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Comparing and Contrasting Individual-Based and Continuum Models of Within-Host Tuberculosis

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Spatial structure and stochastic cellular interactions can influence outcomes of within-host tuberculosis (TB) infection, but their effects may be represented differently in discrete and continuum modelling frameworks. We develop an idealised stochastic individual-based model (IBM), based on a previously published within-host TB model, and formally derive a mechanistically related deterministic continuum counterpart from its probabilistic rules. To investigate how the two modelling approaches compare, we carry out a simulation-based comparative study between appropriately reduced versions of the two models. The two formulations showed varying degrees of agreement in qualitative clearance and non-clearance outcomes, with agreement generally stronger for non-clearance cases. Even where infection outcomes agreed, substantial differences were observed in temporal dynamics and underlying cellular behaviour. Repeated IBM realisations from the same initial configuration demonstrated additional variability arising from intrinsic stochasticity, while differences between matched continuum and IBM simulations may reflect both stochastic effects and differences in model representation. Initial spatial configuration also influenced infection outcomes across otherwise fixed model conditions. Overall, the continuum and IBM formulations provide complementary perspectives on early within-host TB dynamics, with the continuum model capturing population-level behaviour and the IBM retaining discrete interactions and fine-scale spatial heterogeneity.

Keywords: Tuberculosis; Within-host modelling; Individual-based model; Partial differential equations; Spatial modelling; Stochastic processes

Author Contributions (CRediT)

Aminat Y. Saula: Conceptualisation, Funding acquisition, Investigation, Methodology, Software, Visualisation, Writing – original draft; **Fiona R. Macfarlane:** Software; **Tommaso Lorenzi:** Conceptualisation, Investigation, Methodology, Supervision, Writing – review & editing; **Ruth Bowness:** Conceptualisation, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing.

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1 Introduction

Tuberculosis (TB), resulting from infection with *Mycobacterium tuberculosis* (*Mtb*), primarily affects the lungs, where interactions between the mycobacteria and host immune cells occur within spatially structured tissue environments (Houben et al., 2006; Marino et al., 2011). During infection, immune cells accumulate around *Mtb* to form granulomas, within which local cellular processes contribute to mycobacterial containment or persistence (Marino et al., 2011; Segovia-Juarez et al., 2004). The spatial organisation of mycobacteria and immune cells within infected tissue can shape the course of within-host infection (Segovia-Juarez et al., 2004; Pitcher et al., 2018, 2020). Capturing this spatial heterogeneity is therefore an important consideration when modelling within-host TB dynamics (Pitcher et al., 2018, 2020).

Mathematical models of within-host TB differ in how cellular and spatial processes are represented. Individual-based models (IBMs) describe cells as discrete entities and can capture local interactions, spatial heterogeneity and stochastic behaviour (Gammack et al., 2005; Segovia-Juarez et al., 2004; Macfarlane et al., 2022). These features make them particularly well suited to studying complex spatiotemporal dynamics, such as those underlying the immune response to TB (Wong et al., 2018; Joslyn et al., 2021). Hybrid IBM frameworks extend this approach by coupling discrete cellular agents with continuous descriptions of environmental or molecular factors, such as oxygen and chemokines (Bowness et al., 2018; Marino and Kirschner, 2016; Cilfone et al., 2013; Almeida et al., 2022). Although this level of detail is valuable for representing cell-level behaviour and local interactions, IBM implementations can be computationally demanding and are often less amenable to mathematical analysis (Macfarlane et al., 2022).

In contrast, partial differential equation (PDE) models describe cell populations and other biological quantities as continuous densities or concentrations that vary across space and time (Macfarlane et al., 2022; Bubba et al., 2020). Such formulations provide a natural framework for describing processes including cell migration, diffusion, chemotaxis, and spatial mycobacterial dynamics (Bubba et al., 2020). The continuum formulation therefore provides a complementary population-level description that is more amenable to analytical investigation, sensitivity analysis, and systematic parameter exploration, while the IBM retains stochastic event timing, individual identities and fine-scale spatial heterogeneity (Macfarlane et al., 2022).

In this study, we compare a stochastic within-host IBM with a mechanistically related deterministic continuum formulation. Although IBMs have previously been compared with continuum counterparts in applications such as growing cell populations (Byrne and Drasdo, 2009) and competing cancer-cell phenotypes (Ardaševa et al., 2020), to our knowledge, such a formal continuum counterpart has not previously been developed and directly compared with a mechanistically related spatial hybrid IBM in the context of within-host TB infection.

Both formulations are developed in relation to the hybrid IBM of Bowness et al. (2018), which represents interactions between *Mtb* and immune cells together with continuous oxygen and chemokine concentrations. The stochastic formulation considered here, however, is not the published Bowness et al. (2018) implementation itself. Instead, we construct an idealised stochastic formulation based on that model, incorporating several extensions and simplifications. These include multiple occupancy of spatial sites and modified interaction rules, for enhanced cellular interactions.

We start by formalising the probabilistic rules of this idealised stochastic formulation. These rules are then used to formally derive a deterministic continuum counterpart comprising a system of coupled PDEs for the dynamics of the densities of mycobacteria, macrophages and T cells, together with the dynamics of the concentrations of oxygen and chemokines. The derivation captures the principal mechanisms of the stochastic formulation at the population level rather than every discrete event or algorithmic detail. Consequently, the correspondence between the two formulations should not be interpreted as exact event-level equivalence.

For computational feasibility, we subsequently reduce the complete continuum formulation before numerical

implementation. We then implement a reduced stochastic IBM containing the same selected cell populations and key biological processes, so that the numerical comparison can be performed under closely matched initial spatial configurations. The two formulations are compared using closely matched blood vessel locations, resting macrophage distributions, and initial mycobacterial positions. This comparison allows us to examine agreement and disagreement in clearance outcomes, stochastic variability in the IBM, and differences in temporal and spatial dynamics.

The article is organised as follows. In § 2, we introduce the stochastic individual-based formulation and its probabilistic rules. In § 3, we present its continuum counterpart, with the formal mean-field derivation provided in § A. In § 4, we introduce the reduced versions of the two formulations and describe their numerical implementation. We also describe how closely matched blood vessel locations, initial mycobacterial coordinates, and resting macrophage distributions are transferred between the two formulations. In § 5, we compare the temporal dynamics of the reduced PDE and stochastic IBM under one fixed parameter regime across ten closely matched initial spatial configurations, with four IBM realisations considered for each configuration, and examine selected spatial patterns. Finally, in § 6, we summarise our findings, discuss the influence of initial spatial configuration and intrinsic IBM stochasticity on agreement and disagreement between the formulations, and outline the limitations of the present comparison and directions for future research.

2 Stochastic Individual-Based Formulation

We construct an idealised stochastic individual-based formulation based on the model developed by [Bowness et al. \(2018\)](#) to represent interactions between *Mtb* and immune cells within a localised section of lung tissue. The formulation retains the key biological mechanisms represented in [Bowness et al. \(2018\)](#), including macrophage and T cell responses, mycobacterial growth, and spatially varying oxygen and chemokine concentrations. Several aspects of the discrete formulation are modified or simplified to facilitate derivation of a formal continuum counterpart. The cell types and their associated states are shown in [Figure 1](#). The model incorporates the following biological processes:

1. **Phenotypic Switching of Mycobacteria:** *Mtb* bacilli exhibit phenotypic switching between slow- and fast-growing states based on the local concentration of oxygen. Surplus oxygen promotes fast growth, facilitating rapid replication, while limited oxygen induces a slow-growing state.
2. **Replication:** Mycobacterial replication occurs within a Moore neighbourhood of order 3 when sufficient space is available. Otherwise, mycobacteria enter a ‘quiescent’ state until space becomes available.
3. **Recruitment:** Immune cells are recruited via blood vessels. In [Bowness et al. \(2018\)](#), the blood vessels were either uniformly or randomly distributed. Macrophages, the innate immune cells, are initially recruited in their resting state. An increase in extracellular mycobacterial burden triggers an adaptive immune response, leading to the recruitment of T cells.
4. **Phagocytosis of Mycobacteria:** Macrophages transition to an infected state after phagocytosing extracellular mycobacteria.
5. **Cell Activation:** Resting macrophages can become activated if T cells are within their Moore neighbourhood. For modelling simplicity, T cells are represented as a single cell type encompassing both macrophage activation and cytotoxic functions.
6. **Migration of Cells:** Resting macrophages migrate via an unbiased random walk. Activated and infected macrophages secrete chemokines ([Algood et al., 2003](#)), which guide the chemotactic movement of infected and activated macrophages, and T cells. Chemotaxis is modelled as a biased random walk in response to local chemokine concentration gradients.

7. Cytotoxic Killing of Target Cells: Activated macrophages are effective at killing mycobacteria, with T cells also playing a crucial role in eliminating infected macrophages and mycobacteria within them.

Several modifications are introduced relative to the published implementation of [Bowness et al. \(2018\)](#). In particular, the stochastic formulation allows multiple occupancy of lattice sites. This enables mycobacterial offspring to remain at or near the parent location and allows selected immune cell interactions, such as phagocytosis, to occur without requiring each lattice site to contain only a single cell. We also adopt a different approach from [Bowness et al. \(2018\)](#) for modelling the radius of interaction between cells.

In addition to chemotactic migration, T cells also perform unbiased random walks, allowing them to explore their local microenvironment and interact with other cells and molecules ([Riggs et al., 2008](#); [Krummel et al., 2016](#)). This added behaviour compared to [Bowness et al. \(2018\)](#) enables T cells to continue surveying the local tissue environment for infection and maintain cytotoxic activity even at low chemokine concentrations. Where a chemotactic signal is present, chemokine-directed migration takes precedence over unbiased random migration.

These modifications define the stochastic formulation used throughout this study. They are introduced to enhance the key within-host TB mechanisms of the [Bowness et al. \(2018\)](#) framework while producing a discrete formulation from which a formal continuum counterpart can be derived. The resulting correspondence is therefore mechanistic and population-level rather than an exact event-level reproduction of the published [Bowness et al. \(2018\)](#) implementation.

Remark 1. *In the original model, chronically infected macrophages arise when infected macrophages accumulate *Mtb* beyond a specified threshold. In contrast to [Bowness et al. \(2018\)](#), we exclude chronically infected macrophages and bursting phenomena. These processes are omitted from the stochastic formulation as part of the simplifications introduced to facilitate derivation and comparison with the formal continuum counterpart.*

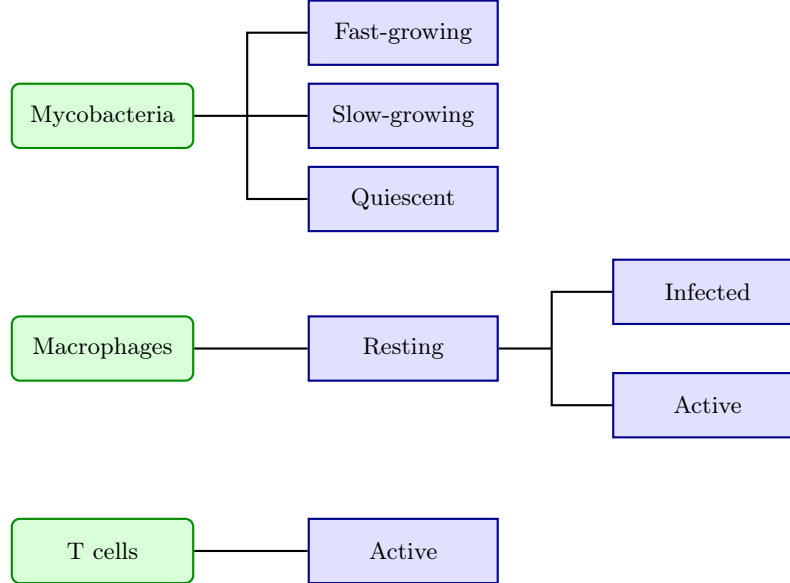


Figure 1: Cell types and their associated states represented in the stochastic individual-based formulation.

