in categorizing any type of multiscale models of infectious disease systems that integrate two scales at a time is only that the two scales incorporated into the multiscale model must be adjacent to each other (microscale/lower scale and macroscale/upper scale). Since this condition is satisfied by cytoimmuno-epidemiological models because the two scales incorporated in this type of multiscale models (within-cell scale and between-cell scale) are adjacent, then the five integration frameworks can also be used in categorizing cytoimmuno-epidemiological models. In addition, except for criterion IV, all the other criteria (I, II, III and V) are not explicit regarding the scales of infection to be incorporated into the multiscale model since they only specify the following aspects of the scales:

- the flow of information between any two adjacent scales (criterion I),
- the relationship between any two adjacent scales (criterion II),
- the order in which any two adjacent scales are incorporated into the multiscale model (criterion III), and
- the nature of the mathematical representation or formalism used to describe any two adjacent scales (criterion V).

This implies that all the other four criteria (I, II, III and V) are also applicable in categorizing cytoimmuno-epidemiological models. However, criterion IV is explicit regarding the level of biological organization whose two adjacent scales of infection are incorporated...
into the multiscale model (the host level). Therefore, the categorization framework presented in Section 3 for categorizing multiscale models of infectious disease systems that integrate the within-host scale and the between-host scale is also applicable in categorizing cytoimmuno-epidemiological models by suitably modifying criterion IV which specifies the level of biological organization considered in the transmission of the infectious disease system and whose two adjacent scales of infection are incorporated into the multiscale model. In the case of cytoimmuno-epidemiological models the level of biological organization of the infectious disease whose two adjacent scales of infection incorporated into the multiscale model is the cell level. In this case the two adjacent scales of infection are the within-cell scale and the between-cell scale as previously stated. In order to categorize and classify cytoimmuno-epidemiological models using the categorization framework presented in Section 3, all the five integration frameworks will be applicable in categorizing cytoimmuno-epidemiological models except that the microscale and the macroscale are now the within-cell scale and the between-cell scale. Further, criteria I, II, III and V will also be applicable in categorizing cytoimmuno-epidemiological models except that criterion IV will have to be modified to suit the description of the cell level of infection to become:

Criterion IV: The level of biodiversity involved in the transmission of the infectious disease system involved which may include the simplest situation where only a single-pathogen and single-target cell population species are considered and the more complex situations where the diversity among target cell species (multi-target cell infections) and/or diversity among pathogen species (multi-pathogen infections) and/or diversity within a single-pathogen species (multi-strain infections) and/or diversity within target cell species (multi-target cell group infections, e.g. for HIV infection some target cells (e.g. CD4 T cells) become latently infected while others become actively infected upon infection) are considered.

In this case, the categorization framework presented in Section 3 when applied in the categorization of cytoimmuno-epidemiological models will result in five categories of multiscale models (IMSMs, NMSMs, EMSMs, HMSMs, CMSMs) with their associated classes which are exactly the same categories and classes as for HL-IEMs presented in Section 4 except that in this case the host considered is not a whole organism (human, vector, animal, plant) but a target cell (CD4 T cell, Macrophage, epithelial cell, red blood cell, etc.). Therefore, the categorization framework presented in Section 3 is also applicable in categorizing cytoimmuno-epidemiological models by appropriately modifying criterion IV so that the host considered becomes the cell.

One area in which progress has been made in the development of cytoimmuno-epidemiological models is in the transmission dynamics of viral infections. This has generated the development of different categories of cytoimmuno-epidemiological models for the transmission dynamics of viral infections including poliovirus, human immunodeficiency virus (HIV), influenza virus, and hepatitis C virus (HCV) to obtain a systems-level understanding of the transmission dynamics of these intracellular pathogens. For viral infectious disease systems, their spread within an infected individual is influenced by within-cell scale and between-cell scale processes. At the within-cell scale, molecular processes such as viral transport, disassembly, integration, transcription, translation, assembly and eventually export influence the efficiency of viral reproductive capacity and hence viral spread [61]. At the between-cell scale, availability of target cells, cell motility,
surrounding tissue environment, and immune response also influence viral spread [61]. In what follows we briefly review the different cytoimmuno-epidemiological models that have been developed to address different aspects of these viral infections. We also categorize these multiscale based on the initial categorization framework presented in Section 3 with a modification of criterion IV so that the host considered in the multiscale models is no longer a whole organism (human, vector, animal, plant) but a cell.

One of the pioneering works in the cytoimmuno-epidemiological modelling of viral infections was presented by Krakauer and Komarova [59] in the context of poliovirus. This multiscale model combines within-cell replication kinetics and protein synthesis, and between-cell population dynamics of virion production and transmission for poliovirus. The initial model in [59] is homogeneously described by ODE submodels where the within-cell submodel is unidirectionally coupled to the between-cell submodel and thus we classify it as a unidirectionally coupled nested multiscale model (UNID-NMSM). The model was further simplified into a simplification based nested multiscale model (SIMP-NMSM) by reducing the within-cell submodel into a composite parameter that feeds into the between-cell submodel. The authors illustrated how the two scales of infection (within-cell scale and between-cell scale) interact to produce trade-offs in the life history strategy of the poliovirus without consideration of host mortality. They found that viruses evolve towards intermediate rather than maximum encapsidation rates. This can be understood as selection for intermediate virulence through cellular persistence. The authors also characterized a theoretical persistence threshold arising from the trade-off between genome replication and genetic translation within the cell. They were able to present counter-intuitive relationships whereby increasing genome decay rates and rates of encapsidation lead to increases in the abundance of virus-encoded proteins. Data from poliovirus suggest that viruses might be unable to resolve the vertical conflicts of interests among different levels of selection. In a related development two cytoimmuno-epidemiological models were also presented in [44, 45] in the context of general viral infections. In the first of these papers [44], a multiscale model was developed integrating within-cell scale and between-cell scale using integro-partial differential equations where the within-cell submodel is unidirectionally coupled to the between-cell submodel. Thus we classify this cytoimmuno-epidemiological model as a UNID-NMSM. From the analysis of this multiscale model, the results demonstrate that, in contrast to commonly used models, the cell population balance provides a more intuitive and flexible modelling framework for incorporating both the within-cell scale and between-cell scale events occurring during viral infections. This improved capability to represent the trends in the biological measurements of interest offers a more systematic and quantitative understanding of how viral infections propagate and how to best control this propagation. In [45], the authors identified assumptions that lead to exact, selective decoupling of the interaction between the within-cell scale submodel and the between-cell scale submodel, effectively facilitating solution of first, the within-cell scale submodel, and subsequently the between-cell scale submodel. This decoupling leads to a SIMP-NMSM composed of within-cell scale submodel and between-cell scale submodel of viral infections that have been previously reported and lead to a significant reduction in the computational expense required to solve the multiscale model.

