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The Universal Theory for Multiscale Modelling of Infectious Disease Dynamics

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Abstract: The replication-transmission relativity theory, currently used to inform the development of multiscale models of infectious disease dynamics, needs a revision and extension to accommodate new basic science and clinical information about infectious disease dynamics. In this article, we revise and extend the replication-transmission relativity theory into a new scientific theory of infectious disease dynamics called the universal theory for the multiscale modelling of infectious disease dynamics. This new theory states that, for every host–pathogen interaction that results in an infectious disease system, there is no privileged or absolute scale of a disease system form that would determine the dynamics of the infectious disease system, only interactions between the scales of a level of organisation of the pathogen-centred disease system form and the scales of the corresponding levels of organisation of the host-centred disease system form. We further explain the utility of this theory, which is reflected in its flexibility and ability to incorporate new information and explain previous information that could not be accounted for by the replication-transmission relativity theory of infectious disease dynamics.

Keywords: multiscale modelling of infectious disease dynamics; the replication-transmission relativity theory of infectious disease dynamics; pathogen-centred disease system form; host-centred disease system form; multiscale modelling of malaria disease system

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1. Introduction

Progress in the study of infectious disease systems dynamics as complex systems using multiscale modelling methods needs to be made over with a new scientific theory that represents a paradigm shift by revising and extending the replication-transmission relativity theory [1]. However, new scientific theories succeed when they re-order old knowledge into a new framework such that the new framework which they introduce makes it possible to break barriers in our understanding of many open questions and solve problems deemed important but barely addressed. The replication-transmission relativity theory [1], which states that at every level of organisation of an infectious disease system there is no privileged or absolute scale which would determine disease dynamics, only interactions between the microscale and macroscale, is presently used to inform the study of infectious disease dynamics using multiscale modelling methods. This theory is not well suited to capturing the dynamic complexity of infectious disease systems because it only considers their multiscale dynamics from a pathogen-centred perspective [2] while disregarding their multiscale dynamics from a host-centred perspective.

The aim of this article is to revise and extend the replication-transmission relativity theory [1] in a radical way into a new scientific theory of infectious disease dynamics called the universal theory for multiscale modelling of infectious dynamics, which incorporates both the pathogen-centred and the host-centred perspectives to the multiscale dynamics of infectious disease systems. This new theory states that, for every host-pathogen interaction

that results in an infectious disease system, there is no privileged or absolute scale of a disease system form which would determine the dynamics of the infectious disease system, only interactions between the scales of a level of organisation of the pathogen-centred disease system form and the scales of the corresponding levels of organisation of the host-centred disease system form. This theory puts forth the view that the multiscale modelling of host-pathogen interaction in infectious disease dynamics is about considering the interaction of the scales of a level of organisation of the pathogen-centred disease system form on one hand and the scales of the corresponding levels of organisation of the host-centred disease system form on the other hand. Each of these two different disease system forms has a different multilevel and multiscale organisation and thus requires a different multilevel and multiscale modelling approach; that is, there are two different multiscale modelling approaches of the two different disease system forms of an infectious disease system, each of which is only partially true or provides partial information about the multiscale dynamics of an infectious disease system. Therefore, the pathogen-centred disease system form and the host-centred disease system form are considered to be mutually exclusive and complementary disease system forms of a single infectious disease system.

The weakness of the replication-transmission relativity theory arises from the fact that it privileges the scales of a level of organisation of the pathogen-centred disease system form while neglecting the scales of the corresponding levels of organisation of the host-centred disease system form in the multiscale dynamics of an infectious disease system. However, the universal theory for multiscale modelling of infectious disease dynamics requires that both the scales of a level of organisation of the pathogen-centred disease system form and the scales of the corresponding levels of organisation of the host-centred disease system form be integrated into a single multiscale model of infectious disease dynamics. The contents of the rest of this paper are organised as follows. In Section 2, we interpret the universal theory for the multiscale modelling of infectious disease dynamics. This is followed by Section 3, where we present the multilevel and multiscale organisation of the pathogen-centred disease system form. The multilevel and multiscale organisation of the host-centred disease system form is presented in Section 4. To illustrate ideas, we present a process-based multiscale model of the pathogen-centred disease system form of a malaria disease system as an example in Section 5. The dynamics of the pathogen-centred disease system form of the malaria disease system is analysed using the reproductive number in Section 6 and further analysed in Section 7 using numerical methods. The paper ends with concluding remarks in Section 8.

2. Interpretation of the Universal Theory for Multiscale Modelling of Disease Dynamics

The universal theory for the multiscale modelling of infectious disease dynamics, which states that, for every host–pathogen interaction that results in an infectious disease system, there is no privileged or absolute scale of a disease system form that would determine the dynamics of the infectious disease system, only interactions between the scales of a level of organisation of the pathogen-centred disease system form and the scales of the corresponding levels of organisation of the host-centred disease system form, is a radical theory for the multiscale modelling of disease dynamics based on four key assumptions, which are as follows:

[I.] First, that infectious disease dynamics are a result of the interaction of three subsystems, which are the host subsystem, which we call the primary subsystem; the environment subsystem, which we call the secondary subsystem; and the pathogen subsystem, which we call the tertiary subsystem.

[II.] Second, that the environment subsystem is considered to be an extended form of the host subsystem and thus an infectious disease system is considered to be a result of host–pathogen interaction only in such a way that every infectious disease system is considered to exist in two different forms: a host–centred disease system form, which is the form that the whole disease system takes when the host perspective of the interaction is considered,

and a pathogen–centred disease system form, which is the form that the whole disease system takes when the pathogen perspective of the interaction is considered.

[III.] Third, that the two different disease system forms; that is, the host-centred disease system form and the pathogen-centred disease system form, have different multilevel and multiscale organisations and are necessarily described by different types of multiscale models, which are process-based multiscale models for the pathogen-centred disease system form and mechanism-based multiscale models for the host-centred disease system form.

[IV.] Fourth, that, together, the mechanism-based multiscale model of the host-centred disease system form and the process-based multiscale model of the pathogen-centred disease system form present a fuller description of the overall multiscale dynamics of an infectious disease system than either of the two when considered separately.

These four assumptions form a scaffold on which the universal theory, as a formal theory for the multiscale modelling of infectious disease dynamics, is built and tested on. Figure 1 shows a conceptual representation of the universal theory for the multiscale modelling of infectious disease dynamics.

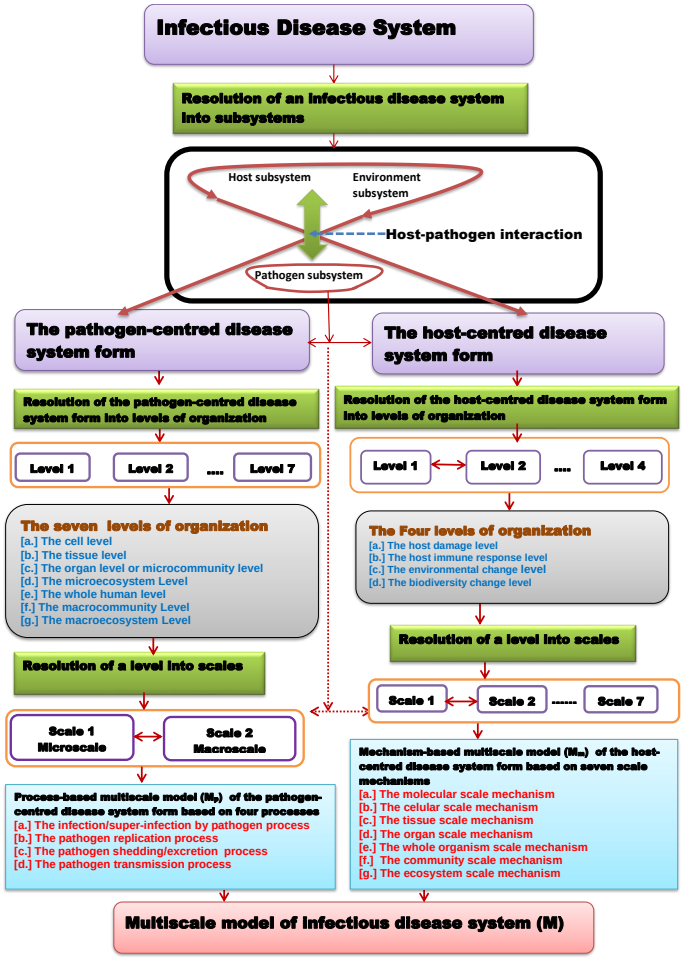


Figure 1. A conceptual representation of the universal theory for multiscale modelling of infectious disease dynamics. In this case, an infectious disease system is considered to consist of two different disease system forms—a pathogen-centred disease system form and a host-centred disease system form—in such a way that the overall multiscale model of infectious disease dynamics M consists of two complementary multiscale models: M_p, a process-based multiscale model that describes the scales of a level of organisation of the pathogen-centred disease system form, and M_m, a mechanism-based multiscale model that describes the scales of the corresponding levels of organisation of the host-centred disease system form so that $M = f(M_p, M_m)$.

From Figure 1, we note that, at the highest level, an infectious disease system is a result of the interaction of three subsystems: [a.] the host subsystem, which we call the primary subsystem, [b.] the environment subsystem, which we call the secondary subsystem, and [c.] the pathogen subsystem, which we call the tertiary subsystem. By invoking assumption II of the universal theory for the multiscale modelling of infectious disease dynamics, which considers the environment subsystem as an extended form of the host subsystem, we note that only two different perspectives are needed to describe the interaction of these three subsystems. First, there is the pathogen-centred perspective of the interaction of these three subsystems—which gives rise to the pathogen-centred disease system form. This disease system form is an outcome of the impact of the host subsystem on the pathogen subsystem in host–pathogen interaction. Second, there is the host-centred perspective of the interaction of these three subsystems, which gives rise to the host-centred disease system form. This disease system form is an outcome of the impact of the pathogen subsystem on the host subsystem in host–pathogen interaction. As illustrated in Figure 1, the pathogen-centred disease system form is organised into seven main levels of organisation, which are [1–3]: [a.] the cell level, [b.] the tissue level, [c.] the organ level or microcommunity level, [d.] the microecosystem level, [e.] the whole organism level, [f.] the macrocommunity level, and [g.] the macroecosystem level. However, the host-centred disease system form is organised into four main levels of organisation, which are: [a.] the host damage level, [b.] the host immune response level, [c.] the environmental change level, and [d.] the biodiversity change level. In addition, Figure 1 shows that each level of the pathogen-centred disease system form can be resolved into two hierarchically organised scales—a microscale and a macroscale—with both scales being hierarchically organised in both space and time. However, each level of the host-centred disease system form can be resolved into seven main scales—[a.] the molecular scale, [b.] the cell scale, [c.] the tissue scale, [d.] the organ scale, [e.] the whole organism scale, [f.] the community scale, and [g.] the ecosystem scale—that are hierarchically organised into physical size scale and time scale.

Further, we note from Figure 1 that the universal theory for the multiscale modelling of infectious disease dynamics is based on mathematical approaches to understanding the multiscale dynamics of infectious disease systems and expresses the mathematical point that the overall multiscale model of infectious disease dynamics M consists of two complementary multiscale models: M_p, a process-based multiscale model that describes the scales of a level of organisation of the pathogen-centred disease system form, and M_m, a mechanism-based multiscale model that describes the scales of the corresponding levels of organisation of the host-centred disease system form so that $M = f(M_p, M_m)$. As shown in Figure 1, the process-based multiscale model M_p of the scales of a level of organisation of the pathogen-centred disease system form is described in terms of four main disease process, which are [a.] the infection or the super-infection by the pathogen process, which involves the movement of the pathogen from the macroscale to the microscale, and thus the term infection is defined as the acquisition of a pathogen at the microscale from the macroscale at any level of organisation of the pathogen-centred disease system form; [b.] the pathogen replication process at the microscale; [c.] the pathogen shedding or excretion process, which involves the movement of the pathogen from the microscale to the macroscale; and [d.] the pathogen transmission process at the macroscale. However, the mechanism-based multiscale model M_m of the scales of the corresponding levels of organisation of the host-centred disease system form is described in terms of up to a maximum of seven main scale mechanisms, which are: [a.] the molecular-scale mechanism, [b.] the cellular-scale mechanism, [c.] the tissue-scale mechanism, [d.] the organ-scale mechanism, [e.] the organism-scale mechanism, [f.] the community-scale mechanism, and [g.] the ecosystem-scale mechanism.

Therefore, in the context of the universal theory for the multiscale modelling of infectious disease dynamics, conceptually represented by Figure 1, the two different disease system forms arise due to the need to account for the two reciprocal impacts of the pathogen

subsystem and the host subsystem on each other in the multiscale dynamics of an infectious disease system as follows: [a.] the impact of the host subsystem on the pathogen subsystem, which gives rise to the pathogen-centred disease system form, and [b.] the impact of the pathogen subsystem on the host subsystem, which gives rise to the host-centred disease system form.

We then conclude from Figure 1 that the universal theory for the multiscale modelling of infectious disease dynamics can be interpreted to mean that, in host–pathogen interaction, the resulting infectious disease system from the mutual impacts of the host subsystem and pathogen subsystem on each other is a pair of interacting disease system forms, which are the pathogen-centred disease system form and the host-centred disease system form, with different multiscale and multilevel organisations and reciprocal influence on each other. This duality in interacting disease system forms with different multiscale and multilevel organisations for each infectious disease system can be interpreted to imply a law of multiscale dynamics of infectious disease systems that states that, for every set of disease processes, which are [a.] the infection/super-infection by pathogen process, [b.] the pathogen replication process, [c.] the pathogen shedding/excretion process, and [d.] the pathogen transmission process, at a level of organisation of the pathogen-centred disease system form, there is an associated set of disease mechanisms, which are [a.] the molecular-scale mechanism, [b.] the cell-scale mechanism, [c.] the tissue-scale mechanism, [d.] the organ-scale mechanism, [e.] the whole-organism-scale mechanism, [f.] the community-scale mechanism, and [g.] the ecosystem-scale mechanism, at corresponding levels of organisation of the host-centred disease system form with reciprocal influence between the processes and mechanisms. This law can be considered as an extension of Newton's third law of motion in mechanics applied to infectious disease dynamics by requiring the disease processes at a level of organisation of the pathogen-centred disease system form and the disease mechanisms at the corresponding levels of organisation of the host-centred disease system form to be considered as characterising action and reaction force pairs in host–pathogen interaction. In the following two sections, we describe in detail the different multilevel and multiscale organisations and possible multiscale modelling frameworks of the pathogen-centred disease system form and the host-centred disease system form.

3. The Pathogen-Centred Disease System Form

In the context of the universal theory for the multiscale modelling of infectious disease dynamics, which is conceptually represented by Figure 1, the pathogen-centred disease system form arises due to the need to account for the impact of the host subsystem on the pathogen subsystem. In what follows, we discuss in detail the multilevel organisation of the pathogen-centred disease system form in Section 3.1 and the multiscale organisation of a level of organisation of the pathogen-centred disease system form in Section 3.2 together with the different categories of multiscale models that are used to describe the pathogen-centred disease system form at different levels of its organisation.

3.1. The Multilevel Organisation of the Pathogen-Centred Disease System Form

The pathogen-centred disease system form is the form that the whole infectious disease system takes when considering the pathogen-centred perspective of the interaction among the three subsystems of an infectious disease system; that is, the host subsystem, the environment subsystem, and the pathogen subsystem. In order to analyse the pathogen-centred disease system form using multiscale modelling methods, its complexity has to be brought down to manageable levels by discretising or decomposing it into different discrete levels of organisation. Based on the structural organisation of the host subsystem and the associated environment subsystem as an extended form of the host subsystem as a habitat for infectious agents, we establish that a pathogen-centred disease system form can be discretised into seven main hierarchical levels of organisation, which are [1–3]: [a.] the cell level, [b.] the tissue level, [c.] the organ or microcommunity level, [d.] the microecosystem level, [e.] the whole organism level, [f.] the macrocommunity level, and

[g.] the macroecosystem level. Figure 2 shows a schematic representation of the seven main hierarchical levels of organisation of a pathogen-centred disease system form in a space-time diagram that portrays the hierarchical nature of the levels, showing a positive correlation in the spatial and temporal scales of varying disease processes.