2.1 Preliminaries and Notations

We translate the model dynamics outlined in § 2 into probabilistic rules to guide the formal derivation of a continuum counterpart. We start by considering a d -dimensional spatial domain $\Omega = (0, l)^d$, where $d = 1$ or $d = 2$. The positions of mycobacterial and immune cells are modelled by $x \in [0, l]$ when $d = 1$ and by the vector $\mathbf{x} = (x, y) \in [0, l]^2$ when $d = 2$, at time $t \in (0, t_f]$.

The discretisation of the time and space variables follows $t_k = k\tau$, $x_i = i\eta$, and $y_j = j\eta$, where $k \in \mathbb{N}_0$ and $(i, j) \in [0, \mathcal{N}]^2 \subset \mathbb{N}_0^2$. Here, $\mathbb{N}_0$ denotes the set of natural numbers including zero. Both $\tau \in \mathbb{R}_+^*$ and $\eta \in \mathbb{R}_+^*$ represent the time-step and space-step, respectively, with $\mathcal{N}$ and η satisfying $\mathcal{N}\eta := l$. We let $\mathbb{R}_+^*$ denote the set of positive real numbers, excluding zero, while $\mathbb{R}_+$ represents the set of positive real numbers (including zero). It is assumed that τ is sufficiently small to ensure that all probabilities defined below remain between 0 and 1. We adopt the notations $\mathbf{i} \equiv i$ and $\mathbf{x}_i \equiv x_i$ for the case $d = 1$, and $\mathbf{i} \equiv (i, j)$ and $\mathbf{x}_i \equiv (x_i, y_j)$ for the case $d = 2$.

We will focus on the two-dimensional (2D) scenario, i.e. we will assume $d = 2$ for the formulation of the probabilistic rules.

We start by defining the discrete cell numbers at position $\mathbf{x}_i$ and time t_k . Let

$$N_{S_i}^k, N_{F_i}^k, N_{Q_i}^k \in \mathbb{N}_0$$

denote the numbers of slow-growing, fast-growing, and quiescent mycobacteria, respectively. Similarly,

$$M_{R_i}^k, M_{A_i}^k, M_{I_i}^k \in \mathbb{N}_0$$

denote the numbers of resting, active, and infected macrophages, respectively, while

$$E_i^k \in \mathbb{N}_0$$

denotes the number of T cells.

The corresponding cell densities are obtained by dividing the cell numbers by the size of a lattice site, namely η^d . Unless otherwise stated, we henceforth consider the 2D setting, so that the densities are obtained by division by η^2 . The corresponding one-dimensional definitions are provided in Appendix A.

At each time step, a check is performed to ensure sufficient space is available at each lattice site before mycobacterial proliferation, growth, or immune cell migration occurs. To model space saturation effects linked to these processes, we introduce two functions: $\Psi(N_i^k)$ for mycobacterial proliferation and growth, and $\Phi(N_i^k)$ for immune cell migration. Here, N_i^k represents the total number of cells (mycobacterial or immune) at site $\mathbf{i}$ at time t_k , that is,

$$N_i^k = N_{S_i}^k + N_{F_i}^k + N_{Q_i}^k + M_{R_i}^k + M_{A_i}^k + M_{I_i}^k + E_i^k. \quad (1)$$

The functions Ψ and Φ satisfy the following assumptions:

$$\Psi(0) = 1, \quad \Psi(\bar{N}) = 0, \quad \Psi : \mathbb{R}_+ \rightarrow \mathbb{R}_+, \quad \frac{\partial \Psi(N)}{\partial N} \begin{cases} < 0 & 0 \leq N < \bar{N}, \\ = 0 & N \geq \bar{N}, \end{cases} \quad \bar{N} \in \mathbb{R}_+^*, \quad (2)$$

$$\Phi(0) = 1, \quad \Phi(\bar{N}) = 0, \quad \Phi : \mathbb{R}_+ \rightarrow \mathbb{R}_+, \quad \frac{\partial \Phi(N)}{\partial N} \begin{cases} < 0 & 0 \leq N < \bar{N}, \\ = 0 & N \geq \bar{N}, \end{cases} \quad \bar{N} \in \mathbb{R}_+^*. \quad (3)$$

Throughout this work, we use the following volume-filling functions, which satisfy the assumptions above:

$$\Psi(N) = \Phi(N) = \left(1 - \frac{N}{\bar{N}}\right)_+. \quad (4)$$

Here, $\bar{N}$ is the number of cells corresponding to the maximum occupancy of a lattice site. The monotonic decrease of $\Psi(N)$ and $\Phi(N)$ for $N < \bar{N}$ captures the fact that as the number of cells increases, the available space at the lattice site decreases. Once the total number of cells, N , reaches $\bar{N}$, both functions flatten, indicating saturation. Beyond this point, no further proliferation, growth, or migration occurs at the lattice site.

For the sake of clarity, in the remainder of the paper, we will also use the following abridged notation:

$$\Psi(N_{\mathbf{i}}^k) \equiv \Psi_{\mathbf{i}}^k, \quad \Phi(N_{\mathbf{i}}^k) \equiv \Phi_{\mathbf{i}}^k. \quad (5)$$

2.2 Dynamics of Oxygen

Let $O_{(i,j)}^k$ represent the concentration of oxygen at a particular time t_k and position $\mathbf{x}_{\mathbf{i}}$. Following the approach in [Bowness et al. \(2018\)](#), oxygen is supplied through a fixed number of blood vessels. The positions of the blood vessels belong to the set $\omega \subset \Omega$, where Ω as stated earlier is the spatial domain.

The dynamics of $O_{(i,j)}^k$ follow the discrete balance equation ([Bubba et al., 2020](#))

$$O_{(i,j)}^{k+1} = O_{(i,j)}^k + \tau\beta_O(\mathcal{L}O^k)_{(i,j)} + \tau\delta_O\mathbf{1}_{\omega(i,j)} - \tau w_{(i,j)}^k, \quad (6)$$

subject to initial conditions and discrete zero-flux boundary conditions as used by [Powathil et al. \(2012\)](#). Here, $\beta_O > 0$ is the diffusion coefficient of oxygen, $\delta_O > 0$ is the rate at which oxygen is supplied from the blood vessel based on $\mathbf{1}_{\omega}(\mathbf{x}_{\mathbf{i}})$, and the term $w_{(i,j)}^k$ is used to model the consumption of oxygen by cells in the system. Each cell type has a different consumption rate ([Bowness et al., 2018](#)): O_{ns} for slow-growing mycobacteria, O_{nf} for fast-growing mycobacteria, O_{nq} for mycobacteria in a quiescent state, O_{mr} for resting macrophages, O_{ma} for active macrophages, O_{mi} for infected macrophages, and O_e for T cells. Therefore, we define the term $w_{(i,j)}^k$ as

$$w_{(i,j)}^k = O_{ns}n_{S(i,j)}^k + O_{nf}n_{F(i,j)}^k + O_{nq}n_{Q(i,j)}^k + O_{mr}m_{R(i,j)}^k + O_{ma}m_{A(i,j)}^k + O_{mi}m_{I(i,j)}^k + O_e e_{(i,j)}^k. \quad (7)$$

Finally, the operator $\mathcal{L}$ used in Eq. (6) is the discrete Laplacian on the lattice $\{x_i\} \times \{y_j\}$, which for a generic discrete function $H_{(i,j)}^k$ is defined as

$$(\mathcal{L}H^k)_{(i,j)} = \frac{1}{\eta^2} \left(H_{(i-1,j)}^k + H_{(i+1,j)}^k + H_{(i,j-1)}^k + H_{(i,j+1)}^k - 4H_{(i,j)}^k \right). \quad (8)$$

This represents the discrete approximation of diffusion across the lattice sites.

2.3 Dynamics of Chemokines

Let $c_{(i,j)}^k$ denote the concentration of chemokines at time t_k and position $\mathbf{x}_{\mathbf{i}}$. Following the approach in [Algood et al. \(2003\)](#), chemokine secretion is carried out by all non-resting macrophages (i.e. active and infected macrophages). The dynamics of $c_{(i,j)}^k$ follow the discrete balance equation

$$c_{(i,j)}^{k+1} = c_{(i,j)}^k + \tau\beta_c(\mathcal{L}c^k)_{(i,j)} + \tau\delta_c a_{(i,j)}^k - \tau\kappa_c c_{(i,j)}^k, \quad (9)$$

subject to suitable initial conditions and discrete zero-flux boundary conditions. The operator $\mathcal{L}$ is the discrete Laplacian defined via Eq. (8). The parameters $\beta_c > 0$, $\delta_c > 0$, and $\kappa_c > 0$ represent the diffusion coefficient of the chemokine, the rate at which the aggregated chemokine is released, and the rate at which chemokine naturally decays, respectively. The term $a_{(i,j)}^k$ represents the density of all non-resting macrophages, that is

$$a_{(i,j)}^k = m_{A_{\mathbf{i}}}^k + m_{I_{\mathbf{i}}}^k. \quad (10)$$

2.4 Dynamics of Extracellular Mycobacteria

As discussed in § 2, proliferating extracellular mycobacteria exhibit phenotypic changes, and we consider two phenotypes: fast- and slow-growing. We assume transitions between these phenotypes to be contingent on the oxygen concentration near the blood vessels (Ser-shen et al., 2016; Bowness et al., 2018). Following successful establishment of infection by *Mtb*, the two mycobacterial phenotypes can replicate and grow extracellularly at different rates. However, this occurs only when there is sufficient space for mycobacterial replication, as outlined in Eq. (2). Otherwise, the mycobacteria enter a quiescent state until a suitable space becomes available at a later time-step. We postulate that a resting macrophage can phagocytose a mycobacterium, leading to the removal of the mycobacterium from the lattice site. Furthermore, mycobacteria are eliminated from the system due to death caused by the cytotoxic actions of active macrophages and T cells. These actions and interactions are modelled as described below.

2.4.1 Phenotypic Changes of Growing Mycobacteria Induced by Oxygen Concentration

The phenotypic change of growing mycobacteria at time t_k and position $\mathbf{x}_i$ is a reversible process involving two directional processes of trait change. In the model, mycobacterial state change depends on the concentration of oxygen. At a particular position $\mathbf{x}_i$, we define a concentration level (O_{high}) above which slow-growing mycobacteria become fast-growing mycobacteria (Bowness et al., 2018). Therefore, we define the probability of the transition from slow- to fast-growing mycobacteria as

$$0 \leq \tau J_{S \rightarrow F}(O_{(i,j)}^k) \leq 1, \quad J_{S \rightarrow F}(O_{(i,j)}^k) = \begin{cases} \frac{O_{(i,j)}^k}{1+O_{(i,j)}^k} & \text{if } O_{(i,j)}^k \geq O_{\text{high}} \\ 0 & \text{otherwise.} \end{cases} \quad (11)$$

However, with more replication of mycobacteria comes a greater demand for oxygen. Eventually, the concentration of oxygen at a particular position $\mathbf{x}_i$ will diminish, falling below a level (O_{low}) that facilitates the change of a mycobacterial cell state from a fast-growing to a slow-growing phenotype (Bowness et al., 2018). Similarly, the probability of the transition from fast- to slow-growing mycobacteria is defined as

$$0 \leq \tau J_{F \rightarrow S}(O_{(i,j)}^k) \leq 1, \quad J_{F \rightarrow S}(O_{(i,j)}^k) = \begin{cases} \frac{1}{1+O_{(i,j)}^k} & \text{if } O_{(i,j)}^k \leq O_{\text{low}} \\ 0 & \text{otherwise.} \end{cases} \quad (12)$$

Note that in Eq. (11) and Eq. (12), the functional forms $\frac{O_{(i,j)}^k}{1+O_{(i,j)}^k}$ and $\frac{1}{1+O_{(i,j)}^k}$, respectively, ensure that the switching factors remain bounded between 0 and 1, while capturing the required monotonic dependence on oxygen concentration: the former increases with $O_{(i,j)}^k$, whereas the latter decreases with $O_{(i,j)}^k$, including in the limit $O_{(i,j)}^k \rightarrow \infty$.