Hosseini and Gabhann [51] introduced one of the first cytoimmuno-epidemiological models for HIV-1 transmission dynamics. For this multiscale model, the within-cell scale is described by ODE submodel whilst the between-cell scale is described by a DDE submodel.
The within-host submodel is unidirectionally coupled to the between-cell scale submodel. In the context of categorizing multiscale models of infectious disease systems that integrate two scales at a time, we categorize this cytoimmuno-epidemiological model as a unidirectionally coupled hybrid multiscale model (UNID-HMSM). The authors used this multiscale model to study the capability of mainly three apolipoprotein B mRNA editing enzyme 3G (APOBEC3G) or (A3G)-based therapies which are: antibody to viral infectivity factor (Vif), upregulation of A3G and mutated forms of A3G. APOBEC3G, also sometimes referred to as A3G, is an enzyme which is a member of the APOBEC family which is a potent inhibitor of HIV infection. In contrast, viral infectivity factor (Vif) - a viral protein, is known to have antagonistic effect on APOBEC3G through protecting the virus by binding to APOBEC3G and causing the degradation of this enzyme. The cytoimmuno-epidemiological model in [51] was used to simulate in vitro experiments that concurrently include A3G-Vif interactions at the within-cell scale and T cell-HIV interactions at between-cell scale. Experimental data was used to validate predictions of this UNID-HMSM. Analysis of this cytoimmuno-epidemiological model predicted that a mutated form of APOBEC3G that does not bind Vif performs far much better at suppressing HIV replication compared to other drugs. The authors also established that the drug should be administered shortly after infection and that it must be available to all cells in order to be effective.

In a remarkable attempt to characterize the cytoimmuno-epidemiology of HIV, a series of multiscale models were presented in [115] to investigate antiviral therapeutic opportunities in targeting two key accessory proteins for HIV-1. The two viral accessory proteins are viral protein U (Vpu) and viral infectivity factor (Vif) which target the host restriction factors, bone marrow stromal cell antigen 2 (BST2) and A3G respectively. A series of three cytoimmuno-epidemiological models was used to explore the potency of these host restriction factors (BST2 and A3G) under protein (Vpu and Vif) targeted therapies. In the first of a series of the three multiscale models, the authors developed a multiscale model of BST2 and Vpu interactions to study the role of the Vpu-induced downregulation on the cytoimmuno-epidemiology of HIV. The BST2 restriction factor is an interferon-induced cellular protein that in some cell types is expressed constitutively. It functions by tethering the budding viral particles to the plasma membrane of producer cells, and thereby reducing viral production. HIV-1 has evolved an accessory protein called Vpu to counter this antiviral activity. In the first multiscale model in [115], which characterizes BST2-Vpu interactions, the within-cell scale submodel is described by an (delay differential equation) DDE model while the between-cell scale submodel is described by an age-since-infection integro-differential equation. Thus, we categorize this multiscale model as a unidirectionally coupled hybrid multiscale model (UNID-HMSM). Analysis of this multiscale model using the concept of basic reproductive ratio demonstrated that the Vpu-induced downregulation of BST2 affects the survival of the virus. Further, using published experimental datasets to obtain HIV-1 dynamics parameters, the authors estimated that an infected cell has to retain around 85% (0.85 in fraction) of BST2 in order to bring the reproductive ratio below 1 and also established correlations for BST2 expression, Vpu-induced downregulation, and virus restriction. Thus, this cytoimmuno-epidemiological model provides a benchmark for how effective inhibitors of Vpu activity must be if they are to restrict the progression of HIV-1 infection in vivo. In the second of a series of the three multiscale models in [115], the authors developed a multiscale model of A3G and Vif interactions to
study the dynamics of HIV-1 as a function of A3G-Vif interactions. As considered in [51], the host restriction factor, A3G, is expressed constitutively and its expression increases in response to interferon stimulation and affects viral replication in two ways. First, following packaging of A3G into budding viruses, A3G obstructs the reverse transcription (RT) process. Second, A3G induces hypermutation of the viral genome. These two effects imply that A3G not only reduces the probability of successful integration (establishment of a provirus) but also causes an increase in the number of deleterious mutations, resulting in an increased fraction of non-infectious progeny viruses. In the second multiscale model in [115], which characterizes A3G-Vif interactions, the within-cell scale submodel is described by a DDE in pathogen dynamics while the between-cell scale submodel is described by an age-structured integro-differential equation. However, the interference of A3G with virus results in three types of viral strains, the A3G+ virus population (V+), the A3G− virus population (V−) and the non-infectious virus (V0). Thus, unlike the first multiscale model, this second multiscale model is categorized as single-host and multi-strain coupled multiscale (SHMP-CMSM) of hybrid type because A3G antiviral activity required additional pathogen species within the age-structured in vivo HIV-1 dynamics submodel at between-cell scale. Simulations of this cytoimmuno-epidemiological model provided a quantitative illustration of the fact that A3G has to succeed at two steps of its mode of action (MOA) in that it first of all be efficiently packaged into a large fraction of budding viruses, and also that it must either effectively block the RT process or induce lethal mutations in a large number of RT events. However, the reproductive ratio drops to below 1 only if A3G is packaged in a majority of progeny viruses. Thus A3G-based antiviral therapies should aim at both reducing the A3G-Vif interaction and also increasing the propensity of A3G to package into budding viruses. In the last of a series of the three multiscale models in [115], the authors developed a SHMP-CMSM of hybrid type to model the combined BST2 and A3G activities in order to explore their interactions. The analysis of this last cytoimmuno-epidemiological shows that the implementation of BST2-Vpu treatment does improve the overall performance of A3G-based interventions.

Just like in HIV transmission dynamics at the cell level of biological organization, cytoimmuno-epidemiological models are needed for studying influenza virus dynamics because its replication cycle also offers multiple targets for therapeutic interventions that efficiently interfere with its replication. In an attempt to satisfy this need, a cytoimmuno-epidemiological for influenza virus was recently presented in [48] to support the development of direct-acting antivirals which integrate the within-cell scale (where the virus synthesizes its proteins, replicates its genome, and assembles new virions) and the between-cell scale (where also the virus spreads to new host cells). For this multiscale model, the within-cell submodel is described by a system of ODEs in [47] while the between-cell scale submodel is described by age-since-infection integro-differential equation. Thus we categorize this multiscale model as a UNID-HMSM. This cytoimmuno-epidemiological model was able to recapitulate a wide range of experimental data across both scales including the time course of all three viral RNA species inside an infected cell and the infection dynamics in cell population. It also enabled the authors to systematically study how interfering with specific steps of the viral life cycle affects virus production. The authors established that inhibitors of viral transcription, replication, protein synthesis, nuclear export, and assembly/release are most effective in decreasing virus titres whereas targeting virus entry primarily delays infection. In addition, the results of the analysis of this UNID-HMSM
suggest that for some antivirals therapy, success strongly depends on the lifespan of infected cells and, thus, on the dynamics of virus-induced apoptosis or the host's immune response. Hence, this cytoimmuno-epidemiological model provides a systems-level understanding of IAV infection and therapy as well as an ideal platform to include further levels of complexity toward a comprehensive description of this infectious disease system.