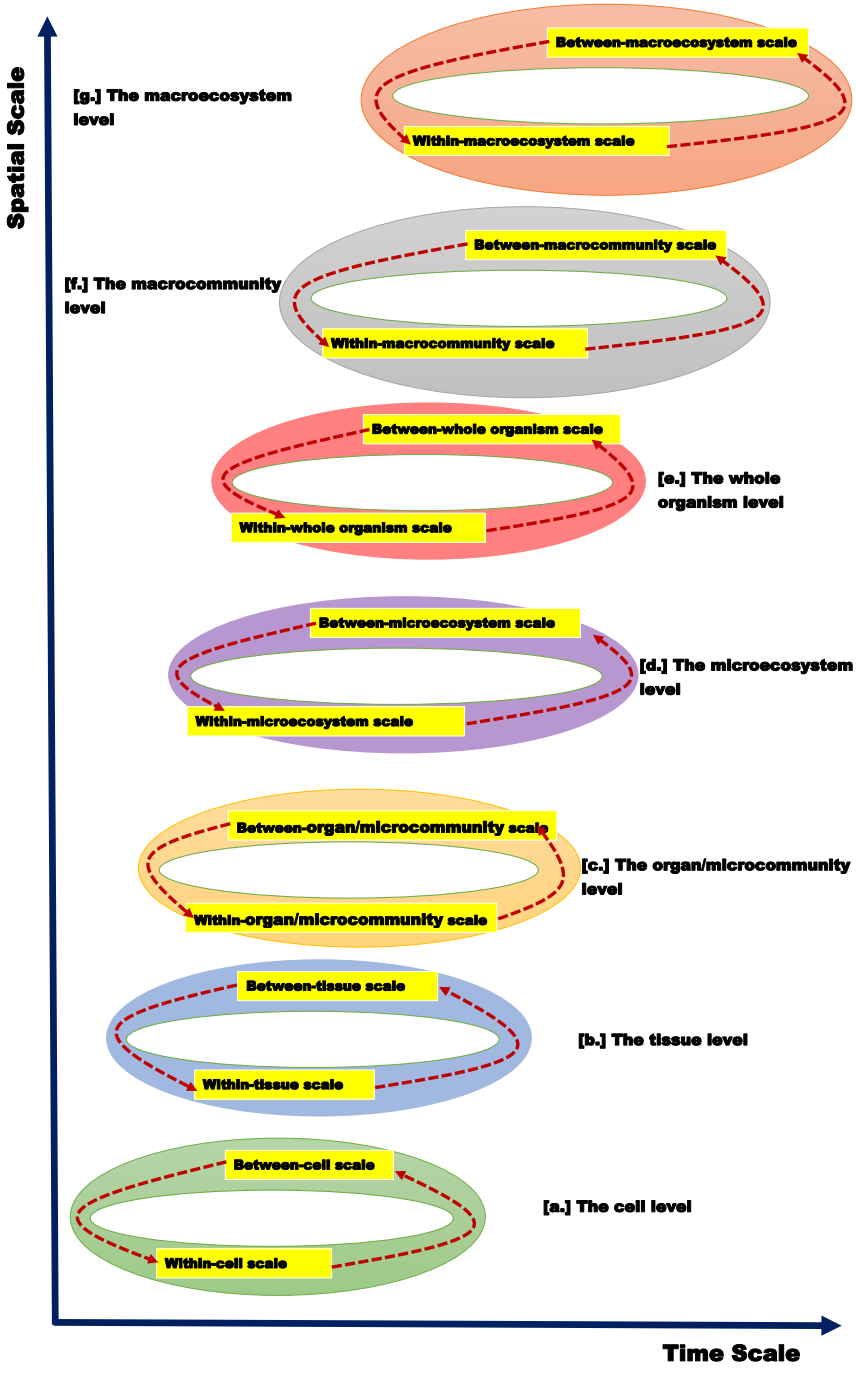


Figure 2. A schematic representation of the seven main levels of organisation of the pathogen-centred disease system form based on the universal theory for multiscale dynamics of infectious disease dynamics, which are [a.] the cell level, [b.] the tissue level, [c.] the organ/microcommunity level, [d.] the microecosystem level, [e.] the whole organism level, [f.] the macrocommunity level, and [g.] the macroecosystem level, in a curved and discretised four-dimensional space-time that combines the three dimensions of space and one dimension of time into a single four-dimensional manifold. The seven levels of organisation of the pathogen-centred disease system form are hierarchically organised in space-time.

In what follows, we briefly describe the seven main levels of organisation of the pathogen-centred disease system form and the associated scales; that is, the microscale and the macroscale, for each level of organisation.

[a.] *The cell level*: The two hierarchically organised scales at this level of organisation of the pathogen-centred disease system form are the within-cell scale, which is the microscale, and the between-cell scale, which is the macroscale.

[b.] *The tissue level*: The two hierarchically organised scales at this level of organisation of the pathogen-centred disease system form are the within-tissue scale, which is the microscale, and the between-tissue scale, which is the macroscale.

[c.] *The organ level or microcommunity level*: For this level of organisation of the pathogen-centred disease system form, the two hierarchically organised scales are the within-organ or within-microcommunity scale, which is the microscale, and the between-organ or between-microcommunity scale, which is the macroscale.

[d.] *The microecosystem level*: The two hierarchically organised scales at this level of organisation of the pathogen-centred disease system form are the within-microecosystem scale, which is the microscale, and the between-microecosystem scale, which is the macroscale.

[e.] *The whole organism level*: At this level of organisation of the pathogen-centred disease system form, the two hierarchically organised scales; that is, the microscale and the macroscale, are the within-whole organism scale and the between-whole organism scale, respectively.

[f.] *The macrocommunity level*: This level of organisation of the pathogen-centred disease system form consists of the within-macrocommunity scale as the microscale and the between-macrocommunity scale as the macroscale.

[g.] *The macroecosystem level*: The two hierarchically organised scales at this level of organisation of the pathogen-centred disease system form are the within-macroecosystem scale, which is the microscale, and the between-macroecosystem scale, which is the macroscale.

As shown in Figure 2, the seven different levels of organisation of the pathogen-centred disease system form are hierarchically organised in both space and time. These seven levels of organisation can be demarcated into three main groups as follows. First, a group of primary levels of organisation consisting of the cell level, the tissue level, and the whole organism level, where the transmission process of the pathogen-centred disease system form is only through the local exchange of pathogen between the microscale and the macroscale in the context of single host species and single pathogen species/strain. Second, a group of secondary levels of organisation consisting of the organ/microcommunity level and the macrocommunity level, where the transmission process of the pathogen-centred disease system form is through both the local and global exchange of pathogen between the microscale and the macroscale, involving single host species and single pathogen species/strain in the context of multiple heterogeneous environments. Third, a group of tertiary levels of organisation consisting of the microecosystem level and the macroecosystem level, where the transmission process of the pathogen-centred disease system form is through a local or both local and global exchange of pathogen between the microscale and the macroscale in the context of multiple host species and or multiple strains/species of pathogens.

3.2. The Multiscale Organisation of the Pathogen-Centred Disease System Form

For the pathogen-centred disease system form, each of its seven levels of organisation illustrated in Figure 2 consists of two scales—a microscale and a macroscale. Figure 3 is a conceptual representation of a typical primary level of organisation of the pathogen-centred disease system form and the interaction of the microscale and macroscale through the four key disease processes [2]: [a.] the infection or super-infection by pathogen process, [b.] the pathogen replication process, [c.] the pathogen shedding or excretion process, and [d.] the pathogen transmission process. The interaction between the microscale and the macroscale of the pathogen-centred disease system form through these four disease processes is described by process-based multiscale models. These multiscale models belong to five different categories, which are [1–3]: [a.] individual-based multi-

scale models (IMSMs), which we also call phenomenological-based multiscale models, [b.] nested multiscale models (NMSMs), [c.] embedded multiscale models (EMSMs), [d.] hybrid multi-scale models (HMSMs), and [e.] coupled multiscale models (CMSMs). This taxonomic categorisation of multiscale models of infectious disease dynamics has been previously discussed in [1–3]. However, it is being further discussed in this article as part of the revision of the replication transmission relativity theory [1] to reflect the new knowledge based on the universal theory of disease dynamics, which dictates that these different categories of multiscale models are process-based multiscale models and thus describe the pathogen-centred disease system form only. In addition, and as illustrated in Figure 3, the development of these different categories of process-based multiscale models involves linking or integrating sub-models across scales by up-scaling and down-scaling variables associated with disease processes across the microscale and the macroscale. This is because, for the pathogen-centred disease system form, the hierarchical scales at any of its seven levels of organisation; that is, the microscale and the macroscale, indicate or represent shifts in the four disease processes; that is, the infection or super-infection by pathogen process, the pathogen replication process, the pathogen shedding or excretion process, and the pathogen transmission process.

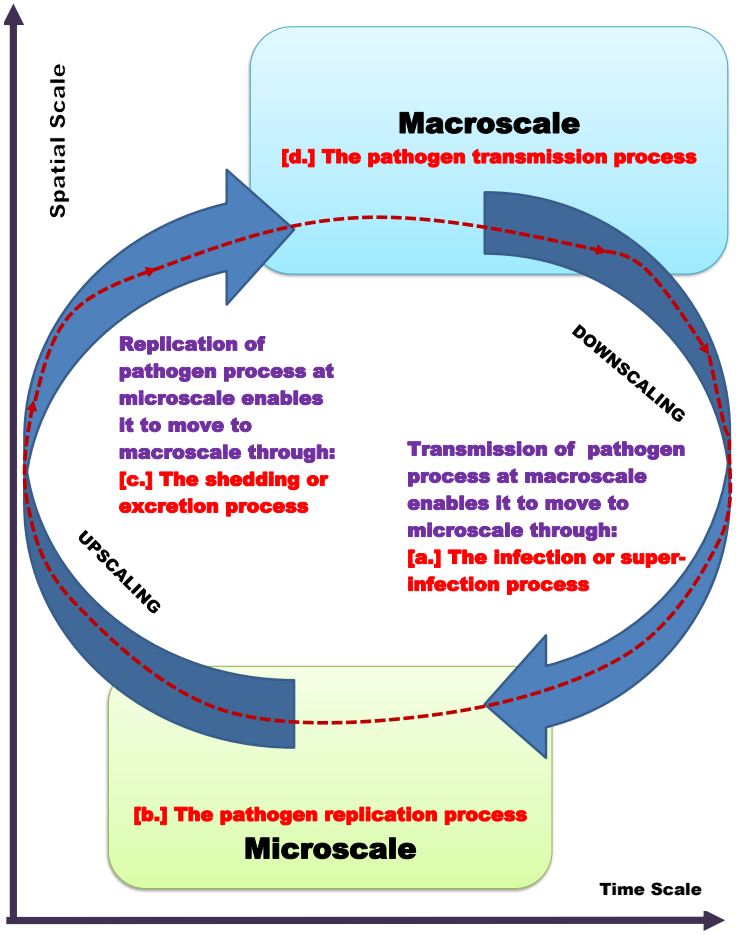


Figure 3. A conceptual representation of a typical primary level of organisation of the pathogen-centred disease system form where the multiscale dynamics of this disease system form involve interaction between a microscale and a macroscale through four main disease processes, which are [a.] the infection or super-infection by pathogen process, [b.] the pathogen replication process, [c.] the pathogen shedding or excretion process, and [d.] the pathogen transmission process, in a curved four-dimensional space-time that combines the three dimensions of space and one dimension of time into a single four-dimensional manifold. The dotted line indicates a conceptual representation of the path of the pathogen along the multiscale cycle.

In light of the new knowledge based on the universal theory of disease dynamics, we note that it is only the interaction of the microscale and the macroscale at a particular level of organisation of the pathogen-centred disease system form that necessarily assumes the replication-transmission relativity theory [1] and not the complete infectious disease system. Therefore, in the context of the universal theory for multiscale modelling of disease dynamics, process-based multiscale models refer to multiscale models of the pathogen-centred disease system form developed by explicitly incorporating four main disease processes that occur in the pathogen subsystem due to the impact of the host subsystem, which include [a.] the infection or super-infection by the pathogen process, [b.] the pathogen replication process, [c.] the pathogen excretion or shedding process, and [d.] the pathogen transmission process, to explain the multiscale temporal and spatial changes of the pathogen-centred disease system form at any of its seven main levels of organisation, which are [a.] the cell level, [b.] the tissue level, [c.] the organ/microcommunity level, [d.] the microecosystem level, [e.] the whole organism level, [f.] the macrocommunity level, and [g.] the macroecosystem level, without taking into consideration how the host subsystem causes these multiple scale processes. In what follows, we briefly describe the five different categories of the process-based multiscale models of the pathogen-centred disease system form and also give examples.

[a.] *Category I—Individual-Based Multiscale Models (IMSMs)*: A generic category of multiscale models that provides a simplified means of describing the multiscale dynamics of the pathogen-centred disease system form at a particular level of its organisation. We also sometimes refer to these individual-based multiscale models (IMSMs) as phenomenological-based multiscale models. This is because in this category of multiscale models, only the microscale is explicitly incorporated into the multiscale model and, as a result, the four main disease processes, which include the infection or super-infection by pathogen process, the pathogen replication process, the pathogen shedding or excretion process, and the pathogen transmission process, are only phenomenologically incorporated into the multiscale model with no explicit representation. In these phenomenological-based multiscale models, no macroscale sub-model is considered and so the macroscale is often observed as emergent behaviour of the microscale entities' behaviour. In order to describe the macroscale, the microscale results are converted by summing, averaging, or performing some detailed statistical analysis of them and aggregating the information into macroscale variables for interpretation at that scale. By failing to explicitly incorporate details of disease processes, phenomenological-based multiscale models only make reference to the complexity of the multiscale dynamics of the pathogen-centred disease system form at a level of its organisation without incorporating the exact content of the complexity. Examples of phenomenological-based multiscale models are agent-based models [4] and graph-theoretic models [5]. Because they implicitly incorporate disease processes of the pathogen-centred disease system form, phenomenological-based multiscale models are typically simpler than the other four categories of multiscale models.

[b.] *Category II—Nested Multiscale Models (NMSMs)*: A generic category of process-based multiscale models developed to characterise the multiscale dynamics of the pathogen-centred disease system form at a particular level of its organisation by incorporating four main disease processes, which include the infection by pathogen process, the pathogen replication process, the pathogen shedding or excretion process, and the pathogen transmission process, across the microscale and the macroscale. In this category of process-based multiscale models, the microscale sub-model and the macroscale sub-model must be described by the same mathematical formalism or mathematical representation and are linked through the exchange of pathogen. For these multiscale models, the macroscale is linked to the microscale through the infection by pathogen process while the microscale is linked to the macroscale through the pathogen shedding or excretion process. A wide range of mathematical techniques can be used to integrate the microscale sub-model and the macroscale sub-model. This gives

rise to different classes of process-based multiscale models of the pathogen-centred disease system form in this category of multiscale models. Typical examples of nested multiscale models include [6] for COVID-19 and [7] for paratuberculosis.

[c.] *Category III—Embedded Multiscale Models (EMSMs)*: A generic category of process-based multiscale models developed to characterise the multiscale dynamics of the pathogen-centred disease system form at a particular level of its organisation by incorporating four main disease processes, which include the super-infection by pathogen process, the pathogen replication process, the pathogen shedding or excretion process, and the pathogen transmission process, across the microscale and the macroscale. For this category of process-based multiscale models, the microscale sub-model and the macroscale sub-model must also be described by the same mathematical formalism or mathematical representation and are linked through the exchange of pathogen. Further, the macroscale is linked to the microscale through the super-infection by pathogen process while the microscale is linked to the macroscale through the pathogen shedding or excretion process. A wide range of mathematical techniques can also be used to integrate the microscale sub-model and the macroscale sub-model. This also gives rise to different classes of process-based multiscale models of the pathogen-centred disease system form in this category of multiscale models. Specific examples of embedded multiscale models are [7] for paratuberculosis and [1] for hookworm infection.

[d.] *Category IV: Hybrid multiscale models (HMSMs)*: A generic category of process-based multiscale models developed to characterise the multiscale dynamics of the pathogen-centred disease system form at a particular level of its organisation by incorporating four main disease processes, which include the infection or super-infection by pathogen process, the pathogen replication process, the pathogen shedding or excretion process, and the pathogen transmission process across the microscale and the macroscale. In this category of multiscale models, the microscale sub-model and macroscale sub-model are described by different mathematical formalisms or mathematical representations, depending on differences between scale variables of the microscale and the macroscale, which can be, for example, due to:

  [i.] The nature of variation in time scale variables, which can be discrete time at one scale and continuous time at the other scale;
  [ii.] The nature of variation in the state variables, which can be stochastic state variables at one scale and deterministic state variables at the other scale;
  [iii.] The nature of variation in the spatial scale, which can be homogeneous spatial variables at one scale described by ODEs, and heterogeneous spatial variables at the other scale described by PDEs, etc. In these process-based multiscale models, the macroscale is linked to the microscale through the infection by pathogen process or super-infection by pathogen process while the microscale is linked to the macroscale through the pathogen shedding or excretion process. A wide range of mathematical techniques can also be used to integrate the microscale sub-model and the macroscale sub-model. This gives rise to different classes of process-based multiscale models of the pathogen-centred disease system form in this category of multiscale models. Typical examples of hybrid multiscale models are [8–10].

[e.] *Category V—Coupled Multiscale Models (CMSMs)*: A generic category of multiscale models, which may be process-based multiscale models, phenomenological-based multiscale models, or a combination of these two types of multiscale models, that provides a simplified means of describing the multiscale dynamics of a pathogen-centred disease system form at a particular level of its organisation. For this category of multiscale models, the process-based multiscale models from any of categories I, II, III, and IV are used as sub-models in the development of multiscale models of the pathogen-centred disease system form. This is because the multiscale models developed in this category consider multiple pathogen strain infections, and/or

multiple pathogen species infections, and/or multiple host group infections, and/or multiple host species infections, and/or multiple communities infections, and/or multiple organ/anatomical compartment infections. They are not like process-based multiscale models of categories I, II, III, and IV, which focus on a specific combination of (i) one-host and (ii) one-pathogen species/strain of a pathogen-centred disease system form relationships in multiscale modelling. Examples of coupled multiscale models are [11] for malaria and [12] for for river blindness, which are described in the context of multiple host species.

These different categories of multiscale models can be further demarcated into three groups. First, we have a group of primary process-based multiscale models, which are multiscale models developed at primary levels of organisation of the pathogen-centred disease system form, and are more suitable for an evaluation of the control of this disease system form. Second, we have a group of secondary process-based multiscale models, which are multiscale models developed at secondary levels of organisation of the pathogen-centred disease system form, and are more suitable for an evaluation of the elimination of this disease system form. Third and last, we have a group of tertiary process-based multiscale models, which are multiscale models developed at tertiary levels of organisation of the pathogen-centred disease system form, and are more suitable for an evaluation of the eradication of this disease system form. One of the pivotal concepts introduced in [11] is that process-based multiscale models can be used to translate existing knowledge about the efficacy of health interventions at the microscale into projected outcomes of the effectiveness of health interventions at the macroscale in the control, elimination, and even eradication of a pathogen-centred disease system form at any of its seven hierarchical levels of organisation. This has important applications in the evaluation of the effectiveness of drugs in different populations.