2.4.2 Proliferation, Expansion, Transition to Quiescent State, Phagocytosis, and Death of Mycobacteria

Proliferation and Growth of Slow-Growing and Fast-Growing Mycobacteria

An initial number of slow-growing mycobacteria that are able to proliferate are placed into the tissue environment. Hence, at every time-step k , provided there is enough space (cf. Eq. (2)), slow-growing mycobacteria are able to proliferate with probability

$$0 \leq \tau \alpha_S \Psi_i^k \leq 1, \quad (13)$$

where $\alpha_S \in \mathbb{R}_+^*$ represents the maximal proliferation rate of slow-growing mycobacteria.

Following proliferation, mycobacterial colonies can grow spatially, allowing slow-growing mycobacteria to occupy neighbouring lattice sites. In a 2D domain, this growth can occur up to 8 neighbouring lattice sites. Thus, we define $\beta_S \in (0, 1)$ as the probability of slow-growing mycobacteria growing to a new position due to proliferation.

For a slow-growing mycobacterium at position $\mathbf{x}_i = (x_i, y_j)$ and time t_k , we define the probabilities of growing into neighbouring sites as in [Table 1](#).

(a) ${}^{\text{UL}}Q_{NS(i,j)}^k = \frac{\beta_S}{8} \Psi_{(i-1,j+1)}^k$	(b) ${}^{\text{ML}}Q_{NS(i,j)}^k = \frac{\beta_S}{8} \Psi_{(i-1,j)}^k$
(c) ${}^{\text{LL}}Q_{NS(i,j)}^k = \frac{\beta_S}{8} \Psi_{(i-1,j-1)}^k$	(d) ${}^{\text{U}}Q_{NS(i,j)}^k = \frac{\beta_S}{8} \Psi_{(i,j+1)}^k$
(e) ${}^{\text{L}}Q_{NS(i,j)}^k = \frac{\beta_S}{8} \Psi_{(i,j-1)}^k$	(f) ${}^{\text{UR}}Q_{NS(i,j)}^k = \frac{\beta_S}{8} \Psi_{(i+1,j+1)}^k$
(g) ${}^{\text{MR}}Q_{NS(i,j)}^k = \frac{\beta_S}{8} \Psi_{(i+1,j)}^k$	(h) ${}^{\text{LR}}Q_{NS(i,j)}^k = \frac{\beta_S}{8} \Psi_{(i+1,j-1)}^k$

Table 1: Probabilities that slow-growing mycobacteria on lattice site (i, j) at time step k will grow into neighbouring lattice sites. (a)-(h) represent the probability of growth into lattice site $(i-1, j+1)$, $(i-1, j)$, $(i-1, j-1)$, $(i, j+1)$, $(i, j-1)$, $(i+1, j+1)$, $(i+1, j)$, and $(i+1, j-1)$, respectively.

Consequently, the probability of remaining on the parent lattice site (i.e. not growing into neighbouring lattice sites) is

$$1 - {}^{\text{UL}}Q_{NS(i,j)}^k - {}^{\text{ML}}Q_{NS(i,j)}^k - {}^{\text{LL}}Q_{NS(i,j)}^k - {}^{\text{U}}Q_{NS(i,j)}^k - {}^{\text{L}}Q_{NS(i,j)}^k - {}^{\text{UR}}Q_{NS(i,j)}^k - {}^{\text{MR}}Q_{NS(i,j)}^k - {}^{\text{LR}}Q_{NS(i,j)}^k. \quad (14)$$

Similarly, we introduce an initial population of fast-growing mycobacteria into the tissue environment. These mycobacteria can rapidly replicate and occupy positions on the lattice site over time (cf. Eq. (2)). Hence, at each time-step k , fast-growing mycobacteria can proliferate with probability

$$0 \leq \tau \alpha_F \Psi_{\mathbf{i}}^k \leq 1, \quad (15)$$

where $\alpha_F \in \mathbb{R}_+^*$ represents the maximal proliferation rate of fast-growing mycobacteria.

As with slow-growing mycobacteria, fast-growing mycobacteria can grow spatially by occupying neighbouring lattice sites. This growth follows the same mechanism as for slow-growing mycobacteria, with $\beta_F \in (0, 1)$ representing the probability of fast-growing mycobacteria growing into a new position due to proliferation.

For a fast-growing mycobacterium at position $\mathbf{x}_i = (x_i, y_j)$ and time t_k , we define the probabilities of growth into neighbouring sites as in [Table 2](#).

(a) ${}^{\text{UL}}Q_{NF(i,j)}^k = \frac{\beta_F}{8} \Psi_{(i-1,j+1)}^k$	(b) ${}^{\text{ML}}Q_{NF(i,j)}^k = \frac{\beta_F}{8} \Psi_{(i-1,j)}^k$
(c) ${}^{\text{LL}}Q_{NF(i,j)}^k = \frac{\beta_F}{8} \Psi_{(i-1,j-1)}^k$	(d) ${}^{\text{U}}Q_{NF(i,j)}^k = \frac{\beta_F}{8} \Psi_{(i,j+1)}^k$
(e) ${}^{\text{L}}Q_{NF(i,j)}^k = \frac{\beta_F}{8} \Psi_{(i,j-1)}^k$	(f) ${}^{\text{UR}}Q_{NF(i,j)}^k = \frac{\beta_F}{8} \Psi_{(i+1,j+1)}^k$
(g) ${}^{\text{MR}}Q_{NF(i,j)}^k = \frac{\beta_F}{8} \Psi_{(i+1,j)}^k$	(h) ${}^{\text{LR}}Q_{NF(i,j)}^k = \frac{\beta_F}{8} \Psi_{(i+1,j-1)}^k$

Table 2: Probabilities that fast-growing mycobacteria on lattice site (i, j) at time step k will grow into neighbouring lattice sites. (a)-(h) represent the probability of growth into lattice site $(i - 1, j + 1)$, $(i - 1, j)$, $(i - 1, j - 1)$, $(i, j + 1)$, $(i, j - 1)$, $(i + 1, j + 1)$, $(i + 1, j)$, and $(i + 1, j - 1)$, respectively.

Consequently, the probability of remaining on the parent lattice site (i.e. not growing into neighbouring lattice sites) is

$$1 - {}^{\text{UL}}Q_{NF(i,j)}^k - {}^{\text{ML}}Q_{NF(i,j)}^k - {}^{\text{LL}}Q_{NF(i,j)}^k - {}^{\text{U}}Q_{NF(i,j)}^k - {}^{\text{L}}Q_{NF(i,j)}^k - {}^{\text{UR}}Q_{NF(i,j)}^k - {}^{\text{MR}}Q_{NF(i,j)}^k - {}^{\text{LR}}Q_{NF(i,j)}^k. \quad (16)$$

Remark 2. *The correspondence between mycobacterial replication in the stochastic and continuum formulations is at the population level rather than at the level of individual replication events. In the stochastic IBM, mycobacterial proliferation and offspring placement remain discrete, with offspring placed on specific lattice sites according to the probabilistic rules described above. In the continuum formulation, these mechanisms are represented through changes in mycobacterial density. The two formulations should therefore not be interpreted as having exact event-level correspondence in mycobacterial replication or offspring placement.*

Transition of Slow-Growing and Fast-Growing Mycobacteria to Quiescent State

If there is insufficient space to accommodate a newly replicated mycobacterium on a certain lattice site, a slow-growing mycobacterium may enter a quiescent state. Therefore, we define the probability of the transition from slow-growing mycobacteria to mycobacteria in a quiescent state as

$$0 \leq \tau w_{S \rightarrow Q} (1 - \Psi_{\mathbf{i}}^k) \leq 1, \quad (17)$$

where $w_{S \rightarrow Q} \in \mathbb{R}_+^*$ represents the maximal rate of transition from slow-growing mycobacteria to quiescent mycobacteria.

The transition probability in Eq. (17) relies on the availability of space to determine the potential transition from a slow-growing state to a quiescent state (cf. Eq. (2)). For $\Psi_{\mathbf{i}}^k = 1$, indicating the availability of space at $(t_k, \mathbf{x}_{\mathbf{i}})$ for proliferation, the term $(1 - \Psi_{\mathbf{i}}^k)$ in Eq. (17) ensures a zero probability that slow-growing mycobacteria will become quiescent when there is space available. Conversely, when $\Psi_{\mathbf{i}}^k = 0$, Eq. (17) ensures a non-zero probability, signifying that slow-growing mycobacteria become quiescent when there is no space available for proliferation.

In a similar way, a fast-growing mycobacterium may enter a quiescent state when proliferation is impossible due to a lack of space. Thus, we define the probability of transition from fast-growing mycobacteria to mycobacteria in the quiescent state as

$$0 \leq \tau w_{F \rightarrow Q} (1 - \Psi_{\mathbf{i}}^k) \leq 1, \quad (18)$$

where $w_{F \rightarrow Q} \in \mathbb{R}_+^*$ represents the maximal rate of transition from fast-growing mycobacteria to quiescent mycobacteria.

Transition of Mycobacteria in Quiescent State to Slow-Growing Mycobacteria

As mentioned earlier, at time t_k , mycobacteria that are unable to proliferate due to space restrictions enter a quiescent state. However, if sufficient space becomes available on a lattice site at time t_k , meeting the conditions specified in Eq. (2), mycobacteria can transition from their quiescent state to a slow-growing state. Therefore, we define the probability of the transition from quiescent state to slow-growing mycobacteria as

$$0 \leq \tau w_{Q \rightarrow S} \Psi_{\mathbf{i}}^k \leq 1. \quad (19)$$

Phagocytosis of Slow-Growing and Fast-Growing Mycobacteria, and Mycobacteria in Quiescent State by Resting Macrophages

In [Bowness et al. \(2018\)](#), resting macrophages perform phagocytosis on mycobacteria, preventing them from growing extracellularly. However, for phagocytosis to occur, the mycobacterium and resting macrophage must be within a specific distance. Therefore, following the modelling strategy proposed by [Almeida et al. \(2022\)](#), we assume that at time t_k , resting macrophages within a radius of ρ (cf. Eq. (22)) from a slow-growing mycobacterium at position (x_i, y_j) may phagocytose the mycobacterium with a probability

$$0 \leq \tau h_{N_S} K_{M_R(i,j)}^k \leq 1, \quad (20)$$

where the parameter h_{N_S} is associated with the efficiency of resting macrophages at phagocytosing slow-growing mycobacteria and the term $K_{M_R(i,j)}^k$ is linked to the number of resting macrophages within a radius of ρ to the mycobacterium at $\mathbf{x}_i$. The quantity $K_{M_R(i,j)}^k \in \mathbb{N}_0$ is defined as

$$K_{M_R(i,j)}^k \equiv K_{M_R}(t_k, x_i, y_j) = h_{M_R} \sum_{(h,l)} \Upsilon(x_i, x_h, y_j, y_l; \rho) M_{R(h,l)}^k, \quad (21)$$

where h_{M_R} is inversely proportional to the maximum number of resting macrophages which can be accommodated within the spatial domain and the function Υ is defined as

$$\Upsilon(x_i, x_h, y_j, y_l; \rho) = \begin{cases} 1 & \text{if } \sqrt{|x_i - x_h|^2 + |y_i - y_l|^2} \leq \rho \\ 0 & \text{if } \sqrt{|x_i - x_h|^2 + |y_i - y_l|^2} > \rho. \end{cases} \quad (22)$$

Further, we postulate that at $(t_k, \mathbf{x}_i)$, a fast-growing mycobacterium may be phagocytosed by resting macrophages at a rate proportional to the number of resting macrophages within a radius of ρ to the mycobacterium. Therefore, we define the probability of this occurrence as

$$0 \leq \tau h_{N_F} K_{M_R(i,j)}^k \leq 1, \quad (23)$$

where the parameter h_{N_F} is associated with the efficiency of resting macrophages at phagocytosing fast-growing mycobacteria and $K_{M_R(i,j)}^k$ is defined via Eq. (21).