In comparison to other viral infections such HIV and influenza virus, more cytoimmuno-epidemiological models have been developed for hepatitis C virus (HCV) (see for example [15, 39, 40, 99, 101]). In the case of HCV infection, this progress in the development of cytoimmuno-epidemiological models has been significantly supported by major advances in technologies for molecular and cell biology such as microscopy techniques for single-cell analysis of within-cell scale HCV replication in vitro [111], to visualize infection dynamics within the liver of humanized mice [104], and to determine the infection status of single cells in liver biopsy samples of HCV-infected patients [56] and thus providing real life data of infection processes for a systems-level understanding of HCV replication and spread at the cell level of biological organization. One of the first cytoimmuno-epidemiological models for HCV transmission dynamics was introduced by Guedj and Neumann [39]. In this study, a simple cytoimmuno-epidemiological model was first presented. This multiscale model is homogeneously described by a system of ordinary differential equations where the within-cell scale submodel is unidirectionally coupled to the between-cell scale submodel. Thus, this cytoimmuno-epidemiological model is categorized as a UNID-NMSM. However, in order to capture the effect of direct-acting antiviral agents (DAAs), the multiscale model was extended to consider two viral strains (the wild-type strain and the resistant strain). Thus we categorize this second cytoimmuno-epidemiological model as a single-host and multi-pathogen/strain coupled multiscale model (SHMP-CMSM) which is homogeneously described by a system of ODEs. Using this cytoimmuno-epidemiological model the authors were able to establish that the rapid decline of wild-type virus results from the ability of DAAs to destabilize its within-cell scale replication and that this ability also favours the rapid emergence, at within-cell scale, of resistant virus. By considering the interactions between within-cell scale and between-cell scale infection the authors also established that resistant virus which is able to maintain a high level of within-cell scale replication, may nevertheless be unable to maintain rapid enough de novo infection rate at the between-cell scale. Hence this SHMP-CMSM predicts that in HCV, and contrary to our experience with HIV, the emergence of productively resistant virus may not systematically prevent a viral decline in the long-term. Thus, this cytoimmuno-epidemiological model can explain the transient viral rebounds observed with DAA treatment as well as the viral resistance found in most patients with viral relapse at the end of DAA combination therapy.

In Ref. [101] another cytoimmuno-epidemiological model of HCV was developed that integrated the within-cell scale and the between-cell scale. The within-cell scale submodel is described by a system of ODEs while the between-cell scale is described by an age-since-infection integro-differential equation submodel. At the between-cell scale, an existing standard system of ODEs model of the viral infection which comprises of three differential equations representing the dynamics of target cells, infected cells and the virus was used. At the within-cell scale, a single ODE modelling the dynamics of the within-cell viral RNA was also used. The two submodels were coupled bidirectionally through time-since-infection and time-since-treatment. Thus, we categorize this multiscale model as a bidirectionally
coupled embedded multiscale model (BIDI-EMSM). This cytoimmuno-epidemiological model was used to investigate the drug effects of viral protease inhibitor danoprevir. The results of the analysis of this multiscale model show that when therapy significantly blocks both intracellular viral RNA production and virus secretion, the serum viral load decline has three phases, with slopes reflecting the rate of serum viral clearance, the rate of loss of intracellular viral RNA, and the rate of loss of intracellular replication templates and infected cells, respectively. The authors also derived analytical approximations of the multiscale model and used one of them to analyse data from patients treated for 14 days with the HCV protease inhibitor danoprevir. Analysis of the cytoimmuno-epidemiological model suggests that danoprevir significantly blocks intracellular viral production (with mean effectiveness 99.2%), enhances intracellular viral RNA degradation about 5-fold, and moderately inhibits viral secretion (with mean effectiveness 56%). This cytoimmuno-epidemiological model can be useful in studying viral dynamics in patients treated with other DAAs and explore their mechanisms of action in the treatment of HCV.

Another cytoimmuno-epidemiological model was used to investigate the drug effects of daclatasvir, a non-structural 5A (NS5A) inhibitor in [40] during HCV treatment. In this multiscale model the within-cell and between-cell submodels are also bidirectionally coupled through time-since-infection and time-since-treatment and therefore is also classified as BIDI-EMSM. Surprisingly, the NS5A inhibitor daclatasvir (BMS-790052) caused a decrease in serum HCV RNA levels by about two orders of magnitude within 6 hours of administration. But, NS5A has no known enzymatic functions, making it hard to understand daclatasvir’s MOA and to estimate its antiviral effectiveness. The analysis of this cytoimmuno-epidemiological model predicted that daclatasvir efficiently blocks two distinct stages of the viral life cycle, namely viral RNA synthesis and virion assembly/secretion with mean effectiveness of 99% and 99.8%, respectively, and yields more precise estimate of the serum HCV half-life, 45 min, that is, around four times shorter than previous estimates. Treatment of within-cell scale HCV RNA in HCV-infected cells with either daclatasvir or polymerase inhibitor NM107 showed a similar pattern of decline. However, daclatasvir treatment led to an immediate and fast decline of between-cell scale HCV titres compared to a delayed (6–9 hours) and slower decline with NM107, confirming an effect of daclatasvir on both viral replication and assembly/secretion.

The BIDI-EMSMs in [40, 101] were further mathematically analysed in [99]. In the analysis of these models, steady states were calculated and detailed stability analysis was also provided. With certain assumptions the authors approximated the viral load decline after treatment initiation. These approximations have been used to analyse viral load data from patients treated with DAAs such as the NS5A inhibitor daclatasvir [101] and the PIs telaprevir [101] and danoprevir [40]. The authors performed numerical simulations to illustrate the effects of DAAs different antiviral actions on the viral load change during therapy. A discussion on other possible ways to incorporate within-cell scale viral dynamics into the cytoimmuno-epidemiological model was also provided. More recently, another cytoimmuno-epidemiological model for the infection dynamics of HCV was developed in [15]. This multiscale model is homogeneously described by a system of ODEs where the within-cell scale submodel is unidirectionally coupled to the between-cell scale submodel. We therefore, categorize this multiscale model as a UNID-NMSM. The cytoimmuno-epidemiological model was used to study patient time courses of viral load under treatment with daclatasvir, an inhibitor of the viral non-structural protein NS5A. Analysis of this
UNID-NMSM predicted that treatment efficacy can be increased by combining daclatasvir with dedicated viral polymerase inhibitors, corresponding to promising current strategies in drug development. Hence, this cytoimmuno-epidemiological model presents a predictive tool for in silico simulations, which can be used to study and optimize direct-acting antiviral drug treatment for HCV.