4. The Host-Centred Disease System Form

In the context of the universal theory for the multiscale modelling of infectious disease dynamics, which is conceptually represented by Figure 1, the host-centred disease system form arises due to the need to account for the impact of the pathogen subsystem on the host subsystem. We now discuss in detail the multilevel organisation of the host-centred disease system form in Section 4.1 and the multiscale organisation of a level of organisation of the host-centred disease system form in Section 4.2 together with the difficulties encountered in the development of mechanism-based multiscale models that are used to describe the host-centred disease system form.

4.1. The Multilevel Organisation of the Host-Centred Disease System Form

The host-centred disease system form is the form that the whole infectious disease system takes when considering the host-centred perspective of the interaction among the three subsystems of an infectious disease system; that is, the host subsystem, the environment subsystem, and the pathogen subsystem. In order to analyse a host-centred disease system form using multiscale modelling methods, its complexity also has to be brought down to manageable levels by discretising or decomposing it into different discrete levels of organisation so that, at each level of organisation, disease dynamics can be analysed in terms of their scales of organisation. Based on the functional organisation of living organisms and their associated environment in which pathogens generate effects, we establish that a host-centred disease system form can be discretised into four main hierarchical levels of organisation, which are: [a.] the host damage level, [b.] the host immune response level, [c.] the environmental change level, and [d.] the biodiversity change level. Figure 4 shows a conceptual representation of these four main levels of organisation of the host-centred disease system form.

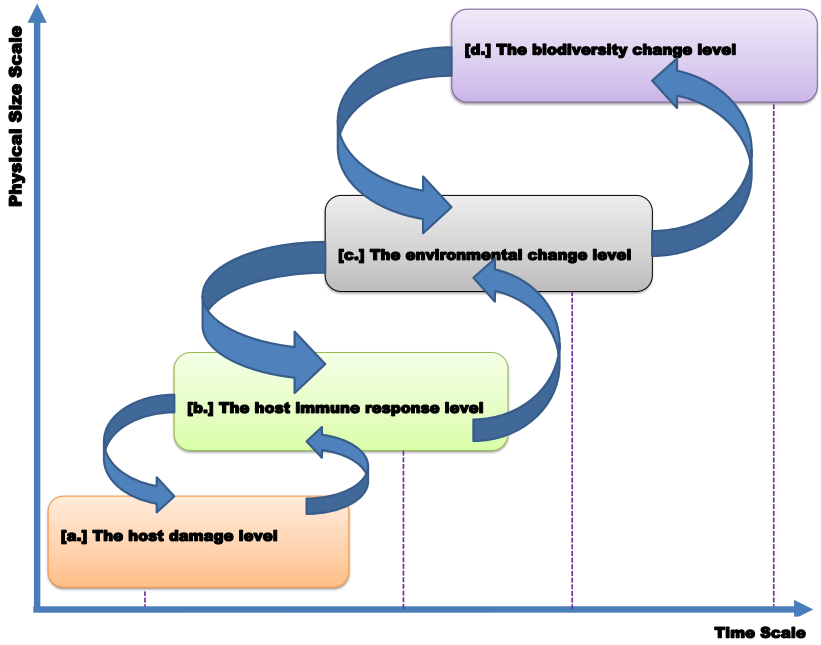


Figure 4. A conceptual representation of the four main levels of organisation of the host-centred disease system form, which are: [a.] the host damage level, [b.] the host immune response level, [c.] the environmental change level, and [d.] the biodiversity change level. These levels of organisation of the host-centred disease system form are hierarchically organised into physical size scale and time scale in such a way that they can be placed at distinct and discrete positions in the hierarchy so that the larger the physical size scale of the biological functional structure that is central to a particular compositional physiological mechanism, the larger the time scale of the time at which the compositional physiological mechanism takes place in the hierarchy.

Each of the four main levels of organisation of the host-centred disease system form consists of two main complementary level forms. In what follows, we describe the four main levels of organisation of the host-centred disease system form and the two main complementary level forms for each level of organisation.

[a.] *The host damage level*: This functional level of organisation of the host-centred disease system form consists of two main complementary level forms: [i.] the pathogen-mediated damage level form and [ii.] the host-mediated damage level form. Usually, the host damage level begins with the pathogen-mediated damage level form, which then triggers the host-mediated damage level form. Currently, host damage can only be quantified in relative terms [13,14]. The term 'relative' is necessitated by the fact that, at present, host damage cannot be fully quantified because precise readouts of host damage remain limited and available mathematical modelling tools and computational platforms are insufficient for the quantification of host damage. When host damage surpasses a threshold that maintains host homeostasis, clinical disease occurs [14]. In the multiscale dynamics of the host-centred disease system form, the host damage level triggers the host immune response level [13,14].

[b.] *The host immune response level*: This functional level of organisation of the host-centred disease system form also consists of two main complementary level forms, which are [i.] the innate immune response level form and [ii.] the adaptive immune response level form. Usually, the host immune response level begins with the innate immune response level form, which then triggers the adaptive host immune response level form. Each of these two complementary level forms of the host immune response level consists of three main scale mechanisms [15–17]: [i.] the molecular scale mechanism, which includes the proteome, lipodome, genome, metabolome, transcriptome, and complex molecular processes, such as gene expression, gene regulatory networks, signaling, and metabolic pathways involved in immunity and inflammation; [ii.] the

cellular scale mechanism, which includes the activities and behaviour of the different immune cells, such as T-cells, B-cells, and different pathogen processes; and [iii.] the tissue scale mechanism, which includes inflammation mechanisms.

[c.] *The environmental change level*: In the context of the universal theory for the multiscale modelling of infectious disease dynamics, this level of organisation of the host-centred disease system form arises because the environment subsystem is considered as an extended form of the host subsystem. This functional level of organisation of the host centred disease system form consists of two main complementary levels forms: [i.] the human-induced environmental-change-level form and [ii.] the naturally induced environmental-change-level form [18]. Usually, the environmental change level begins with the human-induced environmental-change-level form through mechanisms such as land use and population growth, which then triggers the naturally-induced environmental-change-level form such as extreme weather events, natural disasters, and climate change. Environmental change can significantly influence infectious disease dynamics through effects such as the survival and reproductive capacity of vectors and pathogens [19]. In the multiscale dynamics of the host-centred disease system form, the environmental change level triggers the biodiversity change level [20].

[d.] *The biodiversity change level*: In the context of the universal theory for the multiscale modelling of infectious disease dynamics, the term biodiversity or biological diversity refers to the diversity of living organisms implicated in infectious disease dynamics, which are the pathogen subsystem and the host subsystem. This functional level of organisation of the host-centred disease system form also consists of two main complementary level forms: [i.] the pathogen-biodiversity-change-level form, which we also call the microbial-diversity-change-level form or microbiodiversity-change-level form [21], and [ii] the host-biodiversity-change-level form, which we also call the macrobiodiversity-change-level form [22,23]. In multiscale dynamics of the host-centred disease system form, biodiversity change occurs through various evolutionary mechanisms or adaptive mechanisms, which include [i.] mutation mechanisms, and/or [ii.] migration/dispersal mechanisms, and/or [iii.] genetic drift mechanisms, and/or [iv.] natural selection mechanisms. Usually, the biodiversity change level begins with the pathogen-biodiversity-change-level form, which then triggers the host-biodiversity-change-level form, resulting in the reciprocity of change occurring in both the pathogen subsystem and the host subsystem, whereby both the host subsystem and the pathogen subsystem impose evolutionary change on the other in a process involving co-evolutionary mechanisms. In this case, co-evolutionary mechanisms of the host subsystem and pathogen subsystem are a dynamic process of ongoing reciprocal change where a pathogen subsystem imposes an evolutionary influence on a host subsystem, which responds to the evolutionary pressure, in turn imposing an evolutionary influence on the pathogen subsystem, with this cycle potentially repeated over and over again. The outcome of this arms race may involve traits like parasite infectivity, host resistance, parasite host-finding ability, and parasite avoidance behaviour by the host [2]. The multiscale mechanisms of the biodiversity change level of the host-centred disease system form lie at the heart of the emergence and spread of pandemics, resulting in the emergence of new variants at the microbial-diversity-change-level form and new host species at the macrobiodiversity-change-level form.

These four main levels of organisation of the host-centred disease system form can be demarcated into two main groups. First, a group of primary levels of organisation of the host-centred disease system form consisting of the host damage level and the host immune response level. There is much stronger coupling between these two lower levels of organisation of the host-centred disease system form than with the higher levels of organisation of this disease system form since the host damage level triggers the host immune response level [13,14]. Second, a group of secondary levels of organisation of the host-centred disease system form consisting of the environmental change level and the biodiversity change level. There is also much stronger coupling between these two higher

levels of organisation of the host-centred disease system form than with the lower levels of organisation of this disease system form; that is, the primary levels of organisation of the host-centred disease system form, since the environmental change level triggers the biodiversity change level [19,20,24]. The multiscale modelling of the host-centred disease system that incorporates the scales of both the primary levels of organisation and the secondary levels of organisation of the host-centred disease system form is at the core of the multiscale modelling of the ecology and evolution of infectious disease dynamics [22,23].

4.2. The Multiscale Organisation of the Host-Centred Disease System Form

Each level of organisation of the host-centred disease system form is dominated by multiple scale mechanisms that influence its dynamics at different scales. This is because, within each of the four main levels of organisation of the host-centred disease system form, which are [a.] the host damage level, [b.] the host immune response level, [c.] the environmental change level, and [d.] the biodiversity change level, a mechanism is considered compositional in the sense that the mechanism of each level of organisation as a whole can be broken down into organised interactions among the activities of different scale mechanisms at different scales of a level of organisation of this disease system form, with each scale associated with a particular scale mechanism. Based on this understanding, we establish that each of the four main levels of organisation of the host-centred disease system form is organised into seven main hierarchical scales of mechanism, which are: [a.] the molecular scale, [b.] the cell scale, [c.] the tissue scale, [d.] the organ scale, [e.] the whole organism scale, [f.] the community scale, and [g.] the ecosystem scale. Figure 5 is a conceptual representation of the seven main scales of a level of organisation of the host-centred disease system form.

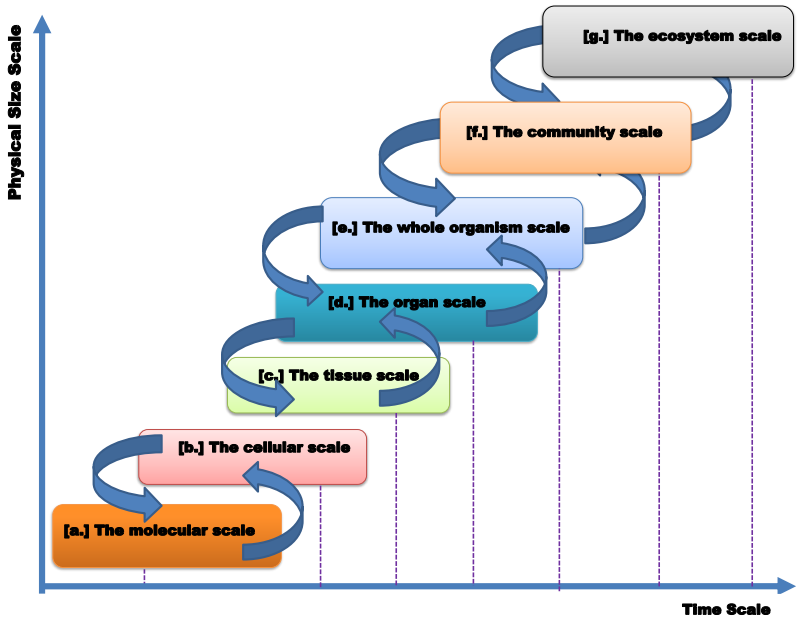


Figure 5. A conceptual representation of the seven main scales that are used to describe each of the four main functional levels of organisation (i.e., the host damage level, the host immune response level, the environmental change level, and the biodiversity change level) of the host-centred disease system form, which are [a.] the molecular scale, [b.] the cell scale, [c.] the tissue scale, [d.] the organ scale, [e.] the whole organism scale, [f.] the community scale, and [g.] the ecosystem scale, using mechanism-based multiscale models. These scales of a level of organisation of the host-centred disease system form are hierarchically organised into physical size scale and time scale so that they can be placed at distinct and discrete positions in the hierarchy such that the larger the physical size scale of the biological functional structure that is central to a particular physiological mechanism, the larger the time scale at which the physiological mechanism takes place.

Because of the different scale mechanisms at each of the four main levels of organisation, a host-centred disease system form is described by mechanism-based multiscale models. These mechanism-based multiscale models are described in terms of the following seven scale mechanisms at each of the four main levels of the host-centred disease system form:

[a.] **The molecular-scale mechanism**: This involves molecular-scale mechanisms at each of the four main levels of organisation of the host-centred disease system form: the host damage level, the host immune response level, the environmental change level, and the biodiversity change level. Examples of molecular-scale mechanisms include mutation and genetic drift at the biodiversity change level [20], and cytokine, chemokine, and antibody mechanisms at the host immune response level [15–17]. Other examples of molecular mechanisms include nutrient cycle mechanisms such as nitrogen cycle and carbon cycle mechanisms at the environmental change level [25].

[b.] **The cellular-scale mechanism**: This involves cellular=scale mechanisms at each of the four main levels of organisation of the host-centred disease system form: the host damage level, the host immune response level, the environmental change level, and the biodiversity change level. Examples of cellular-scale mechanisms include apoptosis and necrosis mechanisms at the host damage level [13], and T-cell, dendritic cell, and B-cell mechanisms, including macrophage mechanisms such as phagocytosis, at the host immune response level [15–17].

[c.] **The tissue-scale mechanism**: This involves tissue-scale mechanisms at each of the four main levels of organisation of the host-centred disease system form: the host damage level, the host immune response level, the environmental change level, and the biodiversity change level. Examples of tissue-scale mechanisms include inflammation and fibrosis at the host immune response level [26].

[d.] **The organ-scale mechanism**: This involves organ-scale mechanisms at each of the four main levels of organisation of the host-centred disease system form: the host damage level, the host immune response level, the environmental change level, and the biodiversity change level. Examples of organ-scale mechanisms include sepsis and gangrene formation [27] at the host damage level.

[e.] **The whole-organism-scale mechanism**: This involves whole-organism-scale mechanisms at each of the four main levels of organisation of the host-centred disease system form: the host damage level, the host immune response level, the environmental change level, and the biodiversity change level. Examples of whole-organism-scale mechanisms include fever mechanisms and behavioural mechanisms such as hydrophobia at the host immune response level [13], and whole organism death at the host damage level.

[f.] **The community-scale mechanism**: This involves community-scale mechanisms at each of the four main levels of organisation of the host-centred disease system form: the host damage level, the host immune response level, the environmental change level, and the biodiversity change level. Examples of community-scale mechanisms include adaptation and natural selection at the biodiversity change level and population extinction at the host damage level.

[g.] **The ecosystem-scale mechanism**: This involves ecosystem-scale mechanisms at each of the four main levels of organisation of the host-centred disease system form: the host damage level, the host immune response level, the environmental change level, and the biodiversity change level. Examples of ecosystem-scale mechanisms include predation, competition, and the dilution effect—in which diverse host communities can reduce disease risk [28,29].

Therefore, mechanism-based multiscale models refer to multiscale models of the host-centred disease system form developed by incorporating multiple scale mechanisms that occur in the host subsystem due to the impact of the pathogen subsystem, which include [a.] molecular-scale mechanisms, [b.] cellular-scale mechanisms, [c.] tissue-scale mechanisms, [d.] organ-scale mechanisms, [e.] whole-organism-scale mechanisms, [f.] community-scale mechanisms, and [g.] ecosystem-scale mechanisms, in order to explain the multiscale

temporal changes of the host-centred disease system form at each of its four main levels of organisation, which are [a.] the host damage level, [b.] the host immune response level, [c.] the environmental change level, and [d.] the biodiversity change level, taking into consideration how the pathogen subsystem causes these multiple scale mechanisms. The difficulty in the development of mechanism-based multiscale models of the host-centred disease system form when compared to the development of process-based multiscale models of the pathogen-centred disease system form is due to the following reasons: [a.] first, each level of the host-centred disease system form consists of two or more scales, with at most seven scales: [i.] the molecular scale, [ii.] cellular scale, [iii.] tissue scale, [iv.] organ scale, [v.] organism scale, [vi.] community scale, and [vii.] ecosystem scale]. This is unlike the pathogen-centred disease, where a level consists of only two scales, a macroscale and a microscale. [b.] Second, there is inter-dependence of levels, level forms, and scales with the simplest mechanism-based multiscale model required to incorporate at least the two primary levels of organisation of the host-centred disease system form: the host damage level and the host immune response level. However, in the pathogen-centred disease system form, only the two scales (i.e., the microscale and the macroscale) at a single level of this disease system form are assumed to be inter-dependent, while the levels are assumed to independent. [c.] Third, there are limitations imposed by observational and experimental tools to reveal the mechanisms at all the seven main scales of mechanism of each level of organisation of the host-centred disease system form, while the processes at each level of the pathogen-centred disease system form are well understood.