Quiescent mycobacteria remain susceptible to phagocytosis. Therefore, at $(t_k, \mathbf{x}_i)$, resting macrophages within a radius of ρ to a mycobacterium in a quiescent state can phagocytose the mycobacterium. The probability of this phagocytosis event is defined as

$$0 \leq \tau h_{N_Q} K_{M_R(i,j)}^k \leq 1, \quad (24)$$

where the parameter h_{N_Q} is associated with the efficiency of resting macrophages at phagocytosing mycobacteria in a quiescent state and $K_{M_R(i,j)}^k$ is defined via Eq. (21).

Cytotoxic Death of Slow-Growing and Fast-Growing Mycobacteria, and Mycobacteria in Quiescent State Induced by Active Macrophages

Active macrophages cytotoxically kill mycobacteria. Hence, at $(t_k, \mathbf{x}_i)$, we allow a slow-growing mycobacterium to die due to the cytotoxic action of active macrophages at a rate proportional to the number of active macrophages within a radius of ρ to the mycobacterium. The probability of this occurrence is defined as

$$0 \leq \tau d_{N_S, M_A} K_{M_A(i,j)}^k \leq 1, \quad (25)$$

where d_{N_S, M_A} is associated with the effectiveness of active macrophages at killing slow-growing mycobacteria and the term $K_{M_A(i,j)}^k$ is linked to the number of active macrophages within a radius of ρ to the mycobacterium at $\mathbf{x}_i$. The quantity $K_{M_A(i,j)}^k \in \mathbb{N}_0$ is defined as

$$K_{M_A(i,j)}^k \equiv K_{M_A}(t_k, x_i, y_j) = h_{M_A} \sum_{(h,l)} \Upsilon(x_i, x_h, y_j, y_l; \rho) M_{A(h,l)}^k, \quad (26)$$

where h_{M_A} is inversely proportional to the maximum number of active macrophages which can be accommodated within the spatial domain and Υ is defined via Eq. (22).

We further postulate that at time t_k and position $\mathbf{x}_i$, active macrophages may kill a fast-growing mycobacterium at a rate proportional to the number of active macrophages within a radius of ρ to the mycobacterium. We define the probability of this occurrence as

$$0 \leq \tau d_{N_F, M_A} K_{M_A(i,j)}^k \leq 1, \quad (27)$$

where d_{N_F, M_A} is associated with the effectiveness of active macrophages at killing fast-growing mycobacteria and $K_{M_A(i,j)}^k$ is defined via Eq. (26).

While mycobacteria in a quiescent state neither exhibit slow nor fast growth, their population still contributes to mycobacterial infection. Consequently, clearance of mycobacteria in a quiescent state is crucial for controlling TB. At $(t_k, \mathbf{x}_i)$, a mycobacterium in a quiescent state may undergo cytotoxic death due to the action of active macrophages when the latter are within a radius of ρ to the mycobacterium. The probability of this occurrence is defined as

$$0 \leq \tau d_{N_Q, M_A} K_{M_A(i,j)}^k \leq 1, \quad (28)$$

where d_{N_Q, M_A} is associated with the efficiency of active macrophages at eliminating mycobacteria in the quiescent state and $K_{M_A(i,j)}^k$ is defined via Eq. (26).

2.5 Dynamics of Macrophages

2.5.1 Dynamics of Resting Macrophages

Recruitment of Resting Macrophages

Prior to the recruitment of resting macrophages, an initial population of resident resting macrophages is deposited into the spatial domain. If needed, more resting macrophages are recruited into the spatial domain through blood vessels located at points contained in the set $\omega \subset \Omega$. This process is regulated by chemokine signaling. In alignment with previous work (Almeida et al., 2022), we regulate the influx of resting macrophages from the blood vessels by $p_{(i,j)}^k$, which is defined as

$$p_{(i,j)}^k = p(t_k, \mathbf{x}_i) = c_{\text{tot}}^k \mathbf{1}_\omega(\mathbf{x}_i), \quad c_{\text{tot}}^k = \sum_{(i,j)} c_{(i,j)}^k \eta^2, \quad (29)$$

where c_{tot}^k represents the total amount of chemokine in the spatial domain at time t_k and $\mathbf{1}_\omega$ is the indicator function of the set $\omega \subset \Omega$. Therefore, between the time-steps k and $k+1$, the density of the resting macrophages that can

enter a blood vessel at position $\mathbf{x}_i$ is controlled by $p_{(i,j)}^k$, such that

$$\tau \delta_{M_R} p_{(i,j)}^k \geq 0, \quad (30)$$

where $\delta_{M_R} \in \mathbb{R}_+^*$ is a constant of proportionality.

Infection of Resting Macrophages

The main function of resting macrophages is to perform phagocytosis of mycobacteria. Moreover, a healthy resting macrophage at $(t_k, \mathbf{x}_i)$ may become infected with probability

$$0 \leq \tau \lambda_{M_R} b_{(i,j)}^k \leq 1, \quad b_{(i,j)}^k = n_{S_{(i,j)}}^k + n_{E_{(i,j)}}^k + n_{Q_{(i,j)}}^k, \quad (31)$$

where $\lambda_{M_R} \in \mathbb{R}_+^*$ is proportional to the rate at which a mycobacterium can infect a resting macrophage, and the term $b_{(i,j)}^k$ is the sum of all mycobacteria density at $(t_k, \mathbf{x}_i)$.

Death of Resting Macrophages

At a time-step k and position $\mathbf{x}_i$, the natural death of a resting macrophage occurs with a probability given by

$$0 \leq \tau d_{M_R} \leq 1, \quad (32)$$

where $d_{M_R} \in \mathbb{R}_+^*$ is the natural death rate of resting macrophages.

Undirected Random Migration of Resting Macrophages

The movement of resting macrophages is constrained to undirected random migration, following a random walk with a movement probability denoted as $\nu \in \mathbb{R}_+^*$, where $0 < \nu \leq 1$. However, the position change from a current lattice site to another is contingent upon the availability of space at neighbouring sites (cf. Eq. (3)). In a 2D domain, immune cells can update their positions through random migration towards up to 8 possible lattice sites. Thus, for a resting macrophage at position $\mathbf{x}_i = (x_i, y_j)$ and time t_k , we represent the probabilities of moving to neighbouring lattice sites via undirected random migration in Table 3.

(a) ${}^{\text{UL}}Q_{M_R(i,j)}^k = \frac{\nu}{8} \Phi_{(i-1,j+1)}^k$	(b) ${}^{\text{ML}}Q_{M_R(i,j)}^k = \frac{\nu}{8} \Phi_{(i-1,j)}^k$
(c) ${}^{\text{LL}}Q_{M_R(i,j)}^k = \frac{\nu}{8} \Phi_{(i-1,j-1)}^k$	(d) ${}^{\text{U}}Q_{M_R(i,j)}^k = \frac{\nu}{8} \Phi_{(i,j+1)}^k$
(e) ${}^{\text{L}}Q_{M_R(i,j)}^k = \frac{\nu}{8} \Phi_{(i,j-1)}^k$	(f) ${}^{\text{UR}}Q_{M_R(i,j)}^k = \frac{\nu}{8} \Phi_{(i+1,j+1)}^k$
(g) ${}^{\text{MR}}Q_{M_R(i,j)}^k = \frac{\nu}{8} \Phi_{(i+1,j)}^k$	(h) ${}^{\text{LR}}Q_{M_R(i,j)}^k = \frac{\nu}{8} \Phi_{(i+1,j-1)}^k$

Table 3: Probabilities of migrating to neighbouring lattice sites via undirected random migration for a resting macrophage on lattice site (i, j) at time-step k . (a)-(h) represent the probability of moving to lattice site $(i-1, j+1)$, $(i-1, j)$, $(i-1, j-1)$, $(i, j+1)$, $(i, j-1)$, $(i+1, j+1)$, $(i+1, j)$, and $(i+1, j-1)$, respectively.

Consequently, the probability of not undergoing undirected random movement is

$$1 - {}^{\text{UL}}Q_{M_R(i,j)}^k - {}^{\text{ML}}Q_{M_R(i,j)}^k - {}^{\text{LL}}Q_{M_R(i,j)}^k - {}^{\text{U}}Q_{M_R(i,j)}^k - {}^{\text{L}}Q_{M_R(i,j)}^k - {}^{\text{UR}}Q_{M_R(i,j)}^k - {}^{\text{MR}}Q_{M_R(i,j)}^k - {}^{\text{LR}}Q_{M_R(i,j)}^k. \quad (33)$$

Activation of Resting Macrophages by T cells

The presence of T cells in the neighbourhood of resting macrophages can activate them. Thus, at $(t_k, \mathbf{x}_i)$, a resting macrophage may become activated when there are T cells within a radius of ρ to the macrophage. The probability of this activation is given by

$$0 \leq \tau A_{M_R, E} K_E(i, j)^k \leq 1, \quad (34)$$

where $A_{M_R, E}$ is associated with the efficiency of T cells at activating resting macrophages and K_E^k is as previously defined via Eq. (40).

2.5.2 Dynamics of Active Macrophages

Death of Active Macrophages

Active macrophages are capable of performing cytotoxic actions on mycobacteria and migrate in response to the upregulation of the chemokine, defined via Eq. (9). Moreover, at a specific time-step k and position $\mathbf{x}_i$, an active macrophage undergoes natural death with probability

$$0 \leq \tau d_{M_A} \leq 1, \quad (35)$$

where $d_{M_A} \in \mathbb{R}_+^*$ is the natural death rate of active macrophages.

Chemotactic Migration of Active Macrophages

We adopt the modelling strategy proposed by Almeida et al. (2022) in deriving the chemotactic migration of active macrophages. The migration strictly follows a biased random walk, characterised by chemotaxis, where the probabilities of moving from one position to another depend on the difference in chemokine concentration between the currently occupied lattice site and neighbouring sites. Additionally, we account for the tendency of active macrophages to migrate towards regions with a higher concentration of the chemokine, introducing a proportionality constant $\mu \in \mathbb{R}_+^*$ to represent their sensitivity to chemokine. The highest possible value which can be attained by the chemokine concentration is denoted by $c_{\max} \in \mathbb{R}_+^*$. In a 2D domain, active macrophages at time t_k may move to up to 8 different positions, provided that there is sufficient space to do so (cf. Eq. (3)). Thus, for an active macrophage on lattice site $\mathbf{i} = (i, j)$ at time-step k , we represent the probabilities of moving to neighbouring lattice sites via chemotaxis in Table 4.

(a) $UL_{MA(i,j)}^k = \mu \Phi_{(i-1,j+1)}^k \frac{(c_{(i-1,j+1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$	(b) $ML_{MA(i,j)}^k = \mu \Phi_{(i-1,j)}^k \frac{(c_{(i-1,j)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$
(c) $LL_{MA(i,j)}^k = \mu \Phi_{(i-1,j-1)}^k \frac{(c_{(i-1,j-1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$	(d) $US_{MA(i,j)}^k = \mu \Phi_{(i,j+1)}^k \frac{(c_{(i,j+1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$
(e) $LS_{MA(i,j)}^k = \mu \Phi_{(i,j-1)}^k \frac{(c_{(i,j-1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$	(f) $UR_{MA(i,j)}^k = \mu \Phi_{(i+1,j+1)}^k \frac{(c_{(i+1,j+1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$
(g) $MR_{MA(i,j)}^k = \mu \Phi_{(i+1,j)}^k \frac{(c_{(i+1,j)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$	(h) $LR_{MA(i,j)}^k = \mu \Phi_{(i+1,j-1)}^k \frac{(c_{(i+1,j-1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$

Table 4: Probabilities of migrating to neighbouring lattice sites via chemotaxis for an active macrophage on lattice site (i, j) at time-step k . (a)-(h) represent the probability of moving to lattice site $(i-1, j+1)$, $(i-1, j)$, $(i-1, j-1)$, $(i, j+1)$, $(i, j-1)$, $(i+1, j+1)$, $(i+1, j)$, and $(i+1, j-1)$, respectively.