In a further boost to the progress in the development of cytoimmuno-epidemiological models for viral infections, some TRAN-NMSMs have been developed to assess the impact of different antiviral drugs on HIV-1 pathogenesis [70, 100]. These cytoimmuno-epidemiological models subdivide the infected cell population into different sub-classes corresponding to different stages in the viral life cycle within an infected cell (binding and Fusion, reverse Transcription, integration, transcription, assembly and budding) which correspond to different biological steps between viral infection of CD4+ T cells and the production of HIV-1 virions. In [100] the authors incorporated an eclipse phase, representing the stage in which infected T cells have not started to produce new virus, into a simple HIV-1 model. Model calculations suggested that the quicker infected T cells progress from the eclipse stage to the productively infected stage, the more likely that a viral strain will persist. Long-term treatment effectiveness of anti-retroviral drugs is often hindered by the frequent emergence of drug resistant virus during therapy. The authors then linked drug resistance to both the rate of progression of the eclipse phase and the rate of viral production of the resistant strain, and explored how the resistant strain could evolve to maximize its within-host viral fitness. The authors derived an optimal progression rate and the optimal viral production rate, which maximize the fitness of a drug resistant strain in the presence of drugs. They further established that the window of opportunity for invasion of drug resistant strains is widened for a higher level of drug efficacy provided that the treatment is not potent enough to eradicate both the sensitive and resistant virus. In [70] a cytoimmuno-epidemiological was presented to study the immuno-pathogenesis of HIV-1 infection. This TRAN-NMSM was used to assess virological responses at both within-cell scale and between-cell scale anti-retroviral drugs. The authors first developed a basic mathematical model of the immuno-pathogenesis of HIV-1 infection that incorporates three distinct stages in the infection cycle of HIV-1: entry of HIV-1 into the cytoplasm of CD4+ T cells, transcription of HIV-1 RNA to DNA within CD4+ T cells, and production of HIV-1 viral particles within CD4+ T cells. Then the TRAN-NMSM was extended to incorporate the effect of three major categories of anti-HIV-1 drugs: fusion/entry inhibitors (FIs), reverse transcriptase inhibitors (RTIs) and PIs. The analysis of this multiscale model established that the actual drug efficacy of FIs and PIs is the same as their effective efficacies while the effective drug efficacy for the RTIs, is dependent on the rate of transcription of the HIV-1 RNA to DNA, and the lifespan of infected CD4+ T cells where virions have only entered the cytoplasm and that this effective efficacy is less than the actual efficacy. This study suggested that, of the three anti-HIV drug categories (FIs, RTIs and PIs), any drug combination of two drugs that includes RTIs is the weakest in the control of HIV-1 infection. Other examples of TRAN-NMSMs are given in Refs. [4, 37, 107, 122].

From this short review, we note that the development of cytoimmuno-epidemiological models is essential in order to establish a clear quantitative understanding of the various processes determining infection dynamics at the cell level of biological organization and use that information to design viral therapeutic agents associated with control
and regulation of molecular systems such as enzymes of biotransformation, transporter proteins controlling cellular influx and/or efflux, target cell receptors, and signal transducing complexes and allow investigating the precise mechanism of action of antiviral agents. Further, we also note that the list of cytoimmuno-epidemiological models reviewed in this study is necessarily incomplete and only serves as a sample presented here to highlight the major progress made so far in multiscale modelling efforts of infectious disease systems at the cell level of biological organization. Table 3 gives a summary of the categorization of cytoimmuno-epidemiological models reviewed in this study.

6. Categorization of multiscale models of infectious disease systems that integrate within-tissue and between-tissue scales

In the context of multiscale models of infectious disease systems that integrate any two adjacent scales at a time, the tissue level is yet another level of biological at which infection by a pathogen can be considered in the development of multiscale models of infectious disease systems. This implies that host–pathogen interactions in an infectious disease system can also play out at tissue-pathogen level. In addition, this level of biological organization (the tissue level) has two limiting scales of infection which are the within-tissue scale and the between-tissue scale leading to the formation of yet another different type of multiscale models of infectious disease systems. In this study we call multiscale models that integrate within-tissue and between-tissue scales tissue level immuno-epidemiological models (TL-IEMs). In addition, we also alternatively call this type of multiscale models histoimmuno-epidemiological models. Thus, we also name this type of multiscale models after a sub-discipline of biology addressing the study of the tissue level of biological organization called histology where the word ‘epidemiological’ in ‘histoimmuno-epidemiological’ is used to imply the study of distribution of infection among tissues. Therefore, histoimmuno-epidemiology becomes the study of the distribution of immune responses and infection in tissue populations, and of the factors influencing this distribution. We note that the categorization framework presented in Section 3 for categorizing multiscale models of infectious disease systems that integrate within-host and between-host scales is equally applicable in categorizing histoimmuno-epidemiological models by suitably modifying criterion IV which specifies the level of biological organization under consideration in the transmission of the infectious disease system and whose two adjacent scales of infection are incorporated into the multiscale model. In order to categorize and classify histoimmuno-epidemiological models using the categorization framework presented in Section 3, all the five integration frameworks will also be applicable in categorizing histoimmuno-epidemiological models except that the microscale and the macroscale are now the within-tissue scale and the between-tissue scale. For reasons similar to those given in Section 5 for categorizing cytoimmuno-epidemiological models, criteria I, II, III and V will also be applicable in categorizing histoimmuno-epidemiological models, except that criterion IV will have to be modified to suit the description of the tissue level of infection. In this case, the categorization framework presented in Section 3 when applied in the categorization of histoimmuno-epidemiological models will also result in five categories of multiscale models (IMSMs, NMSMs, EMSMs, HMSMs, CMSMs) and the relevant classes which are also exactly the same categories and classes as those for HL-IEMs presented in Section 4 except that in this case the host considered is not a whole organism (human,
| Name of category | Acronym | Brief definition | Some key features of the category | Name of class | Acronym | Some key features of the class | References | Comments |
|------------------|---------|------------------|-----------------------------------|---------------|---------|--------------------------------|------------|----------|
| Individual-based Multiscale Models (Category 1) | IMSMs | Cytoimmuno-epidemiological models in which within-cell scale influences between-cell scale without any reciprocal feedback taking into account individual variability | ▶ Uses simultaneous integration framework ▶ Bottom-up multiscale modelling ▶ Unidirectional flow of information from within-cell scale to between-cell scale ▶ Submodels described homogeneously ▶ Between-cell scale results are observed as emergent behaviour of within-cell scale submodel | Network modelling individual-based multiscale models | NETW-IMSMs | Developed using graph theoretic or network modelling techniques | – | ▶ Requires less mathematical skills but needs more computational resources ▶ Takes into account individual variability |
| Nested Multiscale Models (Category 2) | NMSMs | Cytoimmuno-epidemiological models in which within-cell scale influences between-cell scale without any reciprocal feedback | ▶ Uses serial integration framework ▶ Unidirectional flow of information from within-cell scale submodel to between-cell scale submodel ▶ Top-down multiscale modelling ▶ Submodels described homogeneously | Transformation based nested multiscale models | TRAN-NMSMs | Models subdivide the entire infected cell population into various sub-classes corresponding to the different stages of life cycle of pathogen within infected cell | [4, 37, 70, 100, 107 ,122] | ▶ Potentially the simplest multiscale models to develop and analyse although little work has been done in this category |
| Empirical data modelling individual-based multiscale models | EMPI-IMSMs | Developed using statistical modelling techniques which are regression-based | – | Simulation modelling individual-based multiscale models | SIMU-IMSMs | Modelling is based on computational algorithm with no mathematical equations used | – | |
| Hybrid individual-based multiscale models | BRID-MSMs | Entities within a single scale are described in a hybrid way | – | |
| Transformation based nested multiscale models | UNID-NMSMs | Submodels are unidirectionally coupled | [15, 39, 44, 59] | |
| Simplification based nested multiscale models | SIMP-NMSMs | Within-cell submodel is simplified, for example, reduced into a composed parameter that feeds into between-cell submodel | [45, 59] | |
| Category | Models | Description | Example Models |
|----------|--------|-------------|----------------|
| EMSMs (Category 3) | EMSMs | Cytoimmuno-epidemiological models in which within-cell scale and between-cell scale influence each other with reciprocal feedback | Uses embedded integration framework, Bidirectionally coupled embedded multiscale models, BIDI-EMSMs |
| | Simplification based EMSMs | Within-cell and between-cell submodels are coupled into unified multiscale model with reciprocal influence | [40, 99, 101] |
| | Difficult to capture and model the feedback between the within-cell submodel and between-cell submodel | – |
| Hybrid Multiscale models (Category 4) | HMSMs | Cytoimmuno-epidemiological models in which within-cell scale and between-cell scale influence each other with or without reciprocal feedback | Uses multi-domain integration framework, Bidi-directionally coupled hybrid multiscale models, BIDI-HMSMs |
| | Simplification based hybrid HMSMs | Within-cell submodel and between-cell submodel are decoupled into separate and independent submodels | – |
| | Difficult to simulate since one has to simulate separately their different components using specific methods for each of these components | [48, 51, 115] |