5. A Process-Based Multiscale of the Pathogen-Centred Disease System Form of Malaria Disease System as an Example

To illustrate ideas, we present a process-based multiscale model of the pathogen-centred disease system form of a malaria disease system. The universal theory of infectious disease dynamics demands both the process-based multiscale model of the pathogen-centred disease system form and the mechanism-based multiscale model of the host-centred disease system form to be integrated into a single multiscale model of infectious disease dynamics. However, it might not always be possible to account for both the pathogen-centred and the host-centred perspectives in the multiscale modelling of infectious disease dynamics because of current limitations in the availability of mathematical technology required to achieve that. But, the consideration of the possible contributions of both the pathogen-centred disease system form and the host-centred disease system form to the multiscale dynamics of an infectious disease system in line with the dictates of the universal theory for the multiscale modelling of infectious disease dynamics has the potential to provide a systems approach to its multiscale dynamics. The process-based multiscale model of the pathogen-centred disease system of a malaria disease system developed here integrates four sets of variables at the whole organism level, which are as follows:

[a.] *At the between-human scale, we have the following three variables*: $S_H(\tau)$—susceptible human population size; $I_H(\tau)$—infected human population size; and $P_V(\tau)$—community sporozoite load.

[b.] *At the between-mosquito scale, we have the following three variables*: $S_V(\tau)$—susceptible mosquito population size; $I_V(\tau)$—infected mosquito population size; and $G_H(\tau)$—community gametocyte load.

[c.] *At the within-human scale, we have the following four variables*: $R_h(t)$—susceptible erythrocytes (red blood cells); $R_m(t)$—merozoite-infected erythrocytes; $M_h(t)$—merozoites; and $G_h(t)$—gametocyte-infected erythrocytes.

[d.] *At the within-mosquito scale, we have the following five variables*: $G_v(t)$—gametocyte-infected erythrocytes; $G_m(t)$—sex cells called gametes; $Z_v(t)$—zygotes; $O_v(t)$—oocysts; and $P_v(t)$—sporozoites.

Based on these fifteen variables, the coupled multiscale model of the pathogen-centred disease system form of a malaria disease system is given by the process-based multiscale model of scale order one (1). Details of the derivation of this multiscale model are given in

Appendix A. Figure 6 shows a schematic representation of the coupled multiscale model of the pathogen-centred disease system form of a malaria disease system given by (1). The parameters of this coupled multiscale model are given and defined in Tables A1 and A2 in Appendix A.

$$
\begin{cases}
1.\ \frac{dS_H(t)}{dt} = \Lambda_H - \frac{\beta_V P_V(t) S_H(t)}{P_0 + P_V(t)} - \mu_H S_H(t) + \gamma_H I_H(t), \\
2.\ \frac{dI_H(t)}{dt} = \frac{\beta_V P_V(t) S_H(t)}{P_0 + P_V(t)} - \left[\mu_H + \gamma_H + \delta_H\right] I_H(t), \\
3.\ \frac{dP_V(t)}{dt} = P_v(t)\alpha_v \left[I_V(t) + 1\right] - \alpha_V P_V(t), \\
4.\ \frac{dS_V(t)}{dt} = \Lambda_V - \frac{\beta_H G_H(t) S_V(t)}{G_0 + G_H(t)} - \mu_V S_V(t), \\
5.\ \frac{dI_V(t)}{dt} = \frac{\beta_H G_H(t) S_V(t)}{G_0 + G_H(t)} - \left[\mu_V + \delta_V\right] I_V(t), \\
6.\ \frac{dG_H(t)}{dt} = G_h(t)\alpha_h \left[I_H(t) + 1\right] - \alpha_H G_H(t), \\
7.\ \frac{dG_v(t)}{dt} = \frac{\beta_H G_H(t) \left[S_V(t) - 1\right]}{\left[G_0 + G_H(t)\right] \Phi_V \left[I_V(t) + 1\right]} - \left[\alpha_g + \mu_g\right] G_v(t), \\
8.\ \frac{dG_m(t)}{dt} = N_g \alpha_g G_v(t) - \left[\alpha_s + \mu_s\right] G_m(t), \\
9.\ \frac{dZ_v(t)}{dt} = \phi_s \alpha_s G_m(t) - \left[\alpha_z + \mu_z\right] Z_v(t), \\
10.\ \frac{dO_v(t)}{dt} = \alpha_z Z_v(t) - \left[\alpha_k + \mu_k\right] O_v(t), \\
11.\ \frac{dP_v(t)}{dt} = N_k \alpha_k O_v(t) - \left[\alpha_v + \mu_v\right] P_v(t), \\
12.\ \frac{dR_h(t)}{dt} = \Lambda_h - \beta_h R_h(t) M_h(t) - \mu_b R_h(t), \\
13.\ \frac{dR_m(t)}{dt} = (1 - \phi_h)\beta_h R_h(t) M_h(t) - \alpha_m R_m(t), \\
14.\ \frac{dM_h(t)}{dt} = \frac{\beta_V P_V(t) \left[S_H(t) - 1\right]}{\left[P_0 + P_V(t)\right] \Phi_H \left[I_H(t) + 1\right]} + N_m \alpha_m R_m(t) - \mu_m M_h(t), \\
15.\ \frac{dG_h(t)}{dt} = \phi_h \beta_h R_h(t) M_h(t) - \left[\alpha_h + \mu_h\right] G_h(t).
\end{cases}
\tag{1}
$$

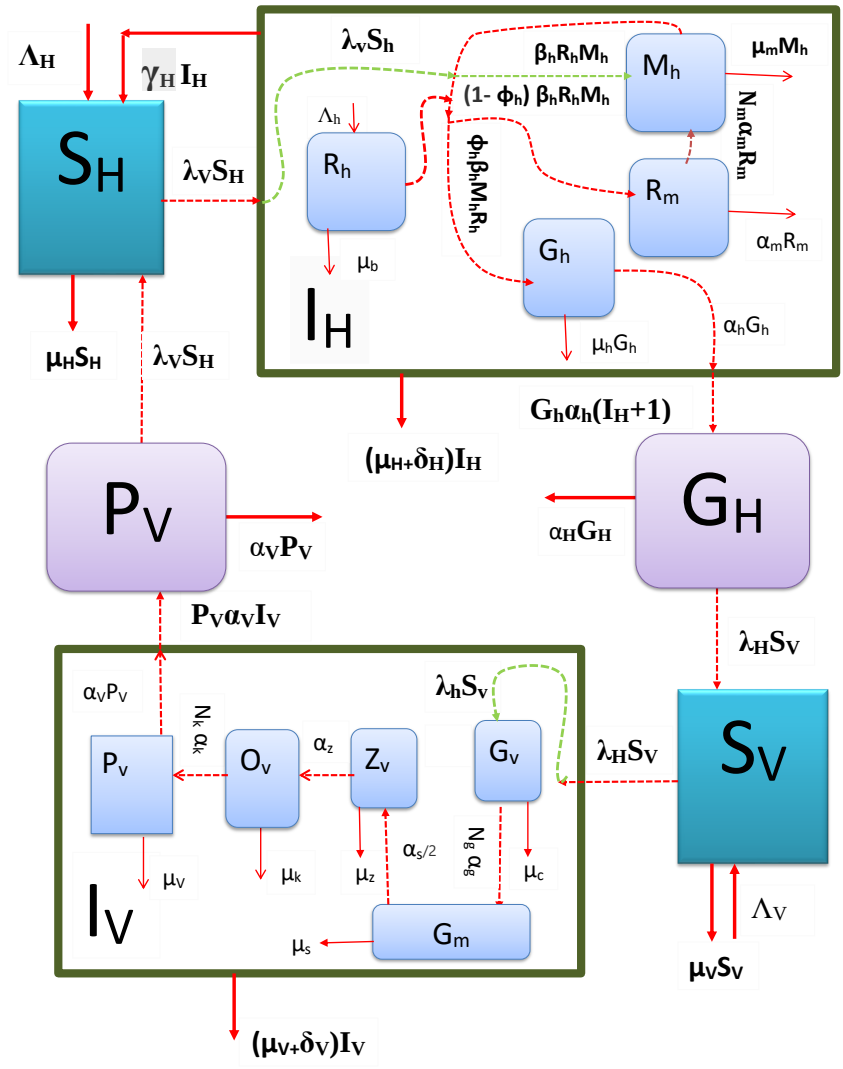


Figure 6. A schematic representation of the process–based multiscale model of the pathogen-centred disease system form of malaria disease system (1). This coupled multiscale model incorporates super-infection in both the human host and the mosquito host in addition to the other three disease processes for both the human host level and the mosquito host level. The four disease processes for a pathogen-centred disease system form for each whole organism level are illustrated in Figure 3.

6. Characterising the Multiscale Dynamics of the Pathogen-Centred Disease System Form of Malaria Disease System Using the Reproductive Number

In the context of the single-scale modelling of a malaria disease system at the whole organism level, the quantity R_0 quantifies the transmission process of this disease system at the macroscale only [30]. However, unlike the reproductive numbers derived from single-scale models of disease dynamics [30], which quantify the transmission process only, here, the reproductive number derived from the multiscale model (1) quantifies all four disease processes of the pathogen-centred disease system form of the malaria disease system—[a.] the super-infection by pathogen process, [b.] the pathogen replication process, [c.] the pathogen shedding or excretion process, and [d.] the pathogen transmission process—across the microscale and the macroscale. We use the next-generation operator approach to derive the basic reproduction number [31] from the process-based multiscale model (1). The process-based multiscale model (1) can be written in the form

$$\begin{cases} 1.\ \frac{dX}{dt} = f(X,Y,Z), \\ 2.\ \frac{dY}{dt} = g(X,Y,Z), \\ 3.\ \frac{dZ}{dt} = h(X,Y,Z), \end{cases} \tag{2}$$

where

$$\begin{cases} 1.\ X = \Big[S_H, S_V, R_h\Big], \\ 2.\ Y = \Big[I_H, I_V, G_v, G_m, Z_v, O_v, P_v, R_m, G_h\Big], \\ 3.\ Z = \Big[P_V, G_G, M_h\Big]. \end{cases} \tag{3}$$

Components X denote the number of susceptibles, while components of Y represent the number of infected individuals that do not transmit the disease. Components of Z represent the number of individuals capable of transmitting the disease. Let

$$\begin{cases} \tilde{g}(X^*,Z) = & \Big[\tilde{g}_1(X^*,Z), \tilde{g}_2(X^*,Z), \tilde{g}_3(X^*,Z), \tilde{g}_4(X^*,Z), \tilde{g}_5(X^*,Z), \\ & \tilde{g}_6(X^*,Z), \tilde{g}_7(X^*,Z), \tilde{g}_8(X^*,Z), \tilde{g}_9(X^*,Z)\Big], \end{cases} \tag{4}$$

with

$$\begin{cases} 1.\ \tilde{g}_1(X^*,Z) = \frac{\beta_V P_V(t)\Lambda_H}{\mu_H\Big[\mu_H+\gamma_H+\delta_H\Big]\Big[P_0+P_V(t)\Big]}, \\ 2.\ \tilde{g}_2(X^*,Z) = \frac{\beta_H G_H(t)\Lambda_V}{\mu_V\Big[\mu_V+\delta_V\Big]\Big[G_0+G_H(t)\Big]}, \\ 3.\ \tilde{g}_3(X^*,Z) = \frac{1}{\Big[\alpha_g+\mu_g\Big]}\cdot\frac{F_V(t)}{\mu_V\Big[\mu_V+\delta_V\Big]}, \\ 4.\ \tilde{g}_4(X^*,Z) = \frac{1}{\Big[\alpha_s+\mu_s\Big]}\cdot\frac{N_g\alpha_g}{\Big[\alpha_g+\mu_g\Big]}\cdot\frac{F_V(t)}{\mu_V\Big[\mu_V+\delta_V\Big]}, \\ 5.\ \tilde{g}_5(X^*,Z) = \frac{1}{\Big[\alpha_z+\mu_z\Big]}\cdot\frac{\phi_s\alpha_s}{\Big[\alpha_s+\mu_s\Big]}\cdot\frac{N_g\alpha_g}{\Big[\alpha_g+\mu_g\Big]}\cdot\frac{F_V(t)}{\mu_V\Big[\mu_V+\delta_V\Big]}, \\ 6.\ \tilde{g}_6(X^*,Z) = \frac{1}{\Big[\alpha_k+\mu_k\Big]}\cdot\frac{\alpha_z}{\Big[\alpha_z+\mu_n\Big]}\cdot\frac{\phi_s\alpha_s}{\Big[\alpha_s+\mu_s\Big]}\cdot\frac{N_g\alpha_g}{\Big[\alpha_g+\mu_g\Big]}\cdot\frac{F_V(t)}{\mu_V\Big[\mu_V+\delta_V\Big]}, \\ 7.\ \tilde{g}_7(X^*,Z) = \frac{1}{\Big[\alpha_v+\mu_v\Big]}\cdot\frac{N_k\alpha_k}{\Big[\alpha_k+\mu_k\Big]}\cdot\frac{\alpha_z}{\Big[\alpha_z+\mu_n\Big]}\cdot\frac{\phi_s\alpha_s}{\Big[\alpha_s+\mu_s\Big]}\cdot\frac{N_g\alpha_g}{\Big[\alpha_g+\mu_g\Big]}\cdot\frac{F_V(t)}{\mu_V\Big[\mu_V+\delta_V\Big]}, \\ 8.\ \tilde{g}_8(X^*,Z) = \frac{(1-\phi_h)\beta_h M_h\Lambda_h}{\alpha_m\mu_b}, \\ 9.\ \tilde{g}_9(X^*,Z) = \frac{\phi_h\beta_h M_h\Lambda_h}{\mu_b\Big[\alpha_h+mu_h\Big]}, \end{cases} \tag{5}$$

where

$$F_V(t) = \frac{\beta_H G_H(t)(\Lambda_V - \mu_V)}{\left[G_0 + G_H(t)\right]\Phi_V\left[\tilde{g}_2(X^*, Z) + 1\right]},$$

for $\Lambda_H > \mu_H$ and $\Lambda_V > \mu_V$. We shall assume in all that follows, unless stated otherwise, that $\Lambda_H > \mu_H$ and $\Lambda_V > \mu_V$.

Let

$$h(X^*, Z) = \begin{cases} h_1 = \frac{\Omega_v \beta_H G_H(t)(\Lambda_V - \mu_V)}{\mu_V\left[\mu_V + \delta_V\right]\Phi_V\left[G_0 + G_H(t)\right]} - \alpha_V P_V(t), \\ h_2 = \frac{\phi_h \beta_h M_h(t) \Lambda_h \alpha_h [\tilde{g}_1(X^*, Z) + 1]}{\mu_b\left[\alpha_h + \mu_h\right]} - \alpha_H G_H(t), \\ h_3 = \frac{\beta_V P_V(t)(\Lambda_H - \mu_H)}{\mu_H\left[P_0 + P_V(t)\right]\Phi_H[\tilde{g}_1(X^*, Z) + 1]} + \frac{N_m \alpha_m (1 - \phi_h)\beta_h M_h(t)\Lambda_h}{\alpha_m \mu_b} - \mu_m M_h(t) \end{cases} \tag{6}$$

where

$$\Omega_v = \frac{\alpha_v}{\left[\alpha_v + \mu_v\right]} \cdot \frac{N_k \alpha_k}{\left[\alpha_k + \mu_k\right]} \cdot \frac{\alpha_z}{\left[\alpha_z + \mu_z\right]} \cdot \frac{\phi_s \alpha_s}{\left[\alpha_s + \mu_s\right]} \cdot \frac{N_g \alpha_g}{\left[\alpha_g + \mu_g\right]}. \tag{7}$$

Let $A = D_Z h(X^*, \tilde{g}(X^*, 0), 0)$ and further assume that A can be written in the form $A = M - D$, where $M \geq 0$ and $D > 0$, a diagonal matrix. Then, A becomes

$$A = \begin{bmatrix} -\alpha_V & \frac{\Omega_v \beta_H (\Lambda_V - \mu_V)}{\mu_V\left[\mu_V + \delta_V\right]\Phi_V G_0} & 0 \\ 0 & -\alpha_H & \frac{\phi_h \beta_h \Lambda_h \alpha_h}{\mu_b\left[\alpha_h + \mu_h\right]} \\ \frac{\beta_V(\Lambda_H - \mu_H)}{\Phi_H \mu_H P_0} & 0 & \frac{N_m \alpha_m (1 - \phi_h)\beta_h \Lambda_h}{\alpha_m \mu_b} - \mu_m, \end{bmatrix}, \tag{8}$$

where Ω_v is given by the expression (7). Since $A = M - D$, we deduce matrices M and D to be

$$M = \begin{bmatrix} 0 & \frac{\Omega_v \beta_H (\Lambda_V - \mu_V)}{\mu_V\left[\mu_V + \delta_V\right]\Phi_V G_0} & 0 \\ 0 & 0 & \frac{\phi_h \beta_h \Lambda_h \alpha_h}{\mu_b\left[\alpha_h + \mu_h\right]} \\ \frac{\beta_V(\Lambda_H - \mu_H)}{\Phi_H \mu_H P_0} & 0 & \frac{N_m \alpha_m (1 - \phi_h)\beta_h \Lambda_h}{\alpha_m \mu_b}, \end{bmatrix}, \quad D = \begin{bmatrix} \alpha_V & 0 & 0 \\ 0 & \alpha_H & 0 \\ 0 & 0 & \mu_m \end{bmatrix}, \tag{9}$$

where Ω_v is given by the expression (7).

Then,

$$MD^{-1} = \begin{bmatrix} 0 & \frac{\Omega_v \beta_H (\Lambda_V - \mu_V)}{\mu_V\left[\mu_V + \delta_V\right]\Phi_V \alpha_H G_0} & 0 \\ 0 & 0 & \frac{\phi_h \beta_h \Lambda_h \alpha_h}{\mu_b \mu_m\left[\alpha_h + \mu_h\right]} \\ \frac{\beta_V(\Lambda_H - \mu_H)}{\Phi_H \mu_H \alpha_V P_0} & 0 & \frac{N_m \alpha_m (1 - \phi_h)\beta_h \Lambda_h}{\alpha_m \mu_b \mu_m}, \end{bmatrix}. \tag{10}$$

where Ω_v is given by the expression (7).