Hence, the probability of not undergoing chemotactic movement is

$$1 - {}^{\text{UL}}S_{MA(i,j)}^k - {}^{\text{ML}}S_{MA(i,j)}^k - {}^{\text{LL}}S_{MA(i,j)}^k - {}^{\text{U}}S_{MA(i,j)}^k - {}^{\text{L}}S_{MA(i,j)}^k - {}^{\text{UR}}S_{MA(i,j)}^k - {}^{\text{MR}}S_{MA(i,j)}^k - {}^{\text{LR}}S_{MA(i,j)}^k. \quad (36)$$

Similar to the approach in [Almeida et al. \(2022\)](#), the division by $c_{\max}$ ensures that the values of the quotient in [Table 4](#) do not exceed 1. Additionally, the presence of the positive part $(\cdot)_+$ ensures that the numerator remains non-negative.

2.5.3 Dynamics of Infected Macrophages

Death of Infected Macrophages

Following the infection of resting macrophages (cf. Eq. (31)), if not eliminated by T cells, at $(t_k, \mathbf{x}_i)$, an infected macrophage may die naturally with probability

$$0 \leq \tau d_{M_I} \leq 1, \quad (37)$$

where $d_{M_I} \in \mathbb{R}_+^*$ is the natural death rate of infected macrophages.

Chemotactic Migration of Infected Macrophages

Infected macrophages undergo a biased random walk, where the probability of moving from one position to another depends on the difference in chemokine concentration between the current lattice site and neighbouring sites. This approach accounts for the tendency of infected macrophages to migrate towards regions with higher chemokine concentrations. To represent their sensitivity to chemokine, we introduce a proportionality constant, $\zeta \in \mathbb{R}_+^*$. In a 2D domain, infected macrophages at time t_k may move to up to 8 different positions, provided sufficient space is available, as described in Eq. (3). Hence, for an infected macrophage on lattice site $\mathbf{i} = (i, j)$ at time-step k , we represent the probabilities of moving to neighbouring lattice sites via chemotaxis in [Table 5](#).

(a) ${}^{\text{UL}}S_{M_I(i,j)}^k = \zeta \Phi_{(i-1,j+1)}^k \frac{(c_{(i-1,j+1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$	(b) ${}^{\text{ML}}S_{M_I(i,j)}^k = \zeta \Phi_{(i-1,j)}^k \frac{(c_{(i-1,j)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$
(c) ${}^{\text{LL}}S_{M_I(i,j)}^k = \zeta \Phi_{(i-1,j-1)}^k \frac{(c_{(i-1,j-1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$	(d) ${}^{\text{U}}S_{M_I(i,j)}^k = \zeta \Phi_{(i,j+1)}^k \frac{(c_{(i,j+1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$
(e) ${}^{\text{L}}S_{M_I(i,j)}^k = \zeta \Phi_{(i,j-1)}^k \frac{(c_{(i,j-1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$	(f) ${}^{\text{UR}}S_{M_I(i,j)}^k = \zeta \Phi_{(i+1,j+1)}^k \frac{(c_{(i+1,j+1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$
(g) ${}^{\text{MR}}S_{M_I(i,j)}^k = \zeta \Phi_{(i+1,j)}^k \frac{(c_{(i+1,j)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$	(h) ${}^{\text{LR}}S_{M_I(i,j)}^k = \zeta \Phi_{(i+1,j-1)}^k \frac{(c_{(i+1,j-1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$

Table 5: Probabilities of migrating to neighbouring lattice sites via chemotaxis for an infected macrophage on lattice site (i, j) at time-step k . (a)-(h) represent the probability of moving to lattice site $(i-1, j+1)$, $(i-1, j)$, $(i-1, j-1)$, $(i, j+1)$, $(i, j-1)$, $(i+1, j+1)$, $(i+1, j)$, and $(i+1, j-1)$, respectively.

Therefore, the probability of not undergoing chemotactic movement is

$$1 - {}^{\text{UL}}S_{M_I(i,j)}^k - {}^{\text{ML}}S_{M_I(i,j)}^k - {}^{\text{LL}}S_{M_I(i,j)}^k - {}^{\text{U}}S_{M_I(i,j)}^k - {}^{\text{L}}S_{M_I(i,j)}^k - {}^{\text{UR}}S_{M_I(i,j)}^k - {}^{\text{MR}}S_{M_I(i,j)}^k - {}^{\text{LR}}S_{M_I(i,j)}^k. \quad (38)$$

Cytotoxic Death of Infected Macrophages Induced by T Cells

According to [Bowness et al. \(2018\)](#), when a T cell is in close proximity to an infected macrophage, it can migrate

towards the macrophage's position and perform cytotoxic killing of the infected macrophage, as well as the intracellular mycobacteria engulfed within the macrophage. Therefore, we postulate that at each time t_k , T cells within a radius of ρ to an infected macrophage at position $\mathbf{x}_i$ can kill the infected macrophage along with its intracellular mycobacteria with probability

$$0 \leq \tau d_{M_I, E} K_{E(i,j)}^k \leq 1, \quad (39)$$

where $d_{M_I, E}$ is associated with the efficiency of T cells at killing infected macrophages and the term $K_{E(i,j)}^k$ is linked to the number of T cells within a radius of ρ to the target cell at $\mathbf{x}_i$. The quantity $K_{E(i,j)}^k \in \mathbb{N}_0$ is defined as

$$K_{E(i,j)}^k \equiv K_E(t_k, x_i, y_j) = h_E \sum_{(h,l)} \Upsilon(x_i, x_h, y_j, y_l; \rho) E_{(h,l)}^k, \quad (40)$$

where h_E is inversely proportional to the maximum number of T cells which can be accommodated within the spatial domain and Υ is defined via Eq. (22).

2.6 Dynamics of T Cells

Recruitment of T Cells

To initiate the adaptive immune response, T cells are recruited into the spatial domain through a fixed number of blood vessels at positions in $\omega \subset \Omega$, when the extracellular mycobacterial load reaches a threshold b_{thresh} . The influx of T cells from the blood vessels is regulated by the function $q_{(i,j)}^k$, defined as

$$q_{(i,j)}^k = q(t_k, \mathbf{x}_i) = f(b_{\text{tot}}^k) \mathbf{1}_\omega(\mathbf{x}_i), \quad b_{\text{tot}}^k = \sum_{(i,j)} b_{(i,j)}^k \eta^2, \quad (41)$$

where $f(b_{\text{tot}}^k)$ is a function of the total mycobacterial density that controls the recruitment rate, $\mathbf{1}_\omega(\mathbf{x}_i)$ is the indicator function that localises the recruitment to the blood vessel locations $\omega \subset \Omega$, and $b_{(i,j)}^k$ is as defined via Eq. (31). Assuming that if the total mycobacterial density exceeds the threshold b_{thresh} , the recruitment rate is proportional to the excess mycobacterial density, we define

$$f(b_{\text{tot}}^k) = (b_{\text{tot}}^k - b_{\text{thresh}})_+ \quad (42)$$

Hence, if the total mycobacterial density b_{tot}^k exceeds the threshold b_{thresh} , the recruitment rate is proportional to the excess $(b_{\text{tot}}^k - b_{\text{thresh}})$. Otherwise, $f(b_{\text{tot}}^k)$ will be zero, and no T cells will be recruited.

Thus, between time steps k and $k+1$, the density of T cells that can enter a blood vessel at position $\mathbf{x}_i$ is controlled by $q_{(i,j)}^k$, such that

$$\tau \delta_E q_{(i,j)}^k \geq 0, \quad (43)$$

where $\delta_E \in \mathbb{R}_+^*$ is a constant of proportionality.

Death of T Cells

Following the recruitment of T cells into the system, they activate resting macrophages and exert cytotoxic actions against mycobacteria and infected macrophages. Furthermore, we postulate that at $(t_k, \mathbf{x}_i)$, a T cell undergoes natural death with probability

$$0 \leq \tau d_E \leq 1, \quad (44)$$

where $d_E \in \mathbb{R}_+^*$ is the natural death rate of T cells.

Chemotactic Migration of T Cells

The migration of T cells from one position to another can occur either via chemotaxis, influenced by the chemokine

concentration $c_{(i,j)}^k$, whose dynamics are given by Eq. (9), or through undirected random movement. When a positive chemokine signal is present in the neighbouring lattice sites, locations with higher chemokine concentrations are more likely to be chosen for T cell migration. Otherwise, the T cell moves to one of the neighbouring lattice sites selected uniformly at random, corresponding to undirected random movement. Hence, T cell chemotaxis is represented as a biased random walk, where the probabilities of migrating to neighbouring lattice sites depend on the positive difference in chemokine concentration between the current lattice site and its neighbouring sites. Furthermore, we account for the propensity of T cells to migrate towards the region of higher concentration of the chemokine using a proportionality constant $\chi \in \mathbb{R}_+^*$. This represents the chemotactic sensitivity of T cells to the chemokine. In a 2D domain, T cells at any current position at time-step k may move to one of the 8 possible positions, based on the availability of space (cf. Eq. (3)). Therefore, for a T cell on the lattice site $\mathbf{i} = (i, j)$ at time-step k , we represent the probabilities of moving to neighbouring lattice sites via chemotaxis in Table 6.

(a) ${}^{\text{UL}}S_{E(i,j)}^k = \chi \Phi_{(i-1,j+1)}^k \frac{(c_{(i-1,j+1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$	(b) ${}^{\text{ML}}S_{E(i,j)}^k = \chi \Phi_{(i-1,j)}^k \frac{(c_{(i-1,j)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$
(c) ${}^{\text{LL}}S_{E(i,j)}^k = \chi \Phi_{(i-1,j-1)}^k \frac{(c_{(i-1,j-1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$	(d) ${}^{\text{U}}S_{E(i,j)}^k = \chi \Phi_{(i,j+1)}^k \frac{(c_{(i,j+1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$
(e) ${}^{\text{L}}S_{E(i,j)}^k = \chi \Phi_{(i,j-1)}^k \frac{(c_{(i,j-1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$	(f) ${}^{\text{UR}}S_{E(i,j)}^k = \chi \Phi_{(i+1,j+1)}^k \frac{(c_{(i+1,j+1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$
(g) ${}^{\text{MR}}S_{E(i,j)}^k = \chi \Phi_{(i+1,j)}^k \frac{(c_{(i+1,j)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$	(h) ${}^{\text{LR}}S_{E(i,j)}^k = \chi \Phi_{(i+1,j-1)}^k \frac{(c_{(i+1,j-1)}^k - c_{(i,j)}^k)_+}{8c_{\max}}$

Table 6: Probabilities of migrating to neighbouring lattice sites via chemotaxis for a T cell on lattice site (i, j) at time-step k . (a)-(h) represent the probability of moving to lattice site $(i-1, j+1)$, $(i-1, j)$, $(i-1, j-1)$, $(i, j+1)$, $(i, j-1)$, $(i+1, j+1)$, $(i+1, j)$, and $(i+1, j-1)$, respectively.

Hence, the probability of not undergoing chemotactic movement is

$$1 - {}^{\text{UL}}S_{E(i,j)}^k - {}^{\text{ML}}S_{E(i,j)}^k - {}^{\text{LL}}S_{E(i,j)}^k - {}^{\text{U}}S_{E(i,j)}^k - {}^{\text{L}}S_{E(i,j)}^k - {}^{\text{UR}}S_{E(i,j)}^k - {}^{\text{MR}}S_{E(i,j)}^k - {}^{\text{LR}}S_{E(i,j)}^k, \quad (45)$$

and the earlier definition for $c_{\max}$ holds.