(continued)
| Name of category | Acronym | Brief definition | Some key features of the category | Name of class | Acronym | Some key features of the class | References | Comments |
|------------------|---------|------------------|----------------------------------|---------------|---------|--------------------------------|------------|----------|
| Coupled Multiscale Models (Category 5) | CMSMs | Cytoimmuno-epidemiological models which take into account the diversity of pathogen and cell species composition | ▶ Uses parallel integration framework  
▶ Immuno-epidemiological models are described homogeneously or in hybrid way  
▶ Takes into account host and pathogen species diversity  
▶ Top-down or bottom-up multiscale modelling or both | Single-target cell multi-pathogen coupled multiscale models | SHMP-CMSMs | These multi-pathogen/multi-strain/multi-target cell/multi-cell group immunoepidemiological models | [39, 115] | ▶ This is most useful in modelling drug resistance and co-infections |
| Multi-target cell single-pathogen coupled multiscale models | MHSP-CMSMs | Involve combination of multi-cell and multi-pathogen/multi-strain/multi-cell group immunoepidemiological models | | MHMP-CMSMs | | | | |
vector, animal, plant) but a tissue. Therefore, the categorization framework presented in Section 3 is also applicable in categorizing histoimmuno-epidemiological models by appropriately modifying criterion IV so that the host considered becomes the tissue.

An important application of histoimmuno-epidemiological models is in the study of granulomatous infectious disease systems. These are infectious disease systems which result in the formation of cellular aggregation structures inside tissue called granulomas. By definition, a granuloma is a focus of chronic inflammation consisting of a microscopic aggregation of macrophages surrounded by a collar of lymphocytes and plasma cells [60]. Therefore, in histoimmuno-epidemiological models, host–pathogen interactions also play out at granuloma–pathogen level. This is unlike in cytoimmuno-epidemiological models considered in Section 5 where host–pathogen interactions play out at the cell-pathogen level. In general, we can roughly classify granulomas into four groups [1]: (i) T cell-mediated immune granulomas formed around infectious agents or infected cells, (ii) granulomas with unknown etiology but with a T lymphocyte-mediated profile, (iii) foreign body granulomas induced by inanimate substances, and (iv) granulomas associated with malignant tumours. The granulomas which are specifically of interest to the study of infectious disease systems are the T cell-mediated immune granulomas formed around infectious agents or infected cells. Therefore, the histoimmuno-epidemiological models relevant for this study are those concerned with the study of the T cell-mediated immune granulomas formed around infectious agents or infected cells. Therefore, the histoimmuno-epidemiological models considered for this study are those concerned with the study of the T cell-mediated immune granulomas formed around infectious agents (for extracellular pathogens) and/or those formed around infected cells (for intracellular pathogens) and includes infectious disease systems caused by the following pathogens [54, 94, 127]:

- **Bacteria**: This includes infectious disease systems such as brucellosis, syphilis, bartonellosis, lymphogranuloma venereum, tuberculosis and leprosy.
- **Fungi**: Examples of granulomatous infectious disease systems caused by fungi are histoplasmosis, coccidioidomycosis and blastomycosis.
- **Protozoa**: A well-known example of granulomatous infectious disease caused by a protozoa is leishmaniasis.
- **Helminths**: The list of granulomatous infectious disease systems caused by helminths includes filariasis, trichinosis and schistosomiasis.

There has been little progress in developing multiscale models of host–pathogen interactions of these infectious disease systems at the granuloma level of biological organization (granuloma–pathogen interactions). The best efforts so far in multiscale modelling of granulomatous infectious disease systems have only mainly produced histoimmuno-epidemiological models for tuberculosis (TB) transmission dynamics. One of the first histoimmuno-epidemiological model in the context of tuberculosis was developed by Segovia-Juarez et al. [108]. Based on the categorization framework for multiscale models presented in Section 3, and subject to modification of criterion IV so that the host considered is no longer a whole organism (human, animal, vector, plant), but a tissue, and more specifically a granuloma (in the case of TB), we categorize this histoimmuno-epidemiological as a hybrid individual-based multiscale model (BRID-IMSM). Thus, in this multiscale model, only the within-granuloma submodel, which happened to be an agent-based model (ABM), is used to describe the entire disease system across both the within-granuloma scale and the between-granuloma scale. There are four components
in the BRID-IMSM in [108]: (i) the environment where entities reside, representing a section of the alveolar tissue, (ii) the entities of the multiscale model, consisting of discrete time macrophage and T cell agents, and continuous time chemokine and bacteria variables, and hence the hybrid nature (discrete time/continuous time) of the histoimmuno-epidemiological model, (iii) the rules that govern the dynamical behaviour of the system, representing the biological interactions of the entities, and (iv) the time scales on which these rules are implemented. This histoimmuno-epidemiological model was used to identify control mechanisms of granuloma formation in *Mycobacterium tuberculosis* (Mtb) infection in humans. Through sensitivity analysis, a set of parameters was identified that controls outcomes that can be qualitatively classified into three distinct categories corresponding to distinct granuloma clinical/pathological outcomes: (a) clearance - which is characterized by elimination of extracellular bacteria, absence of infected and chronically infected macrophages and little or no necrotic tissue, (b) small, slow growing solid granulomas leading to containment - which is also characterized by the survival of extracellular bacteria in regions surrounded by a small amount of necrotic tissue, and/or slow bacterial growth within infected macrophages; however, in this case, the immune system can in some cases eliminate infected and chronically infected macrophages, and (c) large, necrotic granulomas - leading to disseminated infection, with large and increasing amount of necrosis, and extracellular bacteria can spread across the environment. To date, this histoimmuno-epidemiological model has been progressively refined to investigate a wide variety of aspects in TB transmission dynamics.