The basic reproductive number is the spectral radius (dominant eigenvalue) of the matrix MD^{-1}; that is,

$$R_0 = \rho(MD^{-1}).$$

In this case, the reproductive number is obtained as the dominant eigenvalue from the cubic equation

$$\lambda^3 - p\lambda^2 - q = 0 \tag{11}$$

Using the formula for solving cubic equations, the reproductive number can be shown to be

$$\begin{cases} R_0 = \frac{p}{3} + \sqrt[3]{\left[\frac{27q-2p^2}{54}\right] + \sqrt[2]{\left[\frac{27q-2p^2}{54}\right]^2 - \frac{p^6}{729}}} \\ \quad + \sqrt[3]{\left[\frac{27q-2p^2}{54}\right] - \sqrt[2]{\left[\frac{27q-2p^2}{54}\right]^2 - \frac{p^6}{729}}} \end{cases} \tag{12}$$

where

$$\begin{cases} p = \frac{N_m\alpha_m(1-\phi_h)\beta_h\Lambda_h}{\alpha_m\mu_b\mu_m} \\ q = \frac{\Omega_v\beta_H(\Lambda_V-\mu_V)}{\mu_V\left[\mu_V+\delta_V\right]\Phi_V\alpha_H G_0} \cdot \frac{\beta_V(\Lambda_H-\mu_H)}{\Phi_H\mu_H\alpha_V P_0} \cdot \frac{\phi_h\beta_h\Lambda_h\alpha_h}{\mu_b\left[\alpha_h+\mu_h\right]}, \end{cases} \tag{13}$$

and Ω_v is given by the expression (7).

The reproductive number (12) derived from the coupled multiscale model (1) of the pathogen-centred disease system form of a malaria disease system indicates that it is a combination of all four main disease processes—[a.] the super-infection by pathogen process, [b.] the pathogen replication process, [c.] the pathogen shedding or excretion process, and [d.] the pathogen transmission process—across the microscale and the macroscale. This indicates that there is reciprocal influence between the microscale malaria disease dynamics and macroscale malaria disease dynamics for its pathogen-centred disease system form. Thus, the multiscale nature of the pathogen-centred disease system form of a malaria disease system described by the coupled multiscale model (1) is confirmed.

7. Characterising the Multiscale Dynamics of the Pathogen-Centred Disease System Form of Malaria Disease System Using Numerical Methods

In this section, we design a non-standard finite difference (NSFD) scheme that approximates the process-based multiscale model of scale order one (1). The non-standard finite difference (NSFD) scheme that we design for the process-based multiscale of a malaria disease system of scale order one (1) is based on the procedures and rules developed by Mickens [32–35]. Let $X^k = \left[S_H^k, I_H^k, P_V^k, S_V^k, I_V^k, G_H^k, R_h^k, R_m^k, M_h^k, G_h^k\right]^T$ be the sequence of the solution, which must be non-negative and satisfy the underlying biological properties of the process-based multiscale model (1) for $k \in \mathbb{N}$ and the time step size $h = \Delta t$. The NSFD scheme to solve the system (1) is designed so that it satisfies the conservation law property proposed by Mickens [32,35]. If we let $\lambda_V^k = \frac{\beta_V P_H^k}{P_0+P_H^k}$ and $\lambda_H^k = \frac{\beta_H G_H^k}{(G_0+G_H^k)}$, then the NSFD scheme that approximates the process-based multiscale model (1) becomes:

$$
\begin{cases}
1.\ S_H^{k+1} = \frac{\phi_1(h)\Lambda_H + S_H^k + \phi_1\gamma_H I_H^k}{1+\phi_1(h)\mu_H + \phi_1(h)\lambda_V^k}, \\
2.\ I_H^{k+1} = \frac{\phi_2(h)\lambda_V^k S_H^{k+1} + I_H^k}{1+\phi_2(h)(\mu_H+\delta_H+\alpha_H)}, \\
3.\ S_V^{k+1} = \frac{\phi_3(h)\Lambda_V + S_V^k}{1+\phi_3(h)\mu_V + \phi_3(h)*\lambda_H^k)}, \\
4.\ I_V^{k+1} = \frac{\phi_4(h)\lambda_H^k S_V^{k+1} + I_V^k}{1+\phi_4(h)(\alpha_V+\delta_V)}, \\
5.\ P_V^{k+1} = \frac{\phi_5(h) I_V^{k+1}\alpha_h P_v^k + P_V^k}{1+\phi_5(h)\alpha_V}, \\
6.\ G_H^{k+1} = \frac{\phi_6(h)\alpha_h I_V^{k+1} + G_H^k}{1+\phi_6(h)\alpha_H}, \\
7.\ G_v^{k+1} = \frac{\frac{\phi_7{}^{(h)}\lambda_H^k(S_V^{k+1}-1)}{\Phi_V(I_V^{k+1}+1)} + G_v^k}{1+\phi_7(h)\alpha_g+\mu_g}, \\
8.\ G_m^{k+1} = \frac{\phi_8(h)N_g\alpha_g G_v^{k+1} + G_m^k}{1+\phi_8(h)\alpha_s+\mu_s}, \\
9.\ Z_v^{k+1} = \frac{\phi_9(h)\phi_s\alpha_s G_m^{k+1} + G_v^k}{1+\phi_9(h)\alpha_z+\mu_z}, \\
10.\ O_v^{k+1} = \frac{\phi_{10}(h)\alpha_z Z_v^{k+1} + O_v^k}{1+\phi_{10}(h)\alpha_k+\mu_K}, \\
11.\ P_v^{k+1} = \frac{\phi_{11}(h)N_k\alpha_k O_v^{k+1} + P_v^k}{1+\phi_{11}(h)\alpha_v+\mu_v}, \\
12.\ R_h^{k+1} = \frac{\phi_{12}(h)\Lambda_h + G_h^k}{1+\phi_{12}(h)\alpha_m + |phi_1 2(h) M_h^k}, \\
13.\ R_m^{k+1} = \frac{\phi_{13}(h)(1+\phi_h)\beta_h R_h^{k+1} M_h^k + R_m^k}{1+\phi_{13}(h)\alpha_m}, \\
14.\ G_h^{k+1} = \frac{\phi_{14}(h)\phi_h\beta_h R_h^{k+1} M_h^k + G_h^k}{1+\phi_{14}(h)(\alpha_h+\mu_h)}, \\
15.\ M_h^{k+1} = \frac{\phi_{15}(h)\lambda_V^k(S_H^{k+1}-1) + M_h^k + N_m\alpha_m R_m^{k+1}}{\Phi_H(I_H^{k+1}+1)(1+\phi_{15}(h)\mu_m)},
\end{cases}
\tag{14}
$$

where

1. $\phi_1(h) = \frac{e^{h\mu_H}-1}{\mu_H}$;
2. $\phi_2(h) = \frac{e^{h(\delta_H+\delta_H+\mu_H)}-1}{\delta_H+\delta_H+\mu_H}$;
3. $\phi_3(h) = \frac{e^{h\mu_V}-1}{\mu_V}$;
4. $\phi_4(h) = \frac{e^{h(\alpha_V+\mu_V)}-1}{\alpha_V+\mu_V}$;
5. $\phi_5(h) = \frac{e^{h\alpha_V}-1}{\alpha_V}$;
6. $\phi_6(h) = \frac{e^{h\alpha_H}-1}{\alpha_H}$;
7. $\phi_7(h) = \frac{e^{h(\alpha_g+\mu_g)}-1}{\alpha_g+\mu_g}$;
8. $\phi_8(h) = \frac{e^{h(\alpha_s+\mu_s)}-1}{\alpha_s+\mu_s}$;
9. $\phi_9(h) = \frac{e^{h(\alpha_z+\mu_z)}-1}{\alpha_z+\mu_z}$;
10. $\phi_{10}(h) = \frac{e^{h(\alpha_k+\mu_k)}-1}{\alpha_k+\mu_k}$;

11. $\phi_{11}(h) = \frac{e^{h(\alpha_v+\mu_v)}-1}{\alpha_v+\mu_v}$;
12. $\phi_{12}(h) = \frac{e^{h\mu_h}-1}{\mu_h}$;
13. $\phi_{13}(h) = \frac{e^{h\alpha_m}-1}{\alpha_m}$;
14. $\phi_{14}(h) = \frac{e^{h(\alpha_h+\mu_h)}-1}{\alpha_h+\mu_h}$;
15. $\phi_{15}(h) = \frac{e^{h\mu_m}-1}{\mu_m}$.

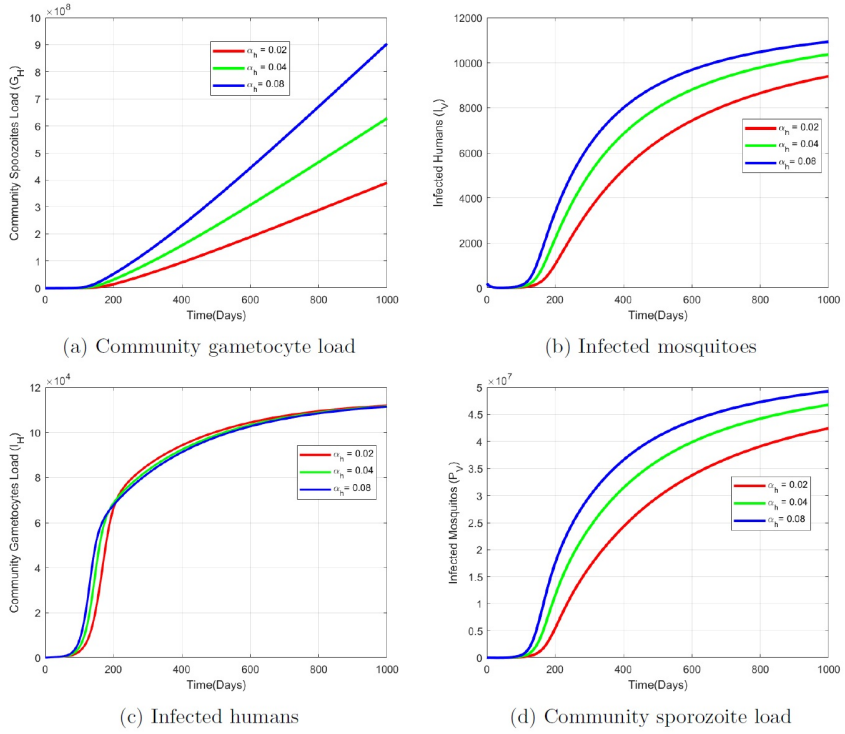
The simulations for the process-based multiscale of a malaria disease system of scale order one (1) are performed using the NSFD scheme (14) and coded with MatLab. The parameters used in the simulations for the process-based multiscale of the pathogen-centred disease system form of a malaria disease system of scale order one (1) are summarised in Tables A1 and A2 in Appendix A.

Figure 7 shows changes in (a) the community gametocyte load (G_H), (b) population of infected mosquitoes (I_V), (c) population of infected humans (I_H), and (d) community sporozoite load (P_V) for different values of the rate at which the gametocytes develop and become infectious to mosquitoes $\alpha_h : \alpha_h = 0.02, \alpha_h = 0.04, \alpha_h = 0.08$. These results show that as that rate at which gametocytes develop and become infectious to mosquitoes at the within-human scale increases, so does the transmission rate of the pathogen-centred disease system form of the malaria disease system at both the between-human scale and the between-mosquito scale.

Figure 8 shows changes in (a) the community gametocyte load (G_H), (b) population of infected mosquitoes (I_V), (c) population of infected humans (I_H), and (d) community sporozoite load (P_V) for different values of the rate at which sporozoites become infectious to humans $\alpha_v : \alpha_v = 0.025, \alpha_v = 0.045, \alpha_v = 0.085$. These results also show that as the rate at which sporozoites become infectious to humans α_v increases at the within-human scale, so does the transmission rate of the pathogen-centred disease system form of the malaria disease system at both the between-human scale and the between-mosquito scale.

Figure 9 shows changes in (a) gametocyte-infected erythrocytes (G_h), (b) the population of merozoites (M_h), (c) merozoite-infected erythrocytes (R_m), and (d) susceptible erythrocytes (R_h) for different values of the contact rate of mosquitoes with the infectious reservoir of humans $\beta_H : \beta_H = 0.00356, \beta_H = 0.0356, \beta_H = 0.356$. The results show that as the contact rate of mosquitoes with the infectious reservoir of humans β_H increases at the macroscale, there is an insignificant increase in malaria parasite load at the within-human scale. This is expected because the malaria parasite has a replication cycle at the within-human scale that occurs at a very fast time scale. As a result, the malaria parasite load increase at the within-human scale is determined more by parasite replication than by the super-infection process.

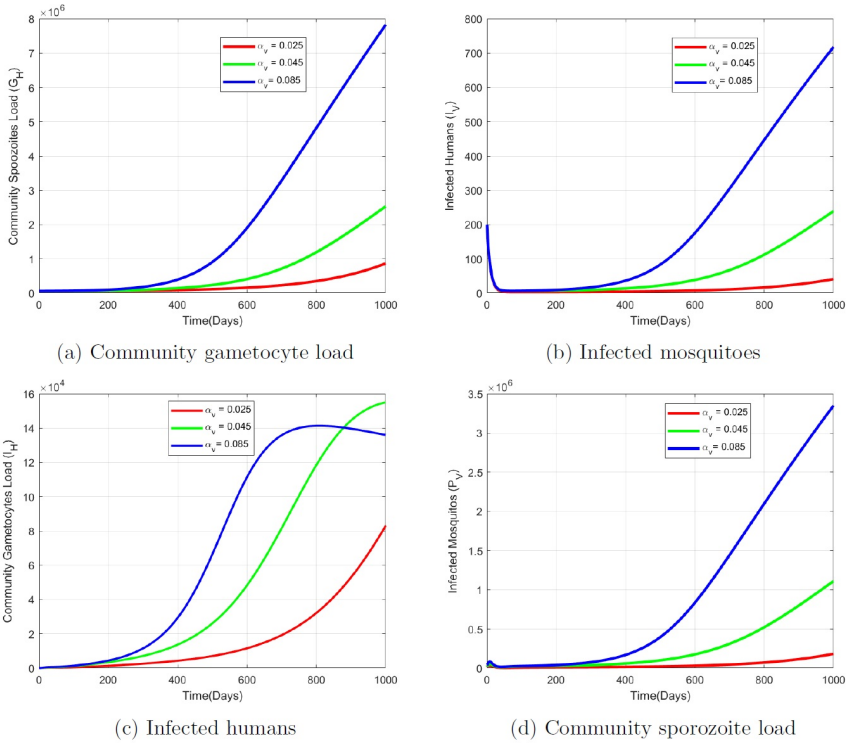
Figure 10 shows changes in (a) gametocyte-infected erythtcytes (G_h), (b) the population of merozoites (M_h), (c) merozoite-infected erythrocytes (R_m), and (d) susceptible erythrocytes (R_h) for different values of contact rate of humans with the infectious reservoir of mosquitoes $\beta_V : \beta_V = 0.003, \beta_V = 0.03, \beta_V = 0.3$. The results show that as the contact rate of humans with the infectious reservoir of mosquitoes β_V increases at the macroscale, there is also an insignificant increase in malaria parasite load at the within-human scale. This is also expected because the malaria parasite has a replication cycle at the within-human scale that occurs at a very fast time scale. As a result, the malaria parasite load increase at the within-human scale is determined more by parasite replication than by the super-infection process.



(a) Community gametocyte load (b) Infected mosquitoes

(c) Infected humans (d) Community sporozoite load

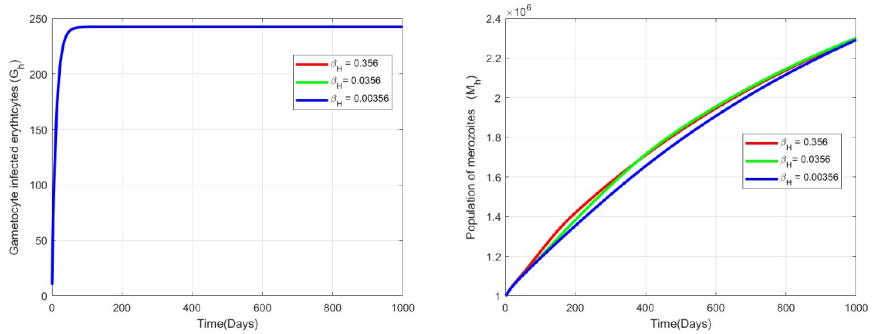
Figure 7. Shows changes in (**a**) community gametocyte load (G_H), (**b**) population of infected mosquitoes (I_V), (**c**) population of infected humans (I_H), and (**d**) community sporozoite load (P_V) for different values of the rate at which the gametocytes develop and become infectious α_h: $\alpha_h = 0.02$, $\alpha_h = 0.04$, $\alpha_h = 0.08$.



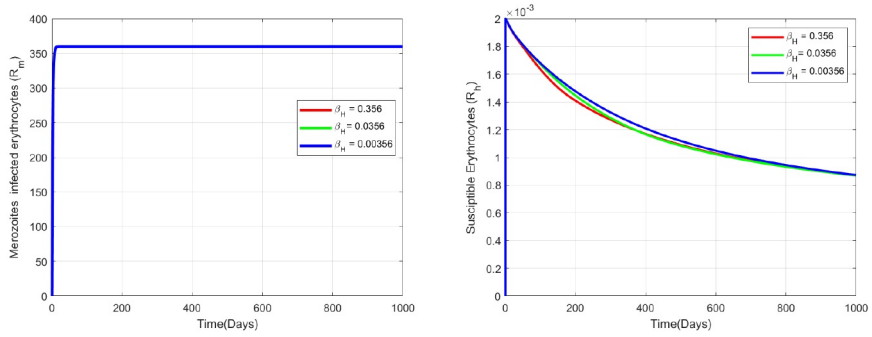
(a) Community gametocyte load (b) Infected mosquitoes

(c) Infected humans (d) Community sporozoite load

Figure 8. Shows the changes in (**a**) community gametocyte load (G_H), (**b**) population of infected mosquitoes (I_V), (**c**) population of infected humans (I_H), and (**d**) community sporozoite load (P_V) for different values of the rate at which sporozoites become infectious to humans α_v: $\alpha_v = 0.025$, $\alpha_v = 0.045$, $\alpha_v = 0.085$.