Undirected Random Migration of T Cells

Random migration of T cells is modelled by assuming T cells undergo a random walk with a movement probability denoted as $\xi \in \mathbb{R}_+^*$, where $0 < \xi \leq 1$. Similar to chemotactic migration, T cells can randomly change their positions to up to 8 possible lattice sites, provided there is available space (cf. Eq. (3)). Thus, for a T cell on the lattice site $\mathbf{i} = (i, j)$ at time-step k , we represent the probabilities of moving to neighbouring lattice sites via undirected random migration in Table 7.

(a) ${}^{\text{UL}}Q_{E(i,j)}^k = \Phi_{(i-1,j+1)}^k \frac{\xi}{8}$	(b) ${}^{\text{ML}}Q_{E(i,j)}^k = \Phi_{(i-1,j)}^k \frac{\xi}{8}$
(c) ${}^{\text{LL}}Q_{E(i,j)}^k = \Phi_{(i-1,j-1)}^k \frac{\xi}{8}$	(d) ${}^{\text{U}}Q_{E(i,j)}^k = \Phi_{(i,j+1)}^k \frac{\xi}{8}$
(e) ${}^{\text{L}}Q_{E(i,j)}^k = \Phi_{(i,j-1)}^k \frac{\xi}{8}$	(f) ${}^{\text{UR}}Q_{E(i,j)}^k = \Phi_{(i+1,j+1)}^k \frac{\xi}{8}$
(g) ${}^{\text{MR}}Q_{E(i,j)}^k = \Phi_{(i+1,j)}^k \frac{\xi}{8}$	(h) ${}^{\text{LR}}Q_{E(i,j)}^k = \Phi_{(i+1,j-1)}^k \frac{\xi}{8}$

Table 7: Probabilities of migrating to neighbouring lattice sites via undirected random migration for a T cell on lattice site (i, j) at time-step k . (a)-(h) represent the probability of moving to lattice site $(i-1, j+1)$, $(i-1, j)$, $(i-1, j-1)$, $(i, j+1)$, $(i, j-1)$, $(i+1, j+1)$, $(i+1, j)$, and $(i+1, j-1)$, respectively.

Hence, the probability of not undergoing undirected random movement is

$$1 - {}^{\text{UL}}Q_{E(i,j)}^k - {}^{\text{ML}}Q_{E(i,j)}^k - {}^{\text{LL}}Q_{E(i,j)}^k - {}^{\text{U}}Q_{E(i,j)}^k - {}^{\text{L}}Q_{E(i,j)}^k - {}^{\text{UR}}Q_{E(i,j)}^k - {}^{\text{MR}}Q_{E(i,j)}^k - Q_{E(\text{LR}(i,j))}. \quad (46)$$

Following the above mathematical formalisation of the actions and interactions of each individual element in the IBM, the continuum counterpart of this model can be formally derived, as shown in the next section.

3 Deterministic Continuum Counterpart

We focus on a one-dimensional (1D) setting to simplify the formal derivation of the continuum formulation. We employ the probabilistic rules governing the actions and interactions of cells, described in § 2, to formulate the mass balance equations for the corresponding cell densities (see Appendix A). Then, we let the time-step $\tau \rightarrow 0$ and the space-step $\eta \rightarrow 0$, in such a way that

$$\begin{aligned} \frac{\beta_S \eta^2}{2\tau} &\rightarrow \gamma_{N_S} \in \mathbb{R}_*^+, & \frac{\beta_F \eta^2}{2\tau} &\rightarrow \gamma_{N_F} \in \mathbb{R}_*^+, & \frac{\nu \eta^2}{2\tau} &\rightarrow \gamma_{M_R} \in \mathbb{R}_*^+, & \frac{\mu \eta^2}{2\tau c_{\max}} &\rightarrow \chi_{M_A} \in \mathbb{R}_*^+, \\ \frac{\zeta \eta^2}{2\tau c_{\max}} &\rightarrow \chi_{M_I} \in \mathbb{R}_*^+, & \frac{\chi \eta^2}{2\tau c_{\max}} &\rightarrow \chi_E \in \mathbb{R}_*^+, & \frac{\xi \eta^2}{2\tau} &\rightarrow \gamma_E \in \mathbb{R}_*^+ & \text{ as } & \tau, \eta \rightarrow 0, \end{aligned} \quad (47)$$

using the formal method outlined in (Bubba et al., 2020; Almeida et al., 2022) to derive the continuum counterpart of the idealised stochastic formulation. This results in the following coupled system of PDEs for the densities of slow-growing mycobacteria, $n_S(t, x)$, fast-growing mycobacteria, $n_F(t, x)$, mycobacteria in quiescent state, $n_Q(t, x)$, resting macrophages, $m_R(t, x)$, active macrophages, $m_A(t, x)$, infected macrophages, $m_I(t, x)$, T cells, $e(t, x)$, oxygen concentration, $O(t, x)$, and chemokine concentration, $c(t, x)$ (see Appendix A for the formal mean-field derivation of the PDEs):

$$\left\{ \begin{aligned}
& \partial_t n_S - \gamma_{N_S} \partial_x [\psi(n) \partial_x n_S - n_S \partial_x \psi(n)] = \alpha_S \psi(n) n_S + J_{F \rightarrow S}(O) n_F + w_{Q \rightarrow S} \psi(n) n_Q \\
& \quad - \left[J_{S \rightarrow F}(O) + w_{S \rightarrow Q} (1 - \psi(n)) + h_{N_S} K_{M_R} + d_{N_S, M_A} K_{M_A} \right] n_S, \\
& \partial_t n_F - \gamma_{N_F} \partial_x [\psi(n) \partial_x n_F - n_F \partial_x \psi(n)] = \alpha_F \psi(n) n_F + J_{S \rightarrow F}(O) n_S \\
& \quad - \left[J_{F \rightarrow S}(O) + w_{F \rightarrow Q} (1 - \psi(n)) + h_{N_F} K_{M_R} + d_{N_F, M_A} K_{M_A} \right] n_F, \\
& \partial_t n_Q = w_{S \rightarrow Q} (1 - \psi(n)) n_S + w_{F \rightarrow Q} (1 - \psi(n)) n_F \\
& \quad - \left[w_{Q \rightarrow S} \psi(n) + h_{N_Q} K_{M_R} + d_{N_Q, M_A} K_{M_A} \right] n_Q, \\
& \partial_t m_R - \gamma_{M_R} \partial_x [\phi(n) \partial_x m_R - m_R \partial_x \phi(n)] = \delta_{M_R} p - \left[\lambda_{M_R} b + A_{M_R, E} K_E + d_{M_R} \right] m_R, \quad x \in \Omega, \ t \in (0, t_f]. \\
& \partial_t m_A + \partial_x [\chi_{M_A} \phi(n) m_A \partial_x c] = A_{M_R, E} K_E m_R - d_{M_A} m_A, \\
& \partial_t m_I + \partial_x [\chi_{M_I} \phi(n) m_I \partial_x c] = \lambda_{M_R} b m_R - \left[d_{M_I} + d_{M_I, E} K_E \right] m_I, \\
& \partial_t e + \partial_x [\chi_E \phi(n) e \partial_x c] - \gamma_E \partial_x [\phi(n) \partial_x e - e \partial_x \phi(n)] = \delta_E q - d_E e, \\
& \partial_t O - \beta_O \partial_{xx}^2 O = \delta_O \mathbf{1}_\omega(x) - w, \\
& \partial_t c - \beta_c \partial_{xx}^2 c = \delta_c a - \kappa_c c,
\end{aligned} \right. \tag{48}$$

In the above system of PDEs, we use the following definitions

$$\begin{aligned}
n(t, x) &= n_S(t, x) + n_F(t, x) + n_Q(t, x) + m_R(t, x) + m_A(t, x) + m_I(t, x) + e(t, x), \\
w(t, x) &= O_{n_S} n_S(t, x) + O_{n_F} n_F(t, x) + O_{n_Q} n_Q(t, x) + O_{m_R} m_R(t, x) + O_{m_A} m_A(t, x) + O_{m_I} m_I(t, x) + O_e e(t, x), \\
b(t, x) &= n_S(t, x) + n_F(t, x) + n_Q(t, x), \quad a(t, x) = m_A(t, x) + m_I(t, x), \\
K_{M_R}(t, x) &= h_{M_R} \int_{\Omega} \Upsilon(x, x'; \rho) m_R(t, x') dx', \quad K_{M_A}(t, x) = h_{M_A} \int_{\Omega} \Upsilon(x, x'; \rho) m_A(t, x') dx', \\
K_E(t, x) &= h_E \int_{\Omega} \Upsilon(x, x'; \rho) e(t, x') dx', \quad p(t, x) = c_{\text{tot}}(t) \mathbf{1}_\omega(x), \quad c_{\text{tot}}(t) = \int_{\Omega} c(t, x) dx, \\
q(t, x) &= f(b_{\text{tot}}(t)) \mathbf{1}_\omega(x), \quad b_{\text{tot}}(t) = \int_{\Omega} b(t, x) dx.
\end{aligned}$$

Boundary conditions. Following the IBM rule that prevents mycobacteria or immune cells from leaving the spatial domain Ω , the continuum model satisfies zero-flux boundary conditions on $\partial\Omega$ for the system of PDEs in

(48). This applies to all equations with a transport term in (48); therefore, n_Q is exempted, since its governing equation contains none, consistent with the IBM rules. Homogeneous Neumann boundary conditions are imposed for the oxygen and chemokine concentrations:

$$\left\{ \begin{array}{l} -\gamma_{N_S} [\psi(n) \partial_x n_S - n_S \partial_x \psi(n)] = 0, \\ -\gamma_{N_F} [\psi(n) \partial_x n_F - n_F \partial_x \psi(n)] = 0, \\ -\gamma_{M_R} [\phi(n) \partial_x m_R - m_R \partial_x \phi(n)] = 0, \\ \chi_{M_A} \phi(n) m_A \partial_x c = 0, \\ \chi_{M_I} \phi(n) m_I \partial_x c = 0, \\ \chi_E \phi(n) e \partial_x c - \gamma_E [\phi(n) \partial_x e - e \partial_x \phi(n)] = 0, \\ \partial_x O = 0, \\ \partial_x c = 0, \end{array} \right. \quad x \in \partial\Omega, \quad t \in (0, t_f]. \quad (49)$$

We define the volume-filling functions ψ and ϕ as the continuum counterparts of the IBM volume-filling functions Ψ and Φ defined via Eqs. (2) and (3). Analogously, ψ and ϕ satisfy similar assumptions:

$$\psi(0) = 1, \quad \psi(\bar{n}) = 0, \quad \psi : \mathbb{R}_+ \rightarrow \mathbb{R}_+, \quad \frac{d\psi(n)}{dn} \begin{cases} < 0, & 0 \leq n < \bar{n}, \\ = 0, & n \geq \bar{n}, \end{cases} \quad \bar{n} \in \mathbb{R}_+^*. \quad (50)$$

$$\phi(0) = 1, \quad \phi(\bar{n}) = 0, \quad \phi : \mathbb{R}_+ \rightarrow \mathbb{R}_+, \quad \frac{d\phi(n)}{dn} \begin{cases} < 0, & 0 \leq n < \bar{n}, \\ = 0, & n \geq \bar{n}, \end{cases} \quad \bar{n} \in \mathbb{R}_+^*. \quad (51)$$

For the remainder of this paper, we define the volume-filling functions for the continuum model by

$$\psi(n) = \phi(n) = \left(1 - \frac{n}{\bar{n}}\right)_+, \quad (52)$$

where $\bar{n} = \bar{N}/\eta$, with η denoting the space-step size. Here, $\bar{n}$ is the critical cell density corresponding to the maximum occupancy of a spatial position.