By extending the BRID-IMSM in [108], another BRID-IMSM was presented in [97]. This histoimmuno-epidemiological model was applied to understand the different roles of tumour necrosis factor-α (TNF-α) in control of tuberculosis in a single granuloma which include control of cellular migration, induction of chemokine/TNF secretion, activation of macrophages and apoptosis. Analysis of this histoimmuno-epidemiological model showed that the multiple TNF-α activities contribute to the control TB infection within a single granuloma, with macrophage activation as the major effector mechanism for controlling Mtb growth. The results of the analysis of the model further suggested that bacterial numbers are a strong contributing factor to granuloma structure with TNF-α. In relationship to apoptotic effect, the results of the analysis of this histoimmuno-epidemiological model show that TNF-α-dependent apoptosis may reduce inflammation at the cost of impairing Mtb clearance. Based on a further refinement of [108] a BRID-IMSM was developed in [25] that includes molecular, cellular and tissue level events that occur during granuloma formation and maintenance in the lung. This histoimmuno-epidemiological model was used to investigate the critical role played by TNF-α. Model predictions established that TNF-α receptor 1 internalization kinetics play a critical role in infection control within a granuloma, controlling whether there is clearance of bacteria, excessive inflammation, containment of bacteria within a stable granuloma, or uncontrolled growth of bacteria. In addition to elucidating processes involved in immunity to Mtb infection that may be new therapeutic targets, the results further suggest that there is an inter-play between TNF-α and Mtb levels at within-granuloma scale that is controlled by the combined effects of both molecular and cellular level processes.

Building on their previous work [97, 108], the authors developed another BRID-IMSM in [13] to explore the complex dynamics of Interleukin-10 (IL-10) and TNF-α. These are
key anti- and pro-inflammatory cytokines which are elicited during host immune response to Mtb infection. Understanding the antagonistic effects of these two cytokines is difficult due to the complexity of immune responses acting across different levels of biological organization (molecular level, cellular level and tissue level). Six main results were obtained in the analysis of this histommuo-epidemiological model. First, the results show that IL-10 is necessary to control activation levels and to prevent tissue damage in a granuloma. Second, simulations also predict that three groups of TNF-α and IL-10 parameters, representing processes relevant to cytokine synthesis, signalling, and spatial distribution, control concentrations of TNF-α and IL-10 in a granuloma environment and eventually determine infection outcome, at the tissue scale, over the long-term. Third, the results demonstrate that each parameter group is balancing a trade-off between host-induced tissue damage and bactericidal processes through various TNF-α and IL-10 mechanisms. Fourth, the spatial localization of TNF-α and IL-10 is important in focusing bactericidal and inflammatory activities in a granuloma. Fifth, the results suggest, together with earlier studies on granuloma formation, that the spatial organization of immune cells within a granuloma, where infected macrophages and Mtb reside in the centre of this dense and heterogeneous structure, is ideal for optimal control of bacteria. Sixth and finally the results demonstrate for the first time that a balance of TNF-α and IL-10 concentrations is essential to mediate between Mtb infection control and prevention of host-induced tissue damage. In particular, the results predict that granulomas with biased anti-inflammatory environments, having higher average concentrations of IL-10 than TNF-α, promote containment of bacteria and prevention of host tissue damage instead of bacterial clearance with high levels of healthy tissue damage.

To date, several other refinements of previous versions of the BRID-IMSMs in [13, 25, 97, 108] have been implemented to investigate a variety of other issues in the histommuo-epidemiology of tuberculosis. The specific refinements include those in the following histommuo-epidemiological models, which are all categorized as BRID-IMSMs because the entities of the ABM are described in discrete time/continuous time formats.

(i) In [14], which was used to investigate several novel roles of IL-10 in TB granulomas in order to identify IL-10 related mechanisms that could be used as adjunctive therapies during TB infection.

(ii) In [66], in which the BRID-IMSM was used to study different approaches for designing therapies for TB which are: immunomodulation with the cytokines TNF-α and IL-10, oral and inhaled antibiotics, and vaccination.

(iii) In [109], where the histommuo-epidemiological model was used to investigate the effects of hypoxia (a condition in which a region of the body is deprived of adequate oxygen supply at tissue level) on host immune response efficacy and Mtb persistence.

(iv) In [95], where the histommuo-epidemiological model was presented to map metabolite and gene perturbations to granuloma sterilization.

(v) In [71], where the multiscale model (a BRID-IMSM) was used as a predictive tool to determine the key roles for dendritic cells in tuberculosis infection focusing on investigating the impact of dendritic cell dynamics on important aspects of immunity which include antigen presentation, T cell priming, memory T cell generation and ultimately into TB infection dynamics.
All in all, we note that the development of histoimmuno-epidemiological models would contribute to reduced treatment time for infectious disease systems such as tuberculosis and provide additional targets for new drugs. This is because the granuloma itself as a level of biological organization at which infection can take place presumably complicates treatment since this dense and heterogeneous tissue may present an obstacle for drugs to reach the site of infection.

7. Categorization of multiscale models of infection disease systems that integrate several scales of infection

So far we have been discussing about categorizing multiscale models of infectious disease systems that integrate two scales at a time. However, more complex multiscale models of infectious disease systems can be developed by integrating several scales into a single multiscale model of an infectious disease system. In this study we call such multiscale models multiple level immuno-epidemiological models (ML-IEMs). Further, we also alternatively call these multiscale models polyscale immuno-epidemiological models. Therefore, polyscale immuno-epidemiological models are multiscale models of infectious disease systems which incorporate at least two levels of biological organization while integrating at least three scales of infection associated with these levels. Thus, polyscale immuno-epidemiology becomes the study of the distribution of immune responses and infection in multiple level populations that may include a combination of cell level populations, tissue level populations, organ level populations and host level populations and at least three scales associated with these levels. There is need to accelerate and expand the opportunity for the development of polyscale immuno-epidemiological models to become an integral part of infectious disease research, much as it is now with multiscale models of infectious disease systems that integrate two scales at a time (HL-IEMs, CL-IEMs and TL-IEMs).