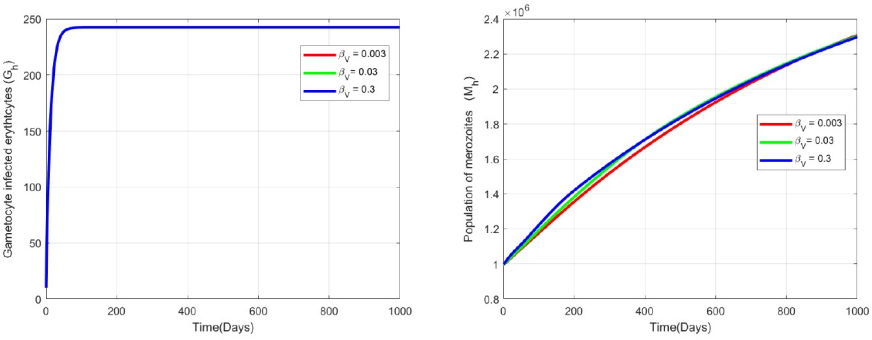


(a) Gametocyte infected erythtcytes (b) Population of merozoites

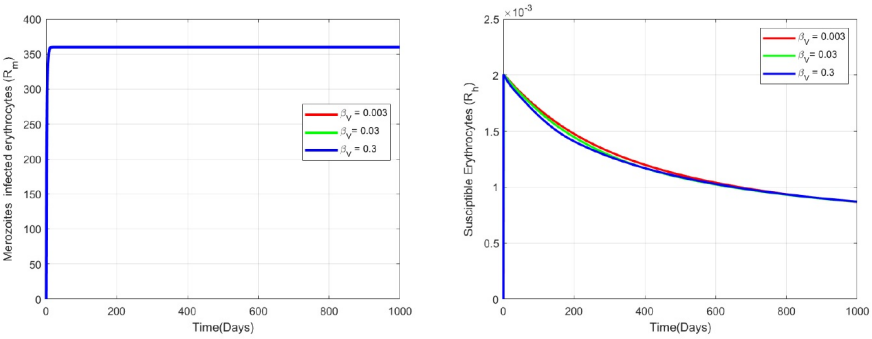


(c) Merozoites infected erythrocytes (d) Susceptible Erythrocytes

Figure 9. Shows changes in (**a**) gametocyte–infected erythrocytes (G_h), (**b**) population of merozoites (M_h), (**c**) merozoite–infected erythrocytes (R_m), and (**d**) susceptible erythrocytes (R_h) for different values of contact rate of mosquitoes with the infectious reservoir of humans β_H: $\beta_H = 0.00356$, $\beta_H = 0.0356$, $\beta_H = 0.356$.



(a) Gametocyte infected erythtcytes (b) Population of merozoites

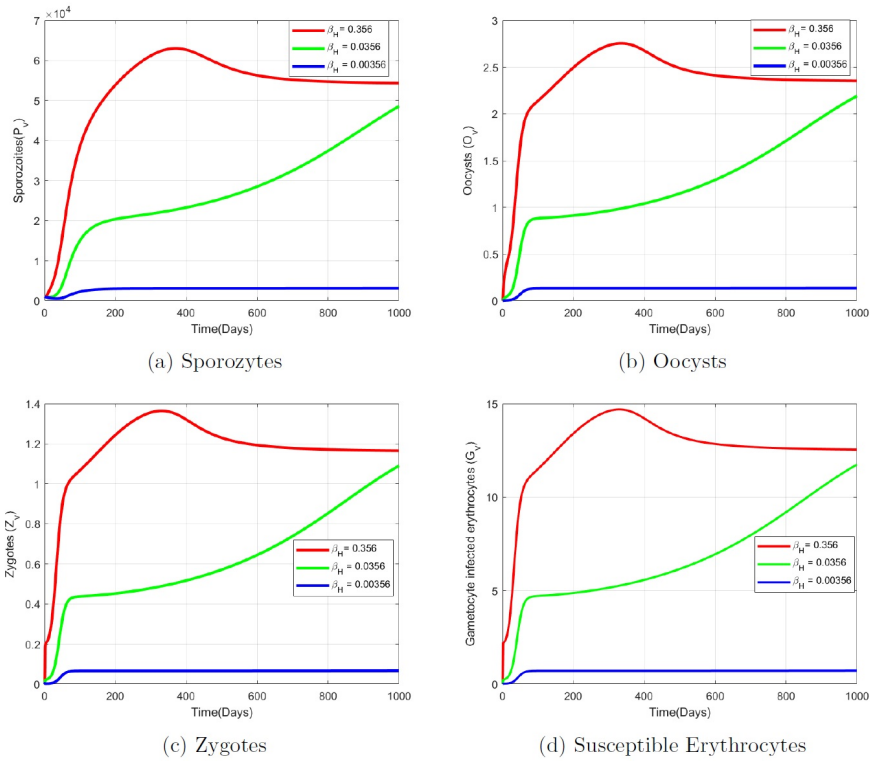


(c) Merozoites infected erythrocytes (d) Susceptible Erythrocytes

Figure 10. Shows changes in (**a**) gametocyte-infected erythtcytes (G_h), (**b**) population of merozoites (M_h), (**c**) merozoite-infected erythrocytes (R_m), and (**d**) susceptible erythrocytes (R_h) for different values of contact rate of humans with the infectious reservoir of mosquitoes β_V: $\beta_V = 0.003$, $\beta_V = 0.03$, $\beta_V = 0.3$.

Figure 11 shows changes in (a) sporozytes (P_v), (b) oocysts (O_v), (c) zygotes (Z_v), and (d) gametocyte-infected erythrocytes (G_v) for different values of the contact rate of humans with the infectious reservoir of mosquitoes β_V: $\beta_V = 0.003$, $\beta_V = 0.03$, $\beta_V = 0.3$. The results show that as the contact rate of humans with the infectious reservoir of mosquitoes β_V increases, there is also a significant increase in malaria parasite load at the within-mosquito scale. This also makes sense because the malaria parasite has no replication cycle at the within-mosquito scale. As a result, the malaria parasite load increase at the within-mosquito scale is determined more by the super-infection process of the within-mosquito scale.

Figure 12 shows changes in (a) sporozytes (P_v), (b) oocysts (O_v), (c) zygotes (Z_v), and (d) gametocyte-infected erythrocytes (G_v) for different values of the contact rate of mosquitoes with the infectious reservoir of humans β_H: $\beta_H = 0.00356$, $\beta_H = 0.0356$, $\beta_H = 0.356$. The results show that as the contact rate of mosquitoes with the infectious reservoir of humans β_H increases, there is a significant increase in malaria parasite load at the within-mosquito scale. This makes sense because the malaria parasite has no replication cycle at the within-mosquito scale. As a result, the malaria parasite load increase at the within-mosquito scale is determined more by the super-infection process of the within-mosquito scale.



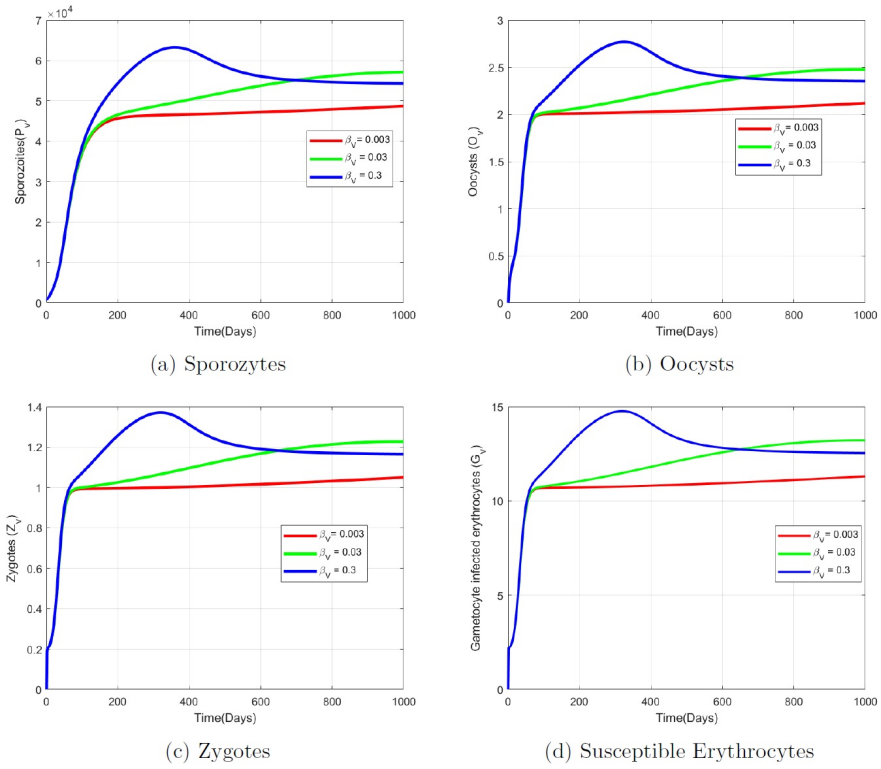
(a) Sporozytes (b) Oocysts

(c) Zygotes (d) Susceptible Erythrocytes

Figure 11. Shows changes in (**a**) sporozytes (P_v), (**b**) oocysts (O_v), (**c**) zygotes (Z_v), and (**d**) gametocyte-infected erythrocytes (G_v) for different values of contact rate of mosquitoes with the infectious reservoir of humans β_H: $\beta_H = 0.00356$, $\beta_H = 0.0356$, $\beta_H = 0.356$.

Overall, all these numerical results show that unlike single-scale models of the pathogen-centred disease system form [30], which only consider the transmission process in malaria disease system dynamics, all four disease processes, which include [a.] the infection or super-infection by the pathogen process, [b.] the pathogen replication process, [c.] the pathogen excretion or shedding process, and [d.] the pathogen transmission process, that occur at the different scales; that is, the macroscale and microscale, of the pathogen-centred disease system form of malaria disease influence each in a reciprocal way for this disease system form. However, like all other modelling approaches, the process-based multiscale for malaria disease presented in this manuscript has its limitations. Further work carried out to improve the multiscale will require validation of the process-based

multiscale model of the malaria disease system to account for uncertainties in data (clinical, experimental, demographic, and epidemiological) at both the microscale and microscale, as well as at the different temporal scales. The challenge is that there are no simple rules to follow when validating multiscale models of infectious disease dynamics. The parameters were not derived from a single epidemic situation. The demographic and epidemiology represent a general epidemic for developing countries. Therefore, the multiscale model presented models a general malaria epidemic situation for developing countries.



(a) Sporozytes (b) Oocysts

(c) Zygotes (d) Susceptible Erythrocytes

Figure 12. Shows changes in (**a**) sporozytes (P_v), (**b**) oocysts (O_v), (**c**) zygotes (Z_v), and (**d**) gametocyte-infected erythrocytes (G_v) for different values of contact rate of humans with the infectious reservoir of mosquitoes β_V: $\beta_V = 0.003$, $\beta_V = 0.03$, $\beta_V = 0.3$.

8. Discussion and Conclusions

The universal theory for multiscale modelling of infectious disease dynamics, which states that, for every host–pathogen interaction that results in an infectious disease system, there is no privileged or absolute scale of a disease system form that would determine the dynamics of the infectious disease system, only interactions between the scales of a level of organisation of the pathogen-centred disease system form and the scales of the corresponding levels of organisation of the host-centred disease system form, represents a historic opportunity to transform the way that we study the multiscale dynamics of infectious disease systems. It provides a wholly new paradigm for the multiscale modelling of infectious disease using mechanism-based multiscale models and process-based multiscale models. This new scientific theory revises and extends the replication-transmission relativity theory for the multiscale modelling of infectious disease dynamics [1] in a radical way and has great potential to transform mainstream thinking about the multiscale modelling of infectious systems. This is achieved by making possible the prospect that future progress in answering control, elimination, and even eradication questions of infectious disease systems is established on sound theoretical foundations using multiscale modelling methods. The theory explains the fact that an infectious disease system admits two different disease system form representations, which are the pathogen-centred disease system form and the host-centred disease system form. These two different disease system forms are considered to be mutually

exclusive and complementary in their description of the multiscale dynamics of infectious disease systems. However, this scientific theory, as a conceptual breakthrough, is yet to reach its full potential in terms of scale integration and heuristic knowledge production once the mathematical and computational methods for the development of mechanism-based multiscale models of the host-centred disease system forms are fully established. Therefore, the research agenda for multiscale modelling as a complex systems science approach for the study of infectious disease dynamics in the coming years should place a greater emphasis on establishing the mathematical and computational methods for the development of mechanism-based multiscale models of the host-centred disease system form. We foresee the development of mechanism-based multiscale models of the host damage level and the biodiversity change level of the host-centred disease system form as grand challenges that will introduce gaps and bottlenecks along this future research path.

In order to illustrate the partial progress that has been achieved due to these grand challenges that introduce gaps and bottlenecks in the application of the universal theory for the multiscale modelling of infectious disease dynamics, we presented a coupled multiscale model of the pathogen-centred disease system form of a malaria disease system. For the pathogen-centred disease system form of the malaria disease system, the findings suggest that there are important medical planning consequences at the microscale to consider during the processes of epidemiological planning at the macroscale and vice versa in that a treatment that cures a patient of malaria at the microscale is equally good for both the patient and the general public because this patient no longer possesses a transmission risk for the malaria parasite towards both humans and mosquitoes at the macroscale.

Author Contributions: Conceptualization, W.G. methodology, W.G.; software, K.M.; validation, W.G. and K.M.; formal analysis, W.G.; investigation, K.M.; resources, W.G.; data curation, K.M.; writing—original draft preparation, W.G.; writing—review and editing, W.G. and K.M.; visualization, K.M.; supervision, W.G.; project administration, W.G.; funding acquisition, W.G. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The authors declare that the data supporting the findings of this study are available within the paper.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A. Derivation of the Process-Based Multiscale Model of the Pathogen-Centred Disease System Form of Malaria Disease System as an Example

The derivation of the process-based multiscale model of the pathogen-centred disease system form of a malaria disease system is an extension of a previously derived single-scale malaria model [30] and a previously derived coupled multiscale model of a malaria disease system [11]. Based on the taxonomic categorisation of process-based multiscale models into five main categories, which was first established in [2,36] and discussed further in this article in Section 3.2 as part of the revision of the replication-transmission relativity theory [1], coupled multiscale models are established by integrating multiscale models from the other four categories of multiscale models of the pathogen-centred disease system form. The coupled multiscale model in [11] of the malaria disease system was established by integrating a nested multiscale at the whole human level with an embedded multiscale model at the whole mosquito level. However, in this article, the coupled multiscale model is developed by integrating an embedded multiscale model at the whole human level with another embedded multiscale model at the whole mosquito level. This is because super-infection can occur in both the mosquito host and the human host. In an embedded multiscale model, the macroscale influences the microscale through super-infection; that is, repeated infection before the host recovers from the initial infectious episode [37]. From a mathematical point of view, the macroscale influences the microscale through

macroscale variables and parameters in an embedded multiscale model [37]. However, in a nested multiscale, the macroscale influences the microscale through initial infective inoculum [1]. Mathematically, this means that the macroscale influences the microscale through initial conditions [7]. In the article [11], the derivation of the coupled multiscale model of the pathogen-centred disease system form of the malaria disease system was not fully presented, including its transformation from a multiscale model of scale order two to a multiscale of scale order one. In what follows, details of the derivation of the coupled multiscale model of the pathogen-centred disease system form of a malaria disease system are fully presented for the first time as a four-stage process as follows.

Appendix A.1. Stage I: Single-Scale Sub-models of the Process-Based Multiscale Model of the Pathogen-Centred Disease System Form of Malaria Disease System

At this stage, we present the derivation of the four single-scale sub-models of the pathogen-centred disease system form of a malaria disease system based on [11,30].