4 The Reduced Model

The complete continuum model presented in § 3 is computationally expensive for numerical simulation. Hence, we present a reduced continuum model based on the system of PDEs in Eq. (48). While Eq. (48) is presented in 1D, extension to 2D follows analogously.

In the reduced model formulation, we retain and rename fast-growing mycobacteria as proliferating extracellular mycobacteria, with density $n_P(t, \mathbf{x})$. Hence, oxygen-dependent phenotypic switching, as well as transition to a quiescent state, is disabled. The model further retains the densities of resting macrophages, $m_R(t, \mathbf{x})$, infected macrophages, $m_I(t, \mathbf{x})$, active T cells, $e(t, \mathbf{x})$, and the chemokine concentration, $c(t, \mathbf{x})$. Hence, the reduced model omits slow-growing mycobacteria, mycobacteria in a quiescent state, active macrophages, and oxygen concentration.

Furthermore, to preserve a mechanism corresponding to the killing of extracellular mycobacteria by active macrophages in the complete model (cf. Eq. (48)), we make the modelling assumption that T cells can directly kill proliferating extracellular mycobacteria in both reduced formulations. The cytotoxic death of proliferating extracellular mycobacteria is modelled analogously to the T cell-mediated cytotoxic death of infected macrophages

in Eqs. (39) and (40). Its probabilistic formulation is presented in Appendix B.1.4, and the corresponding continuum term derivation follows the same approach as that employed for the T cell-mediated infected macrophage death in Appendix A.2.3.

For the numerical comparison, we make several further simplifying assumptions in the reduced continuum model. In particular, the spatial spread of proliferating extracellular mycobacteria arising from offspring placement and the undirected migration of resting macrophages and T cells are represented by linear diffusion. Crowding in proliferating mycobacterial growth is represented through the local proliferating mycobacterial density n_P , while crowding in the chemotactic movement of infected macrophages and T cells is represented through the total cell density n . Furthermore, the non-local interaction terms K_{M_R} and K_E of the complete continuum model are replaced in the reduced continuum model by the local terms $h_{M_R}m_R$ and h_Ee , respectively. These further simplifications apply only to the reduced continuum model used for the numerical comparison; the complete continuum model and its formal derivation in § 3 remain unchanged. The resulting reduced continuum model preserves the principal interactions between mycobacteria and the selected immune cell populations, while remaining computationally tractable for numerical simulation.

To facilitate comparison between the two modelling formulations, we implement a reduced stochastic IBM containing the same selected cell populations and key biological processes. However, in the reduced models used for the numerical comparison, selected processes are implemented differently in the two formulations. In particular, resting macrophage migration and recruitment are represented differently in the two reduced models. Resting macrophage migration is represented by undirected linear diffusion in the reduced continuum model, whereas resting macrophage movement in the implemented stochastic IBM follows a chemokine-biased random walk. The chemokine bias in the stochastic IBM is a phenomenological modelling choice used to represent effective preferential movement of resting macrophages towards infected regions, while the reduced continuum model deliberately adopts the simpler undirected diffusion representation. Resting macrophage recruitment is also represented differently: in the continuum model, recruitment occurs through a chemokine-dependent source term localised at blood vessel positions, whereas in the stochastic IBM it is implemented through discrete probabilistic recruitment events at vessel locations. These are model-specific representations of the same underlying recruitment process rather than intended one-to-one mathematical mappings between the two formulations.

Remark 3. *The magnitude of chemokine-directed migration by resting macrophages in the reduced stochastic IBM is not well quantified experimentally. Therefore, the chemotactic bias is treated as a phenomenological modelling assumption representing effective preferential movement towards infected regions.*

Hence, the coupled system of PDEs for the reduced continuum model is given by

$$\left\{ \begin{array}{l} \partial_t n_P - \nabla \cdot [\gamma_{N_P} \nabla n_P] = \alpha_P \psi_{\text{red}}(n_P) n_P - [h_{N_P} h_{M_R} m_R + d_{N_P, E} h_E e] n_P, \\ \partial_t m_R - \nabla \cdot [\gamma_{M_R} \nabla m_R] = \delta_{M_R} p - [\lambda_{M_R} n_P + d_{M_R}] m_R, \\ \partial_t m_I + \nabla \cdot [\chi_{M_I} \phi_{\text{red}}(n) m_I \nabla c] = \lambda_{M_R} n_P m_R - [d_{M_I} + d_{M_I, E} h_E e] m_I, \\ \partial_t e + \nabla \cdot [\chi_E \phi_{\text{red}}(n) e \nabla c] - \nabla \cdot [\gamma_E \nabla e] = \delta_E q - d_E e, \\ \partial_t c - \beta_c \Delta c = \delta_c m_I - \kappa_c c, \end{array} \right. \quad \mathbf{x} \in \Omega, \quad t \in (0, t_f]. \quad (53)$$

Furthermore, for the above reduced system of PDEs, we use the following definitions:

$$\begin{aligned} n(t, \mathbf{x}) &= n_P(t, \mathbf{x}) + m_R(t, \mathbf{x}) + m_I(t, \mathbf{x}) + e(t, \mathbf{x}), \\ p(t, \mathbf{x}) &= c_{\text{tot}}(t) \mathbf{1}_\omega(\mathbf{x}), \quad c_{\text{tot}}(t) = \int_{\Omega} c(t, \mathbf{x}) d\mathbf{x}, \\ q(t, \mathbf{x}) &= f(b_{\text{tot}}(t)) \mathbf{1}_\omega(\mathbf{x}), \quad b_{\text{tot}}(t) = \int_{\Omega} n_P(t, \mathbf{x}) d\mathbf{x}. \end{aligned}$$

For the reduced continuum model, we define the crowding functions by

$$\psi_{\text{red}}(n_P) = 1 - \frac{n_P}{\bar{n}}, \quad \phi_{\text{red}}(n) = 1 - \frac{n}{\bar{n}}, \quad (54)$$

with $\bar{n} = \bar{N}/\eta^2$. Here, ψ_{red} accounts for crowding in proliferating mycobacterial growth through the local proliferating mycobacterial density, whereas ϕ_{red} accounts for total cell occupancy in the chemotactic movement terms.

Consistent with the transport terms in the reduced continuum model, we impose zero-flux boundary conditions on $\partial\Omega$, given by

$$\begin{cases} -\gamma_{N_P} \nabla n_P \cdot \mathbf{n} = 0, \\ -\gamma_{M_R} \nabla m_R \cdot \mathbf{n} = 0, \\ \chi_{M_I} \phi_{\text{red}}(n) m_I \nabla c \cdot \mathbf{n} = 0, \\ [\chi_E \phi_{\text{red}}(n) e \nabla c - \gamma_E \nabla e] \cdot \mathbf{n} = 0, \\ \nabla c \cdot \mathbf{n} = 0, \end{cases} \quad \mathbf{x} \in \partial\Omega, \quad t \in [0, t_f]. \quad (55)$$

4.1 Numerical Implementation

We present the numerical implementation employed for the reduced continuum model and the reduced stochastic IBM in § 4.1.1 and § 4.1.2, respectively. Both formulations are implemented as a $2mm \times 2mm$ cross-section of lung tissue, approximated by a 100×100 uniform lattice, as used in [Bowness et al. \(2018\)](#).

The numerical implementation specifies the spatial and temporal discretisations used and the implementation of the boundary conditions. Full details of the PDE finite-difference scheme and the stochastic IBM algorithm are provided in Appendix B. We also use closely matched initial configurations of blood vessel locations, resting macrophage distributions, and proliferating extracellular mycobacterial positions for comparison between the two formulations. These configurations are generated for the continuum model and transferred to the stochastic IBM as closely as permitted by its discrete spatial implementation. The procedure used to construct and transfer the initial configurations is described in § 4.1.3.

Following [Bowness et al. \(2018\)](#), both formulations adopt a random distribution of 49 blood vessels through which immune cells are recruited throughout the 2D domain. The models also represent chemokine concentration as a continuum, and initialised both systems with an initial population of 12 proliferating extracellular mycobacteria, 105 resting macrophages, and zero infected macrophages and T cells.

4.1.1 Numerical Implementation of the Reduced Continuum Model

The reduced continuum model (53) was solved on the spatial domain

$$\Omega = (0, 0.2) \times (0, 0.2) \text{ cm}^2$$

over the time interval $t \in (0, 96]$ h, and numerical outputs were recorded every 0.1 h. The domain was discretised using a uniform 100×100 lattice, with space-step sizes

$$\Delta x = \Delta y \approx 0.002.$$

The numerical solution at time $t_k = k\Delta t$ is denoted by

$$n_{P,i,j}^k, \quad m_{R,i,j}^k, \quad m_{I,i,j}^k, \quad e_{i,j}^k, \quad c_{i,j}^k,$$

where (i, j) indexes the lattice. A time-step of

$$\Delta t = 10^{-5}$$

was used. At each time-step k , the total cell density

$$n_{i,j}^k = n_{P,i,j}^k + m_{R,i,j}^k + m_{I,i,j}^k + e_{i,j}^k$$

was calculated from the current solution. The total cell density was then used to evaluate ϕ_{num} , the numerical counterpart of ϕ_{red} , in the chemotactic terms, whereas ψ_{num} , corresponding to ψ_{red} , was evaluated using the local proliferating mycobacterial density $n_{P,i,j}^k$.

For $n_{P,i,j}^k, m_{R,i,j}^k, m_{I,i,j}^k, e_{i,j}^k, c_{i,j}^k$, the right-hand sides were evaluated using the solution at time-step k . Progression to a new time-step $k + 1$ occurs only after all five solutions have been updated by the Forward Euler method. Furthermore, the implementation is set up such that any negative values at t_{k+1} are set to zero. The zero-flux boundary conditions in Eq. (55) were imposed by setting the outward numerical fluxes at the boundary of the computational domain equal to zero.

The governing equations used for the PDE implementation were written in conservative form and discretised using finite differences. Further details on the numerical scheme employed are provided in Appendix B.1.

4.1.2 Numerical Implementation of the Reduced Stochastic IBM

Similar to the continuum model, the reduced IBM was simulated on the same domain and discretised using a lattice, with spacing $\eta = 0.002$ cm. Each IBM lattice site represents an area

$$A_{\text{site}} = \eta^2 = 4 \times 10^{-6} \text{ cm}^2.$$

Proliferating extracellular mycobacteria, resting and infected macrophages, and T cells are represented as discrete agents on the lattice sites. To match the multiple residency framework of the continuum model, multiple agents may occupy the same lattice site in the IBM, provided that their combined area does not exceed the predefined lattice site area. Thus, mycobacterial or immune cell placement, as well as immune cell migration, are subject to an area-based occupancy condition that must be met. Let $\mathcal{R}_{i,j}^k$ denote the set of agents occupying site (i, j) at time t_k . A new agent with area A_{new} may be placed at that site, provided the following condition is satisfied

$$\sum_{\ell \in \mathcal{R}_{i,j}^k} A_{\ell} + A_{\text{new}} \leq A_{\text{site}}.$$

Therefore, we choose the areas assigned to each agent type in the IBM to be consistent with literature-reported cell dimensions. *Mtb* bacilli are rod-like, typically $2\text{--}5\text{ }\mu\text{m}$ in length and $0.2\text{--}0.3\text{ }\mu\text{m}$ in width (Segovia-Juarez et al., 2004). Moreover, when in a resting state, human alveolar macrophages are round or oval in shape and can become irregularly shaped upon phagocytosis, with diameters typically in the range $15\text{--}21\text{ }\mu\text{m}$, and a reported mean diameter of $21.2 \pm 0.3\text{ }\mu\text{m}$ (Krombach et al., 1997; Fakoya et al., 2024). Resting and activated T cells have diameters in the range $8\text{--}10\text{ }\mu\text{m}$ (Cano and Lopera, 2013). Hence, the fixed agent areas used in the IBM are $1.50 \times 10^{-8} \text{ cm}^2$

(corresponding to an effective footprint of $\approx 0.3 \times 5.0 \mu\text{m}$) for a mycobacterium, $3.14 \times 10^{-6} \text{ cm}^2$ ($\approx 20 \mu\text{m}$ diameter) for a macrophage, and $5.03 \times 10^{-7} \text{ cm}^2$ ($\approx 8 \mu\text{m}$ diameter) for a T cell. We have used these areas as effective 2D footprints to enforce spatial crowding in the IBM.