In particular, given the availability of new data, tools and methods, the potential for the development of multiple level immuno-epidemiological models is much greater now than at any time before. Examples of multiple level immuno-epidemiological modelling needs include the following:

Example 1. *Multiple level immuno-epidemiological model which considers infection by a single-pathogen at cell and tissue levels of biological organization:* This will be a polyscale immuno-epidemiological model which considers infection at both cell and tissue levels of biological organization. Thus, this polyscale immuno-epidemiological model would typically characterize cell- tissue–pathogen interactions. In this case, the three scales of infection which may be integrated into a single multiscale model can be: within-cell scale, between-cell scale and between-tissue scale. The polyscale immuno-epidemiological would therefore consist of three submodels: the within-cell scale submodel, which models events inside infected cells; between-cell submodel, which models transmission of the pathogen among cell populations; and between-tissue submodel, which also models transmission of pathogen among tissue populations. Such a polyscale immuno-epidemiological will be useful in characterizing the transmission of Mtb infection in humans where events inside infected macrophages are explicitly modelled as well as spread of Mtb among macrophages inside
infected granulomas together with dynamics of granuloma population within an infected individual.

Example 2. *Multiple level immuno-epidemiological model which considers infection by a single-pathogen at cell, organ and whole organism levels of biological organization:* This is a polyscale immuno-epidemiological model which considers cell-organ-whole organism-pathogen interactions. Such a multiple level immuno-epidemiological would be useful in characterizing the dynamical behaviours of the different scales that are covered by processes of HIV-1 replication and spread within an infected individual. Typically four scales may be integrated into a single multiscale model: within-cell scale, between-cell scale, within-organ scale and between-organ scale. At the within-cell scale, the main processes are viral entry, viral replication, and viral export would be explicitly modelled by a single submodel. At the between-cell scale a submodel would be developed to describe the spread of the virus among cells distinguishing between uninfected, infected and virus-producing infectious cells. At the organ scale a submodel would be developed to describe infection within an organ, such as the gut, blood, the brain and testicles etc., and at the between-organ scale, another submodel would be developed to understand the spread of virus among organs. These four submodels can then be integrated into a single polyscale immuno-epidemiological model and assist in integrating information from the various scales and experimental models within a systematic and quantitative framework.

Example 3. *Multiple level immuno-epidemiological model which considers infection by a single-pathogen at cell and host levels of biological organization:* This polyscale immuno-epidemiological model will typically consider cell-host–pathogen interactions. In this case the three scales that may be integrated into a single polyscale immuno-epidemiological can be: within-cell scale, between-cell scale and between-host scale. Such a polyscale immuno-epidemiological model would explicitly model events inside infected cells, as well as transmission of pathogen among target cell population together with transmission of pathogen among hosts in a community. This multiple level immuno-epidemiological model would be useful in clinical trial designs to assess the population-level impact of antiviral drugs with different modes of action at cellular level, different efficacies at individual level and different impacts at community level.

Example 4. *Multiple level immuno-epidemiological model which considers infection by a single-pathogen at cell, organ and multi-host levels of biological organization:* Such a polyscale immuno-epidemiological will be useful in understanding the transmission of multi-host infections such as IAV infections which involve cross-species infections that include aquatic bird reservoirs as well as transmission events in poultry and in a number of mammalian species, including humans, pigs, horses, seals, and mink and improve our knowledge of AIV especially key new information on the process of host adaptation, and assess the risk these viruses pose to human populations. Such a polyscale immuno-epidemiological model would typically integrate
within-cell, between-cell, within-organ, between-organ, within-host species and between-host species scales. This polyscale immuno-epidemiological model would help to establish a better understanding of the ecological, evolutionary, and molecular mechanisms of influenza emergence in order to be able to accurately determine which viruses pose a risk to human health.

Example 5. *Multiple level immuno-epidemiological model which considers infection by multi-pathogen/multi-strain at host, hospital and community levels of organization:* Such a polyscale immuno-epidemiological model can typically be useful in describing the spread of antibiotic resistance (multi-strain infectious disease systems) at patient level, hospital level and community level. This multiscale models can ideally integrate multiple scales from within-host scale dynamics of treatment and expanding into population-based epidemiological levels at both within-hospital and between-hospital scales together with within-community and between-community scales in order to establish the possible impact of how the treatment of an individual has implications for the wider population at both hospital and community levels.

What emerges from these five examples is that polyscale immuno-epidemiological models can either be single-host single-pathogen infectious disease systems or they can be multi-host/multi-pathogen/multi-strain/multi-group infectious disease systems.

However, we note that the categorization of these more complex multiscale models of infectious disease systems integrating several scales of infection cannot be achieved by using the categorization frameworks for multiscale models that integrate two scales at a time considered in Sections 4, 5 and 6. The categorization of polyscale immuno-epidemiological models can be achieved by greatly simplifying the initial categorization framework presented in Section 3 using the following arguments.

**First,** the linkages between the scales of infection through processes of indirect, top-down and bottom-up become more intricate as the number of scales become large and intertwined making it difficult to identify privileged levels and scales of casuaton [88] and therefore, criteria I, II, III which are part of the categorization framework for multiscale models of infectious disease systems presented in Section 3 will no longer apply because the relationships between the scales described by these criteria become irrelevant when several scales of infection are considered.

**Second,** the five integration frameworks which are part of the categorization framework for multiscale models of infectious disease systems presented in Section 3 no longer apply because these integration frameworks only apply when two scales of infection are integrated and therefore can no longer be used to categorize multiscale models of infectious diseases integrating several scales of infection.

These two arguments simplify the initial categorization framework presented in Section 3 to only two criteria (criteria VI and V). This leaves us with a categorization framework for polyscale immuno-epidemiological models composed of only two criteria: criterion IV and Criterion V. Now, using criterion IV and Criterion V as the categorization framework for
polyscale immuno-epidemiological models, we can roughly demarcate polyscale immuno-epidemiological models into four categories which are:

(a) \textit{Single-homogeneously multiscale models (SHG-MSMs)}: These are single-host single-pathogen multiscale models of infectious disease systems that incorporate multiple levels of biological organization while integrating at least three scales associated with these levels in which a single formalism is used in the mathematical representation of the submodels describing these scales of infection.

(b) \textit{Single-hybrid multiscale models (SHB-MSMs)}: These are single-host single-pathogen multiscale models of infectious disease systems that incorporate multiple levels of biological organization while integrating at least three scales associated with these levels in which different formalisms are used in the mathematical representation of the submodels describing these scales of infection.

(c) \textit{Multi-homogeneously multiscale models (MHG-MSMs)}: These are multiscale models for multi-host and/or multi-pathogen and/or multi-strain and/or multi-group infectious disease systems that incorporate multiple levels of biological organization for each host implicated in the transmission of the infectious disease system while integrating at least three scales associated with these levels in which a single formalism is used in the mathematical representation of the submodels describing these scales of infection.

(d) \textit{Multi-hybrid multiscale models (MHB-MSMs)}: These are also multiscale models for multi-host and/or multi-pathogen and/or multi-strain and/or multi-group infectious disease systems that incorporate multiple levels of biological organization for each host implicated in the transmission of the infectious disease system while integrating at least three scales associated with these levels in which different formalisms are used in the mathematical representation of the submodels describing these scales of infection.