[a.] **The between-human scale sub-model**: The development of a single-scale malaria sub-model at the macroscale of the whole human level of organisation of the pathogen-centred disease system form of a malaria disease system based on [30] involves establishing a new variable called community pathogen load $P_V(\tau)$. For the whole human level of organisation, the community pathogen load $P_V(\tau)$ is the community sporozoite load. This community sporozoite load $P_V(\tau)$ is a measure of the total infectious reservoir of mosquitoes in the community; that is, an aggregate population-level biomarker of a community's sporozoite burden over a specific time period [11]. It is a useful metric for assessing the overall impact of malaria health interventions targeted at the mosquito vector or the uptake of malaria interventions targeted at the mosquito vector and quantifying their impact on the transmission of malaria from mosquitoes to humans as [30]: [i.] an indicator of a community's level of infectiousness and transmission probability of malaria to humans, [ii.] a measure of the effectiveness of malaria interventions targeted at the mosquito vector, and [iii.] a proximal maker of malaria incidence among mosquitoes and their potential to propagate malaria to humans. Then, the single-scale malaria sub-model becomes an SIPS; that is, susceptible human hosts $S_H(\tau)$, infected human hosts $I_H(\tau)$, community sporozoite load $P_V(\tau)$, and susceptible human hosts $S_H(\tau)$, as follows:

$$\begin{cases} 1.\ \frac{dS_H(\tau)}{d\tau} = \widetilde{\Lambda}_H - \frac{\widetilde{\beta}_V P_V(\tau) S_H(\tau)}{P_0 + P_V(\tau)} - \widetilde{\mu}_H S_H(\tau) + \widetilde{\gamma}_H I_H(\tau), \\ 2.\ \frac{dI_H(\tau)}{d\tau} = \frac{\widetilde{\beta}_V P_V(\tau) S_H(\tau)}{P_0 + P_V(\tau)} - \left[\widetilde{\mu}_H + \widetilde{\gamma}_H + \widetilde{\delta}_H\right] I_H(\tau), \\ 3.\ \frac{dP_V(\tau)}{d\tau} = N_v \widetilde{\alpha}_v I_V(\tau) - \widetilde{\alpha}_V P_V(\tau). \end{cases} \tag{A1}$$

The three variables of the between-human host scale sub-model (A1)

$$\left[S_H(\tau), I_H(\tau), P_V(\tau)\right], \tag{A2}$$

vary at slow time scale τ. The units of the seven between-human host scale sub-model parameters

$$\left[\widetilde{\Lambda}_H, \widetilde{\beta}_V, \widetilde{\mu}_H, \widetilde{\delta}_H, \widetilde{\alpha}_v, \widetilde{\gamma}_H, \widetilde{\alpha}_H\right], \tag{A3}$$

are per annum and have meanings as defined in Table A1. As indicated in [30], the expression

$$\lambda_V(P_V(\tau)) = \frac{P_V(\tau)}{P_0 + P_V(\tau)}, \tag{A4}$$

in the sub-model (A1) is the probability that a random bite by a mosquito vector in a particular community with a community sporozoite load $P_V(\tau)$ will infect the human

host with malaria in that community. Since the transmission rate of malaria (A4), which we also refer to as the infectivity response function of malaria, is a probability, it can be modelled by any function $\lambda_V(P_V(\tau))$ with the specification that $\lambda_V : [0, \infty) \longrightarrow [0, 1]$. Further, since the function $\lambda_V(P_V(\tau))$ is a probability, it must have the following properties [30]:

[i.] Property I: The probability of infection vanishes in the absence of pathogen [i.e., $\lambda_V(0) = 0$] and approaches 1 as the community sporozoite load becomes large [i.e., $\lim_{P_V(\tau)\to\infty} \lambda_V(P_V(\tau)) = 1$];

[ii.] Property II: The probability of infection $\lambda_V(P_V(\tau))$ increases with the community sporozoite load $P_V(\tau)$; that is, $\lambda'_V(P_V(\tau)) > 0$, where the prime denotes the derivative with respect to the argument.

Therefore, in the sub-model (A1), any function, $\lambda_V(P_V(\tau))$, that satisfies the above two properties can be used in place of the one derived from the Holling type I functional form (A4).

Table A1. Between-host (human and mosquito) parameter values and their description.

Parameter	Description	Parameter Value and Range	Units	Source/Rational
α_V	Rate of elimination of community sporozoite load	0.9 [0.09–0.99]	day^{-1}	Variable
Λ_V	Rate of supply of susceptible mosquitoes	6000 [5000–7000]	day^{-1}	Variable
β_V	Contact rate of humans with the infectious reservoir of mosquitoes	0.2 [0.1–0.5]	day^{-1}	[38]
G_0	Half-saturation constant for community gametocyte load	5×10^8 [1×10^8–10×10^8]	day^{-1}	Variable
μ_V	Natural death rate of mosquitoes	0.12 [0.033–0.3]	day^{-1}	[39,40]
δ_V	Infection-induced death rate of mosquitoes	0.00000426 [0.00000426–0.00000533]	day^{-1}	Assumed
Λ_H	Rate of supply of susceptible humans	1000 [1000–2000]	day^{-1}	Assumed
β_H	Contact rate of mosquitoes with the infectious reservoir of humans	0.3 [0.1–0.5]	day^{-1}	[41]
α_H	Rate of elimination of community gametocyte load	0.0000913 [0.000467–0.000274]	day^{-1}	Variable
μ_H	Natural death rate of humans	0.00004 [0.00001–0.00008]	day^{-1}	[39]
γ_H	Natural recovery rate of humans	0.25 [0.1–0.5]	day^{-1}	Variable
P_0	Half-saturation constant for community sporozoite load	1×10^8 [1×10^7–5×10^8]	day^{-1}	Variable
δ_H	Disease-induced death rate of humans	0.0027 [0.0001–0.5]	day^{-1}	Assumed
Φ_H	Proportion of new infected humans in the total infected human population	0.001 [0.0001–0.5]	Number	Assumed
Φ_V	Proportion of new infected mosquito vectors in the total infected mosquito vector population	0.002 [0.0001–0.5]	Number	Assumed

[b.] **The between-mosquito scale sub-model**: Similarly, following [30], the community pathogen load $G_H(\tau)$ for the whole mosquito level of organisation of the pathogen-centred disease system form of the malaria disease system is the community gametocyte load. This community gametocyte load $G_H(\tau)$ is a measure of the total infectious reservoir of humans in the community; that is, an aggregate population-level biomarker of a community's gametocyte burden over a specific time period [11]. It is a useful metric for assessing the overall impact of malaria health interventions targeted at the human host or the uptake of malaria interventions targeted at the human host and quantifying their impact on the transmission of malaria from humans to mosquitoes as [30]: [i.] an indicator of a community's level of infectiousness and transmission probability of malaria to mosquitoes, [ii.] a measure of the effectiveness of malaria interventions targeted at the whole human host scale, and [iii.] a proximal maker of malaria incidence among humans and their potential to propagate malaria to mosquito vectors. Then, the single-scale malaria sub-model becomes an SIP; that

is, susceptible mosquito hosts $S_V(\tau)$, infected mosquito hosts $I_V(\tau)$, and community gametocyte load $G_H(\tau)$, as follows:

$$\begin{cases} 1.\ \frac{dS_V(t)}{d\tau} = \widetilde{\Lambda}_V - \frac{\widetilde{\beta}_H G_H(\tau) S_V(\tau)}{G_0 + G_H(\tau)} - \widetilde{\mu}_V S_V(\tau), \\ 2.\ \frac{dI_V(t)}{d\tau} = \frac{\widetilde{\beta}_H G_H(\tau) S_V(\tau)}{G_0 + G_H(\tau)} - \left[\widetilde{\mu}_V + \widetilde{\delta}_V\right] I_V(\tau), \\ 3.\ \frac{dG_H(\tau)}{d\tau} = N_h \widetilde{\alpha}_h I_H(\tau) - \widetilde{\alpha}_H G_H(\tau). \end{cases} \tag{A5}$$

The three variables of the between-mosquito host scale sub-model (A5)

$$\left[S_V(\tau), I_V(\tau), G_H(\tau)\right], \tag{A6}$$

vary at slow time scale τ. The units of the six between-mosquito host scale sub-model parameters

$$\left[\widetilde{\Lambda}_V, \widetilde{\beta}_H, \widetilde{\mu}_V, \widetilde{\delta}_V, \widetilde{\alpha}_h, \widetilde{\alpha}_V\right], \tag{A7}$$

are per annum and also have meanings as defined in Table A1.
Similarly, the expression

$$\lambda_H(G_H(\tau)) = \frac{G_H(\tau)}{G_0 + G_H(\tau)}, \tag{A8}$$

in the sub-model (A5) is the probability that a random bite of a human host by a mosquito vector in a particular community with a community gametocyte load $G_H(\tau)$ will infect the mosquito host with malaria in that community. Since the transmission rate of malaria (A8), which we also refer to as the infectivity response function of malaria, is a probability, it must have the specification that $\lambda_H : [0, \infty) \longrightarrow [0, 1]$. Equally, since the function $\lambda_H(G_H(\tau))$ is a probability, it must have the following properties [30]:

[i.] Property I: The probability of infection vanishes in the absence of pathogen [i.e., $\lambda_H(0) = 0$] and approaches 1 as the community gametocyte load becomes large [i.e., $\lim_{G_H(\tau)\to\infty} \lambda_H(G_H(\tau)) = 1$];

[ii.] Property II: The probability of infection $\lambda_H(G_H(\tau))$ increases with the community gametocyte load $G_H(\tau)$; that is, $\lambda'_H(G_H(\tau)) > 0$, where the prime denotes the derivative with respect to the argument.

Therefore, in the sub-model (A5), any function, $\lambda_H(G_H(\tau))$, that satisfies the above two properties can be used in place of those derived from the Holling type I functional form (A8).

[c.] **The within-human scale sub-model**: Following [11], the within-human scale single-scale sub-model with variables $R_h(t)$—susceptible erythrocytes (red blood cells); $R_m(t)$—merozoite-infected erythrocytes; $M_h(t)$—merozoites; and $G_h(t)$—gametocyte-infected erythrocytes becomes:

$$\begin{cases} 1.\ \frac{dR_h(t)}{dt} &= \Lambda_h - \beta_h R_h(t) M_h(t) - \mu_b R_h(t), \\ 2.\ \frac{dR_m(t)}{dt} &= (1 - \phi_h)\beta_h R_h(t) M_h(t) - \alpha_m R_m(t), \\ 3.\ \frac{dM_h(t)}{dt} &= N_m \alpha_m R_m(s) - \mu_m M_h(t), \\ 4.\ \frac{dG_h(t)}{dt} &= \phi_h \beta_h R_h(t) M_h(t) - \left[\alpha_h + \mu_h\right] G_h(t). \end{cases} \tag{A9}$$

The four variables of the within-human scale sub-model (A9)

$$\left[R_h(t), R_m(t), M_h(t), G_h(t)\right], \tag{A10}$$

vary at fast time scale t. The units of the eight within-human scale sub-model parameters

$$\left[\Lambda_h, \beta_h, \mu_b, \alpha_m, N_m, \mu_m, \alpha_h, \mu_h\right], \tag{A11}$$

are per day and have meanings as defined in Table A2.

Table A2. Within-mosquito and within-human parameter values and their description.

Parameter	Description	Parameter Value and Range	Units	Source/Rational
α_g	Rate at which gametocyte-infected erythrocytes burst	96 [90–100]	day^{-1}	[42]
Λ_v	Rate of uptake of gametocytes through super-infection of mosquito	300 [100–300]	day^{-1}	Variable
μ_g	Death rate of gametocytes	0.0625 [0.0326–0.0725]	day^{-1}	[42]
N_g	Number of gametes produced per gametocyte-infected erythrocyte	2 [1–3]	day^{-1}	Estimated
α_s	Fertilisation rate of gametes	0.08 [0.01–0.2]	$no^{-1}day^{-1}$	[42]
μ_s	Natural decay rate of gametes	58.0 [40–129]	day^{-1}	[42]
α_z	Rate at which zygotes develop into oocysts	0.4240 [0.01–0.05]	day^{-1}	[43]
μ_z	Natural decay rate of zygotes	1 [1–4]	day^{-1}	[42]
α_k	Bursting rate of oocysts to produce sporozoites	0.2 [0.0–1.0]	day^{-1}	Variable
μ_k	Natural decay rate of oocysts	0.01 [0.071–0.143]	day^{-1}	[44]
N_k	Number of sporozoites produced per bursting oocyst	3000 [1000–10,000]	day^{-1}	[42]
α_v	Rate at which sporozoites become infectious to humans	0.025 [0.167–1.00]	day^{-1}	[42]
μ_v	Natural decay rate of sporozoites	0.0001 [0.0001–0.0]	day^{-1}	[42]
Λ_h	Rate of supply of susceptible red blood cells (erythrocytes)	200 [100–300]	day^{-1}	[45]
β_h	Infection rate of erythrocytes by free merozoites	0.1 [2×10^{-9}–0.2]	day^{-1}	[39,46]
μ_b	Natural decay rate of susceptible erythrocytes	0.0083 [0.006–0.01]	day^{-1}	[46]
ϕ_h	Proportion of gametocyte-infected erythrocytes	0.1 [0.1–0.5]	Number	Assumed
μ_m	Natural decay rate of free merozoites	0.001 [0.001–0.5]	day^{-1}	[39,46]
α_m	Rate at which erythrocytes burst to produce merozoites	0.5 [0.1–7.0]	day^{-1}	[46,47]
N_m	Number of merozoites produced per bursting erythrocyte	16 [10–30]	day^{-1}	[46]
α_h	Rate at which gametocytes develop and become infectious	0.02 [0.01–0.9]	day^{-1}	[40]
μ_h	Natural decay rate of gametocyte-infected erythrocytes within infected humans	0.0625 [0.0600–0.0625]	day^{-1}	[40]

1. **The within-mosquito scale sub-model**: Similarly, following [11], the within-mosquito scale sub-model with variables $G_v(t)$—gametocyte infected erythrocytes; $G_m(t)$—sex cells called gametes; $Z_v(t)$—zygotes; $O_v(t)$—oocysts; and $P_v(t)$—sporozoites becomes:

$$\begin{cases} 1. \ \frac{dG_v(t)}{dt} = -\left[\alpha_g + \mu_g\right] G_v(t), \\ 2. \ \frac{dG_m(t)}{dt} = N_g \alpha_g G_v(t) - \left[\alpha_s + \mu_s\right] G_m(t), \\ 3. \ \frac{dZ_v(t)}{dt} = \phi_s \alpha_s G_m(t) - \left[\alpha_z + \mu_z\right] Z_v(t), \\ 4. \ \frac{dO_v(t)}{dt} = \alpha_z Z_v(t) - \left[\alpha_k + \mu_k\right] O_v(t), \\ 5. \ \frac{dP_v(t)}{dt} = N_k \alpha_k O_v(t) - \left[\alpha_v + \mu_v\right] P_v(t). \end{cases} \tag{A12}$$

The main difference between the within-mosquito scale sub-model in [11] and the sub-model (A12) is that this sub-model does not incorporate super-infection in the mosquito vector. The five variables of the within-mosquito scale sub-model given by (A12)

$$\left[G_v(t), G_m(t), Z_v(t), O_v(t), P_v(t)\right], \tag{A13}$$

vary at fast time scale t. The units of the ten within-mosquito scale sub-model parameters

$$\left[\alpha_g, \mu_g, \alpha_p, \mu_s, \alpha_s, \mu_z, \alpha_z, \mu_k, \alpha_k, \mu_v, \alpha_v\right], \tag{A14}$$

are per day and also have meanings as defined in Table A2.

Appendix A.2. Stage II: Integrating the Sub-models into a Single Process-Based Multiscale Model of the Pathogen-Centred Disease System Form of Malaria Disease System of Scale Order Two

The four sub-models of the pathogen-centred disease system form of the malaria disease system can be integrated into a coupled multiscale model by up-scaling individual infectiousness $[P_v(t), G_h(t)]$ to population infectiousness $[P_V(\tau), G_H(\tau)]$ as illustrated in Figure 3. This is achieved by replacing N_v with $P_v(t)$ in the between-human scale submodel (A1) and N_h with $G_h(t)$ in the between-mosquito scale submodel (A5). The integrated process-based multiscale model of the pathogen-centred disease system form of the malaria disease system is given by (A15) as follows:

$$\begin{cases}
1.\ \frac{dS_H(\tau)}{d\tau} = \widetilde{\Lambda}_H - \frac{\widetilde{\beta}_V P_V(\tau) S_H(\tau)}{P_0 + P_V(\tau)} - \widetilde{\mu}_H S_H(\tau) + \widetilde{\gamma}_H I_H(\tau), \\
2.\ \frac{dI_H(\tau)}{d\tau} = \frac{\widetilde{\beta}_V P_V(\tau) S_H(\tau)}{P_0 + P_V(\tau)} - \left[\widetilde{\mu}_H + \widetilde{\gamma}_H + \widetilde{\delta}_H\right] I_H(\tau), \\
3.\ \frac{dP_V(\tau)}{d\tau} = P_v(t)\widetilde{\alpha}_v I_V(\tau) - \widetilde{\alpha}_V P_V(\tau), \\
4.\ \frac{dS_V(\tau)}{d\tau} = \widetilde{\Lambda}_V - \frac{\widetilde{\beta}_H G_H(\tau) S_V(\tau)}{G_0 + G_H(\tau)} - \widetilde{\mu}_V S_V(\tau), \\
5.\ \frac{dI_V(\tau)}{d\tau} = \frac{\widetilde{\beta}_H G_H(\tau) S_V(\tau)}{G_0 + G_H(\tau)} - \left[\widetilde{\mu}_V + \widetilde{\delta}_V\right] I_V(\tau), \\
6.\ \frac{dG_H(\tau)}{d\tau} = G_h(t)\widetilde{\alpha}_h I_H(\tau) - \widetilde{\alpha}_H G_H(\tau), \\
7.\ \frac{dG_v(t)}{dt} = -\left[\alpha_g + \mu_g\right] G_v(t), \\
8.\ \frac{dG_m(t)}{dt} = N_g \alpha_g G_v(t) - \left[\alpha_s + \mu_s\right] G_m(t), \\
9.\ \frac{dZ_v(t)}{dt} = \phi_s \alpha_s G_m(t) - \left[\alpha_z + \mu_z\right] Z_v(t), \\
10.\ \frac{dO_v(t)}{dt} = \alpha_z Z_v(t) - \left[\alpha_k + \mu_k\right] O_v(t), \\
11.\ \frac{dP_v(t)}{dt} = N_k \alpha_k O_v(t) - \left[\alpha_v + \mu_v\right] P_v(t), \\
12.\ \frac{dR_h(t)}{dt} = \Lambda_h - \beta_h R_h(t) M_h(t) - \mu_b R_h(t), \\
13.\ \frac{dR_m(t)}{dt} = (1 - \phi_h)\beta_h R_h(t) M_h(t) - \alpha_m R_m(t), \\
14.\ \frac{dM_h(t)}{dt} = N_m \alpha_m R_m(t) - \mu_m M_h(t), \\
15.\ \frac{dG_h(t)}{dt} = \phi_h \beta_h R_h(t) M_h(t) - \left[\alpha_h + \mu_h\right] G_h(t).
\end{cases} \tag{A15}$$

This is a coupled multiscale model of scale order two that integrates a nested multiscale model at the whole human level with another nested multiscale model at the whole mosquito level.