Thus, the many different interactions of the components of infectious disease systems considered in this study which include cell–pathogen interactions, tissue–pathogen interactions, and host–pathogen interactions, and other more complex interactions, that result in the different types of multiscale models (cytoimmuno-epidemiological models, histoimmuno-epidemiological models, host level immuno-epidemiological models, and polyscale immuno-epidemiological models) imply that in order to better understand infectious disease systems, it is important to view these infectious disease systems as complex dynamical systems that emphasize (i) the multi-level casuation of infectious diseases (cell level, tissue level, organ level, host level, environmental level, etc.), (ii) the multiscale hierarchical nature of these levels in which the cell may be the lowest level of biological organization at which infection by a pathogen can be considered, (iii) the impact of the interactions of the hierarchical scales of these levels, and (iv) the nonlinear feedback loops in the hierarchical cross-scale effects of these interactions.

8. Discussion and conclusions

We are on the verge of an exciting moment in the modelling of infectious disease systems, one in which the fruits of characterizations of living systems at a wide variety of spatial and temporal scales associated with molecular, cellular, tissue, individual host,
population of hosts levels and environmental (physical, biological, geographical, etc.) levels of organization and the impact of computational science are coming together to drive multiscale modelling of infectious disease systems. The aim of this study was to contribute to a general theory of multiscale modelling focused on a specific application area by categorizing multiscale models of infectious disease systems. We first presented an account of infectious disease systems as complex systems and their different hierarchical levels of organization and some of the scales associated with these levels. Then we presented a categorization framework for multiscale models of infectious disease systems that integrate any two adjacent scales at a time (microscale and macroscale) by adapting five integration frameworks which were originally developed for a chemical engineering context to an infectious disease context and formulating five criteria to be used with the integration frameworks. However, unlike in previous studies where only host level immuno-epidemiological models are the only type of multiscale models of infectious disease systems referred to as immuno-epidemiological models, we identified four main different types of immuno-epidemiological models which are:

- **Cell level immuno-epidemiological models (CL-IEMs):** Which we alternatively call cytoimmuno-epidemiological models. These are multiscale models of infectious disease systems for the study of cell (cytology) infection dynamics that integrate two adjacent scales of infection associated with the cell level of biological organization (within-cell and between-cell scales). Therefore, such multiscale models characterize cell–pathogen interactions. The within-cell scale interactions involve interactions between the pathogen and a single cell where the pathogen infects a cell and multiplies within it and the between-cell scale interactions involve interactions between the pathogen and the cell population as the pathogen transmits between cells and circulate within-cell population. This results in multiscale models of infectious disease systems in which events inside infected cells are modelled as well as the spread of pathogen among cells.

- **Tissue level immuno-epidemiological models (TL-IEMs):** Which we alternatively call histoimmuno-epidemiological Models. These are multiscale models of infectious disease systems for the study of tissue (histology) infection dynamics that integrate two adjacent scales of infection associated with the tissue level of biological organization (within-tissue and between-tissue scales). These multiscale models consider tissue–pathogen interactions. This also results in multiscale models of infectious disease systems in which events inside infected tissues are modelled as well as the spread of pathogen among tissues.

- **Host level immuno-epidemiological models (HL-IEMs):** They are multiscale models of infectious disease systems commonly called immuno-epidemiological models and are for the study of host infection dynamics. They integrate two adjacent scales of infection associated with the host level of biological organization (within-host and between-host scales). This results in multiscale models of infectious disease systems in which events inside infected hosts are modelled as well as the spread of pathogen among hosts.

- **Multiple level immuno-epidemiological models (ML-IEMs):** In this study we alternatively call these multiscale models polyscale immuno-epidemiological models. These are multiscale models of infectious disease systems for the study of infection dynamics
at multiple levels of biological organization (e.g. cell and tissue levels, cell and host levels, tissue and host levels, cell and tissue and host levels, etc.) in which at least three scales of infection associated with these levels of biological organization are integrated into a single multiscale model. These are multiscale models which consider for example cell-tissue–pathogen interactions or cell-host-pathogen interactions or tissue-host–pathogen interactions or even cell-tissue host–pathogen interactions. Therefore, unlike other types of multiscale models of infectious disease systems in which we consider only infection at a single level of biological organization (e.g. cell level only or tissue level only or host level only, etc.) polyscale immuno-epidemiological models are multiscale models of infectious disease systems in which for example, events inside infected cells are modelled together with the spread of pathogen among cells as well as events inside infected tissues are modelled together with the spread of pathogen among tissues.

Using the initial categorization framework, we first identified five different categories of host level immuno-epidemiological models (HL-IEMs) with each integration framework corresponding to a different category of multiscale models which are: individual based multiscale models (IMSMs), nested multiscale models (NMSMs), embedded multiscale models (EMSMs), hybrid multiscale models (HMSMs) and coupled multiscale models (CMSMs). We also illustrated that the initial categorization framework for categorizing host level immuno-epidemiological models is also applicable in categorizing other types of immuno-epidemiological models (cytoimmuno-epidemiological models and histoimmuno-epidemiological models) by redefining the host to be a cell (for cytoimmuno-epidemiological models) or a tissue (for histoimmuno-epidemiological models). Further, we also illustrated that by reducing it to only two criteria, the initial categorization framework for categorizing host level immuno-epidemiological models becomes applicable in categorizing polyscale immuno-epidemiological models. The categorization and classification of multiscale models of infectious disease systems presented in this study is useful in bringing some order to the discussion on the structure of multiscale models of infectious disease systems. In particular, this categorization of the different types of multiscale models of infectious disease systems may be found useful as a basis for further refinement, in the discourse of multiscale modelling of infectious disease systems. It will enable infectious disease modellers to discuss the general principles that should apply to each category of multiscale models. Instead of discussing these principles repeatedly whenever a multiscale model of an infectious disease system is being developed, infectious disease modellers will be able to refer to the generic discussion for the category of the multiscale model concerned, and focus instead on the application of that discussion to the particular multiscale model of an infectious disease system being developed, and on issues peculiar to that multiscale model. While this categorization cannot be claimed to be unique, we think that it constitutes a good starting point, which may be found useful as a basis for further refinement in the discourse of multiscale modelling of infectious disease systems. Overall, the development of the different types of immuno-epidemiological models (cytoimmuno-epidemiological models, histoimmuno-epidemiological, host level immuno-epidemiological models and polyscale immuno-epidemiological models) is key to development of personalized medicine where drugs are made based on individual or group characteristics. It is therefore, expected that a clear understanding of the various
interactions among the different components of an infectious disease system playing out at the various levels of biological organization (i.e. cell-pathogen, tissue-pathogen, host-pathogen, etc.) using these different types of multiscale models will eventually herald a new era of what has become known as individualized and proactive medicine, whereby the drugs people are prescribed will depend on their personal genetic makeup, especially where there are significant cost or risk implications.

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