Appendix A.3. Stage III: Scale Order Reduction of the Coupled Multiscale Model of the Pathogen-Centred Disease System Form of Malaria Disease System from a Multiscale Model of Scale Order Two to a Multiscale Model of Scale Order One

In general, the scales; that is, the microscale and the macroscale, of a level of organisation of the pathogen-centred disease form are hierarchically organised in both space and time. Therefore, any process-based multiscale model of the pathogen-centred disease form that incorporates the hierarchy in spatial scales of the microscale and the macroscale and the hierarchy in the times scales of the processes that occur at the microscale and the macroscale, is said to be a process-based multiscale model of scale order two, which is the highest possible scale order for such process-based multiscale models. The scale order of two of a process-based multiscale model can be reduced to scale order one, which is the lowest possible scale order of such process-based multiscale models, by re-casting the multiscale model into a regular perturbation problem or singular perturbation problem [48] and then performing a slow and fast time scale analysis. This reduction in scale order of a process-based multiscale model relies on there being a dimensionless and relatively small parameter ϵ in the process-based multiscale model such that $0 < \epsilon \ll 1$. In such a reduced scale order process-based multiscale model, which does not incorporate the hierarchy of time scales of the processes that occur at the microscale and macroscale, disease processes at both the microscale and the macroscale occur at the same time scale. For an example of a scale order reduction of a process-based multiscale of scale order two to a process-based multiscale of scale order one, see [11] for the pathogen-centred disease system form of a malaria disease system by re-casting the process-based multiscale model into a singular perturbation problem. In this study, the scale order reduction is achieved by recasting the process-based multiscale model system (A15) into a regular perturbation problem by expressing the slow time scale of the processes at the macroscale and the fast time scale of the processes at the microscale in terms of each other using the relationship $\tau = \epsilon t$, where $0 < \epsilon \ll 1$ and ϵ is a constant highlighting the fast time scale t of the within-host scale sub-model compared to the slow time scale τ of the between-host scale sub-model. By performing a fast–slow time scale analysis of the regular perturbation problem, the multiscale model of scale order two (A15) becomes a multiscale model of scale order one (A16) as follows.

$$
\begin{cases}
1.\ \frac{dS_H(t)}{dt} = \epsilon\widetilde{\Lambda}_H - \frac{\epsilon\widetilde{\beta}_V P_V(t) S_H(t)}{P_0+P_V(t)} - \epsilon\widetilde{\mu}_H S_H(t) + \epsilon\widetilde{\gamma}_H I_H(t), \\
2.\ \frac{dI_H(t)}{dt} = \frac{\epsilon\widetilde{\beta}_V P_V(t) S_H(t)}{P_0+P_V(t)} - \left[\epsilon\widetilde{\mu}_H + \epsilon\widetilde{\gamma}_H + \epsilon\widetilde{\delta}_H\right] I_H(t), \\
3.\ \frac{dP_V(t)}{dt} = P_v(t)\epsilon\widetilde{\alpha}_v I_V(t) - \epsilon\widetilde{\alpha}_V P_V(t), \\
4.\ \frac{dS_V(t)}{dt} = \epsilon\widetilde{\Lambda}_V - \frac{\epsilon\widetilde{\beta}_H G_H(t) S_V(t)}{G_0+G_H(t)} S_V(t) - \epsilon\widetilde{\mu}_V, \\
5.\ \frac{dI_V(t)}{dt} = \frac{\epsilon\widetilde{\beta}_H G_H(t) S_V(t)}{G_0+G_H(t)} - \left[\epsilon\widetilde{\mu}_V + \epsilon\widetilde{\delta}_V\right] I_V(t), \\
6.\ \frac{dG_H(\tau)}{d\tau} = G_h(t)\epsilon\widetilde{\alpha}_h I_H(\tau) - \epsilon\widetilde{\alpha}_H G_H(\tau), \\
7.\ \frac{dG_v(t)}{dt} = -\left[\alpha_g + \mu_g\right] G_v(t), \\
8.\ \frac{dG_m(t)}{dt} = N_g\alpha_g G_v(t) - \left[\alpha_s + \mu_s\right] G_m(t), \\
9.\ \frac{dZ_v(t)}{dt} = \phi_s\alpha_s G_m(t) - \left[\alpha_z + \mu_z\right] Z_v(t), \\
10.\ \frac{dO_v(t)}{dt} = \alpha_z Z_v(t) - \left[\alpha_k + \mu_k\right] O_v(t), \\
11.\ \frac{dP_v(t)}{dt} = N_k\alpha_k O_v(t) - \left[\alpha_v + \mu_v\right] P_v(t), \\
12.\ \frac{dR_h(t)}{dt} = \Lambda_h - \beta_h R_h(t) M_h(t) - \mu_b R_h(t), \\
13.\ \frac{dR_m(t)}{dt} = (1-\phi_h)\beta_h R_h(t) M_h(t) - \alpha_m R_m(t), \\
14.\ \frac{dM_h(t)}{dt} = N_m\alpha_m R_m(t) - \mu_m M_h(t), \\
15.\ \frac{dG_h(t)}{dt} = \phi_h\beta_h R_h(t) M_h(t) - \left[\alpha_h + \mu_h\right] G_h(t).
\end{cases}
\tag{A16}
$$

In (A16), the process-based multiscale model is re-cast as a regular perturbation problem. For the process-based multiscale model (A16), choose $\epsilon = 1/365$ so that

$$
\begin{cases}
\epsilon\widetilde{\Lambda}_H = \frac{\widetilde{\Lambda}_H}{365} = \Lambda_H, & \epsilon\widetilde{\beta}_H = \frac{\widetilde{\beta}_H}{365} = \beta_H, \\
\epsilon\widetilde{\mu}_H = \frac{\widetilde{\mu}_H}{365} = \mu_H, & \epsilon\widetilde{\delta}_H = \frac{\widetilde{\delta}_H}{365} = \delta_H, \\
\epsilon\widetilde{\Lambda}_V = \frac{\widetilde{\Lambda}_V}{365} = \Lambda_V, & \epsilon\widetilde{\beta}_V = \frac{\widetilde{\beta}_V}{365} = \beta_V, \\
\epsilon\widetilde{\mu}_V = \frac{\widetilde{\mu}_H}{365} = \mu_V, & \epsilon\widetilde{\delta}_V = \frac{\widetilde{\delta}_H}{365} = \delta_V, \\
\epsilon\widetilde{\alpha}_h = \frac{\widetilde{\alpha}_h}{365} = \alpha_h, & \epsilon\widetilde{\alpha}_v = \frac{\widetilde{\alpha}_v}{365} = \alpha_v, \\
\epsilon\widetilde{\alpha}_V = \frac{\widetilde{\alpha}_V}{365} = \alpha_V, & \epsilon\widetilde{\alpha}_H = \frac{\widetilde{\alpha}_H}{365} = \alpha_H \\
\epsilon\widetilde{\gamma}_H = \frac{\widetilde{\gamma}_H}{365} = \gamma_H.
\end{cases}
\tag{A17}
$$

The thirteen between-host scale parameters given by (A17) of the coupled multiscale model (A16) have units of per annum. The effect of multiplying by 1/365 is that the transformed new parameters

$$\left[\Lambda_H, \beta_V, \mu_H, \delta_H, \Lambda_V, \beta_H, \mu_V, \delta_V, \alpha_h, \gamma_H, \alpha_H, \alpha_v, \alpha_h\right]. \tag{A18}$$

now have units of per day. These units are the same as the units for the within-host scale parameters. The coupled multiscale model of the pathogen-centred disease system form of the malaria disease system of scale order two (A15) becomes a coupled multiscale model of scale order one (A19) as follows:

$$\begin{cases}
1.\ \frac{dS_H(t)}{dt} = \Lambda_H - \frac{\beta_V P_V(t) S_H(t)}{P_0 + P_V(t)} - \mu_H S_H(t) + \gamma_H I_H(t), \\
2.\ \frac{dI_H(t)}{dt} = \frac{\beta_V P_V(t) S_H(t)}{P_0 + P_V(t)} - \left[\mu_H + \gamma_H + \delta_H\right] I_H(t), \\
3.\ \frac{dP_V(t)}{dt} = P_v(t)\alpha_v I_V(t) - \alpha_V P_V(t), \\
4.\ \frac{dS_V(t)}{dt} = \Lambda_V - \frac{\beta_H G_H(t) S_V(t)}{G_0 + G_H(t)} - \mu_V S_V(t), \\
5.\ \frac{dI_V(t)}{dt} = \frac{\beta_H G_H(t) S_V(t)}{G_0 + G_H(t)} - \left[\mu_V + \delta_V\right] I_V(t), \\
6.\ \frac{dG_H(t)}{dt} = G_h(t)\alpha_h I_H(t) - \alpha_H G_H(t), \\
7.\ \frac{dG_v(t)}{dt} = -\left[\alpha_g + \mu_g\right] G_v(t), \\
8.\ \frac{dG_m(t)}{dt} = N_g \alpha_g G_v(t) - \left[\alpha_s + \mu_s\right] G_m(t), \\
9.\ \frac{dZ_v(t)}{dt} = \phi_s \alpha_s G_m(t) - \left[\alpha_z + \mu_z\right] Z_v(t), \\
10.\ \frac{dO_v(t)}{dt} = \alpha_z Z_v(t) - \left[\alpha_k + \mu_k\right] O_v(t), \\
11.\ \frac{dP_v(t)}{dt} = N_k \alpha_k O_v(t) - \left[\alpha_v + \mu_v\right] P_v(t), \\
12.\ \frac{dR_h(t)}{dt} = \Lambda_h - \beta_h R_h(t) M_h(t) - \mu_b R_h(t), \\
13.\ \frac{dR_m(t)}{dt} = (1 - \phi_h)\beta_h R_h(t) M_h(t) - \alpha_m R_m(t), \\
14.\ \frac{dM_h(t)}{dt} = N_m \alpha_m R_m(t) - \mu_m M_h(t), \\
15.\ \frac{dG_h(t)}{dt} = \phi_h \beta_h R_h(t) M_h(t) - \left[\alpha_h + \mu_h\right] G_h(t).
\end{cases} \tag{A19}$$

Unlike the reduced scale order multiscale model (A19), scale order reduction by re-casting the process-based multiscale into a singular perturbation problem as in [11] has the disadvantage of reducing the dimension of the process-based multiscale model and therefore reducing its accuracy. For the coupled multiscale model of scale order one (A19), the dynamics at the microscale and the macroscale vary at the same time scale, t, and the parameters are also expressed in the same units, which are per day. However, the coupled multiscale (A19) can be extended to incorporate the more realistic features of super-infection in both the human host and the mosquito host; that is, repeated infection before the host recovers from the initial infectious episode. In what follows, we convert the coupled multiscale model of scale order one (A19) into a corresponding coupled multiscale model of scale order one with super-infection in both the human host and the mosquito host.

Appendix A.4. Stage IV: Extending the Coupled Multiscale Model of the Pathogen-Centred Disease System Form of Malaria Disease System by Incorporating Variable Super-Infection in Both the Mosquito Host and the Human Host

The necessary mathematical basis for incorporating super-infection in a process-based multiscale model was established in [49]. The approach involves the down-scaling and up-scaling of variables and parameters at both the within-host scale and between-host scale as illustrated in Figure 3. In the context of the process-based multiscale model of the pathogen-centred disease system form of a malaria disease system, this can be achieved as follows:

[a.] **For the Super-infection of the Human Host**: By down-scaling and up-scaling disease process variables and parameters across the microscale and the macroscale as illustrated in Figure 3, we have the following additional expressions:

[i.] *Influence of macroscale on microscale*: The influence of the between-whole mosquito scale (the macroscale for the whole mosquito level) on the within-whole human scale (the microscale for the whole human level) is modeled by down-scaling the uptake of the pathogen in the community through the infection of humans at the between-human scale at a rate $\frac{\beta_V P_V(t) S_H(t)}{P_0+P_V(t)}$ to the repeated infection of the within-human scale at a rate $\frac{\beta_V P_V(t)\left[S_H(t)-1\right]}{\left[P_0+P_V(t)\right]\Phi_H\left[I_H(t)+1\right]}$. However, this representation of super-infection is a refinement of the approach in [49] in the following way. The approach in [49] over-estimates the number of new infections, while, here, the number of new infections is assumed to be a proportion Φ_H of the existing cumulative number of infections.

[ii.] *Influence of microscale on macroscale*: The influence of the within-whole human scale (the microscale for the whole human level) on the between-whole human scale (the macroscale for the whole human level) is modeled by up-scaling the individual human excretion/shedding of the pathogen at the within-whole human scale at a rate $\alpha_h G_h$ to the between-whole mosquito scale at a rate $\left[I_H(t)+1\right]\alpha_h G_h(t)$.

[b.] **For the Super-infection of the Mosquito Host**: Equally, by down-scaling and up-scaling disease process variables and parameters across the microscale and the macroscale as illustrated in Figure 3, we have the following additional expressions:

[i.] *Influence of macroscale on microscale*: The influence of the between-whole human scale (the macroscale for the whole human level) on the within-whole mosquito scale (the microscale for the whole mosquito level) is modeled by down-scaling the uptake of the pathogen in the community through the infection of mosquitoes at the between-mosquito scale at a rate $\frac{\beta_H G_H(t) S_V(t)}{G_0+G_H(t)}$ to the repeated infection of the within-mosquito scale at a rate $\frac{\beta_H G_H(t)\left[S_V(t)-1\right]}{\left[G_0+G_H(t)\right]\Phi_V\left[I_V(t)+1\right]}$. However, this representation of super-infection is also a refinement of the approach in [49] in the following way. The approach in [49] over-estimates the number of new infections, while, here, the number of new infections is assumed to be a proportion Φ_V of the existing cumulative number of infections.

[ii.] *Influence of microscale on macroscale*: The influence of the within-whole mosquito scale (the microscale for the whole mosquito level) on the between-whole human scale (the macroscale for the whole human level) is modeled by up-scaling the individual mosquito excretion/shedding of the pathogen at the within-whole mosquito scale at a rate $\alpha_v P_v$ to the between-whole human scale at a rate $\left[I_V(t)+1\right]\alpha_v P_v(t)$.

We obtain the coupled multiscale model of scale order one (A20) of the pathogen-centred disease system form of a malaria disease system with super-infection in both the human host and the mosquito host as follows.

$$
\begin{cases}
1.\ \frac{dS_H(t)}{dt} = \Lambda_H - \frac{\beta_V P_V(t) S_H(t)}{P_0 + P_V(t)} - \mu_H S_H(t) + \gamma_H I_H(t), \\
2.\ \frac{dI_H(t)}{dt} = \frac{\beta_V P_V(t) S_H(t)}{P_0 + P_V(t)} - \left[\mu_H + \gamma_H + \delta_H\right] I_H(t), \\
3.\ \frac{dP_V(t)}{dt} = P_v(t)\alpha_v \left[I_V(t) + 1\right] - \alpha_V P_V(t), \\
4.\ \frac{dS_V(t)}{dt} = \Lambda_V - \frac{\beta_H G_H(t) S_V(t)}{G_0 + G_H(t)} - \mu_V S_V(t), \\
5.\ \frac{dI_V(t)}{dt} = \frac{\beta_H G_H(t) S_V(t)}{G_0 + G_H(t)} - \left[\mu_V + \delta_V\right] I_V(t), \\
6.\ \frac{dG_H(t)}{dt} = G_h(t)\alpha_h \left[I_H(t) + 1\right] - \alpha_H G_H(t), \\
7.\ \frac{dG_v(t)}{dt} = \frac{\beta_H G_H(t) \left[S_V(t) - 1\right]}{\left[G_0 + G_H(t)\right] \Phi_V \left[I_V(t) + 1\right]} - \left[\alpha_g + \mu_g\right] G_v(t), \\
8.\ \frac{dG_m(t)}{dt} = N_g \alpha_g G_v(t) - \left[\alpha_s + \mu_s\right] G_m(t), \\
9.\ \frac{dZ_v(t)}{dt} = \phi_s \alpha_s G_m(t) - \left[\alpha_z + \mu_z\right] Z_v(t), \\
10.\ \frac{dO_v(t)}{dt} = \alpha_z Z_v(t) - \left[\alpha_k + \mu_k\right] O_v(t), \\
11.\ \frac{dP_v(t)}{dt} = N_k \alpha_k O_v(t) - \left[\alpha_v + \mu_v\right] P_v(t), \\
12.\ \frac{dR_h(t)}{dt} = \Lambda_h - \beta_h R_h(t) M_h(t) - \mu_b R_h(t), \\
13.\ \frac{dR_m(t)}{dt} = (1 - \phi_h)\beta_h R_h(t) M_h(t) - \alpha_m R_m(t), \\
14.\ \frac{dM_h(t)}{dt} = \frac{\beta_V P_V(t) \left[S_H(t) - 1\right]}{\left[P_0 + P_V(t)\right] \Phi_H \left[I_H(t) + 1\right]} + N_m \alpha_m R_m(t) - \mu_m M_h(t), \\
15.\ \frac{dG_h(t)}{dt} = \phi_h \beta_h R_h(t) M_h(t) - \left[\alpha_h + \mu_h\right] G_h(t).
\end{cases}
\tag{A20}
$$

The study of the pathogen-centred disease system form of a malaria disease system using the coupled multiscale model (A20) is presented in Sections 5 and 6.

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