For comparison with the continuum model, each stochastic realisation of the IBM uses a corresponding PDE-seed-generated configuration for initial mycobacterial and resting macrophage deposits, as well as the randomly distributed blood vessel locations. Furthermore, the implementation prohibits the initial deposition of proliferating extracellular mycobacteria and resting macrophages on lattice sites occupied by a blood vessel. Thus, following a successful immune cell recruitment event through the blood vessel, the recruited cell is placed at an available lattice site in the immediate Moore neighbourhood of the recruiting vessel with sufficient available area. However, if there is no neighbouring lattice site with available space, recruitment is abandoned for that blood vessel during the current time-step.

Simulations are performed over $t \in [0, 96]$ h, for each stochastic realisation with a distinct random-number seed, using a time-step of

$$\Delta t_W = 0.001 \text{ h}.$$

The initiation of stochastic cell events is modelled using the IBM Poisson event rule. Specifically, at each time-step, an independent random number $r \sim U(0, 1)$ is generated for each eligible event. These events could be immune cell recruitment, initiation of cell migration, phagocytosis, macrophage state transition, and cytotoxicity. Thus, an event is initiated when

$$r < 1 - \exp(-\gamma F \Delta t_W),$$

where γ is the event rate and F is an event-specific factor. Note that agents in an ongoing event remain locked until the event is completed and therefore cannot initiate another action during that period. Thus, conditional on the corresponding eligibility requirements being satisfied, the probability of event initiation during one time-step is

$$P_{\text{event}} = 1 - \exp(-\gamma F \Delta t_W).$$

Unlike the stochastic cell events described above, replication of proliferating extracellular mycobacteria and lifespan-mediated cell deaths are governed by the age of the agent rather than by the Poisson event rule. Specifically, a mycobacterium attempts replication when its age reaches its assigned replication interval, with successful replication dependent on available space within the neighbouring lattice site of order 3 (i.e. Moore neighbourhood). When an agent's age exceeds its predefined lifespan, it is removed from the system. Similar to the continuum model, outputs were recorded every 0.1 h.

Broadly, each time-step in the IBM comprises cell death, cell updates, vessel recruitment, and chemokine reaction-diffusion update. Further details of the numerical implementation on lifespan-mediated death, mycobacterial and immune cell updates, chemokine update and immune recruitment are provided in Appendix B.2.

4.1.3 Transfer of Matched Initial Configurations

To compare the continuum model and the stochastic IBM under closely matched initial spatial distributions, we ran ten PDE simulations using the same parameter set but different randomly generated initial configurations (with saved PDE seeds for reproducibility). For each PDE seed, the initial blood vessel locations, resting macrophage and mycobacterial deposition coordinates were exported and used to initialise the corresponding IBM simulations. Each of the ten saved seed configurations is then run four times in the IBM, to make a total of forty IBM stochastic realisations (with saved IBM seeds for reproducibility).

As mentioned in § 4.1.2, the IBM implementation prevents the initial deposition of proliferating mycobacteria or resting macrophages on vessel-occupied sites. Therefore, where an exported mycobacterial or resting macrophage

coordinate coincided with a vessel site, the agent was moved to the nearest available non-vessel lattice site. Across the ten extracted PDE configurations, three agent positions were adjusted in three configurations, each by a single lattice site spacing (0.002 cm). These minimal adjustments resolved the conflicts between agent initial deposition and blood vessel locations, while preserving the exported spatial configurations as closely as possible. Where adjustments have been made to fit the stochastic IBM algorithm implementation, the original and adjusted coordinates are reported in Appendix B.3. We further verified that the final transferred configurations retained the original expected population totals for initial proliferating extracellular mycobacteria and resting macrophages.

Table 8 and Table 9 summarise how parameters and initial conditions in the reduced PDE model relate to those in the closely matched IBM configuration. Identical initial conditions and parameter values were used where a direct mapping was possible. Due to the different mathematical formulations of the two models, some biological processes required calibration, reciprocal conversion or other model-specific alignment. Hence, the tables should be interpreted as a summary of how the two modelling frameworks relate to one another, rather than as a one-to-one parameter mapping.

Table 8: Comparison of the simulation setup and initial conditions used in the reduced PDE model and the closely matched IBM configuration.

Parameter/component	Reduced PDE	IBM	Relationship
Simulation setup			
Spatial domain	0.2×0.2 cm	0.2×0.2 cm	Matched
Lattice	100×100	100×100	Matched
Space-step	0.002	0.002 cm	Matched
Simulation duration	96 h	96 h	Matched
Numerical time-step	10^{-5}	10^{-3} h	Model-specific
Output interval	0.1 h	0.1 h	Matched
Number of initial configurations	10	10	Matched (transferred configurations)
Simulations per configuration	1	4	Model-specific (deterministic, stochastic)
Initial-configuration seeds	90–99	Not applicable	Configuration transferred (one seed is used to generate each of the ten PDE configurations; PDE configurations are then transferred to the IBM)
Stochastic-realisation seeds	Not applicable	1001–1004	Model-specific (for each transferred configuration into the IBM)
Initial conditions			
Initial extracellular mycobacteria	12	12	Matched
Initial resting macrophages	105	105	Matched
Initial infected macrophages	0	0	Matched
Initial T cells	0	0	Matched
Blood vessels	49	49	Matched

Notes. *Matched* indicates that identical numerical values or initial conditions were used in both models. *Model-specific* indicates that the numerical quantity or procedure was selected according to the implementation requirements of each model. *Configuration transferred* indicates that the initial configuration was generated in the PDE model and subsequently used to initialise the IBM, rather than being independently regenerated.

Table 9: Comparison of the biological processes and parameter values used in the reduced PDE model and the closely matched stochastic IBM configuration.

Parameter/component	Reduced PDE	IBM	Relationship
Mycobacterial dynamics			
Proliferation, α_P	0.73 h^{-1}	Replication interval sampled from $\mathcal{U}(6.5, 7.5) \text{ h}^a$	Calibrated; mechanistically non-equivalent
Spatial expansion following proliferation, γ_{NP}	1.0×10^{-5}	Offspring-mycobacterium placement within a Moore neighbourhood ^b	Continuum-limit correspondence
Macrophage dynamics			
Resting macrophage phagocytosis, h_{NP}	0.0010480	Uptake probability: 0.279 ^c	Approximate mapping; mechanistically non-equivalent
Resting-to-infected macrophage transition, λ_{MR}	2.925×10^{-4}	Conditional transition probability following successful uptake: 1.0	Part of the approximate uptake-and-infection mapping
Macrophage recruitment, δ_{MR}	25	Per-vessel, per-update probability: 1.5×10^{-6}	Calibrated; mechanistically non-equivalent
Resting macrophage movement, γ_{MR}	Unbiased random migration; 2.5×10^{-4}	Migration interval: 0.18 h ^d ; chemotactic bias: 45	Model-specific movement mechanisms; parameters calibrated for comparison
Infected macrophage chemotaxis, χ_{MI}	0.01	Migration interval: 24 h ^d ; chemotactic bias: 45	Calibrated; mechanistically non-equivalent
Resting macrophage death, d_{MR}	$1.0 \times 10^{-4} \text{ h}^{-1}$	Lifespan: 10 000 h	Reciprocal conversion
Infected macrophage death, d_{MI}	$5.0 \times 10^{-5} \text{ h}^{-1}$	Lifespan: 20 000 h	Reciprocal conversion
T cell dynamics			
Recruitment threshold, $\bar{b}$	Extracellular mycobacterial burden: 10 000	Extracellular mycobacterial burden: 10 000	Matched
Recruitment, δ_E	25	Per-vessel, per-update probability: 1.99×10^{-4}	Calibrated; mechanistically non-equivalent
Undirected movement, γ_E	1.0×10^{-4}	Migration interval: 0.0167 h ^d	Calibrated; mechanistically non-equivalent
Chemotaxis, χ_E	1.0×10^{-6}	Chemotactic bias: 120	Calibrated; mechanistically non-equivalent
Extracellular mycobacterial killing, d_{NPE}	0.024	Killing probability: 0.024	Numerically aligned; model-specific interpretation
Infected macrophage killing, d_{MIE}	0.00050	Killing probability: 0.00050	Numerically aligned; model-specific interpretation
T cell death, d_E	$5.0 \times 10^{-5} \text{ h}^{-1}$	Lifespan: 20 000 h	Reciprocal conversion
Chemokine dynamics			
Diffusion, β_C	0.009	0.009	Matched
Production, δ_C	0.098	0.098	Matched
Decay, κ_C	0.1 h^{-1}	0.1 h^{-1}	Matched

Notes.

^a Each IBM mycobacterium is assigned a replication interval $T_{\text{rep}} \sim \mathcal{U}(6.5, 7.5) \text{ h}$. Following successful replication, the parent and offspring are assigned new independent intervals.

^b Mycobacterial expansion in the IBM occurs through local offspring placement within a maximum neighbourhood of order three, whereas the reduced PDE represents proliferation and spatial spread continuously.

^c The macrophage infection probability was approximated as $p_{\text{eff}} \approx \lambda_{MR}/h_{NP} = 0.0002925/0.0010480 \approx 0.279$. This is implemented in the IBM using $p_{\text{uptake}} = 0.279$ and $p_{\text{switch|uptake}} = 1$, representing an approximate process-level mapping rather than an exact mathematical equivalence.

^d IBM migration parameters denote intervals between movement attempts; hence, smaller values correspond to more frequent movement. Recruitment, phagocytosis, and cytotoxicity are implemented as eligible discrete-event processes and are not directly interchangeable with continuous PDE rates.

Matched: same numerical value in both models; *Calibrated:* selected PDE parameters were adjusted pragmatically to obtain biologically plausible early-infection dynamics (particularly recruitment and migration), before the IBM comparison was performed and were then held fixed for all 10 PDE configurations; *Mechanistically non-equivalent:* the same biological process is represented differently; *Approximate mapping:* chosen to produce comparable effective behaviour; *Numerically aligned:* same value with different mathematical interpretations; *Formal continuum correspondence:* population-level continuum representation of the corresponding discrete process; *Model-specific:* defined only within the corresponding model; *Reciprocal conversion:* a lifespan T is converted to a first-order death rate using $d = 1/T$.

5 Numerical Results

We first compare the qualitative outcomes of the reduced continuum model and the stochastic IBM under one fixed parameter regime across ten closely matched initial configurations, with four IBM realisations performed for each configuration, before examining representative temporal dynamics of the cell populations and chemokine concentration in our models. The parameter values used are listed in [Table 9](#); only the initial spatial configuration varied between PDE simulations, with each configuration then used as the closely matched initial configuration for the corresponding IBM realisations.

5.1 Overall Infection Outcome in the Continuum Model and the IBM

In presenting the overall infection outcome, we analysed simulation results from both the PDE and IBM by classifying simulations as cleared by 96 h when the extracellular proliferating mycobacterial burden fell below one. For the continuum PDE model, this was used as an operational extinction threshold, since the spatially integrated bacterial burden is continuous and may take non-integer values. In the discrete IBM, a burden below one corresponds to zero extracellular proliferating mycobacteria. Simulations that did not satisfy this criterion by 96 h were classified as non-cleared.

Of the ten deterministic continuum model simulations, five cleared by 10 h, driven by effective phagocytosis by resting macrophages. In one additional simulation, clearance occurred later, with the extracellular mycobacterial population first reached a high burden, triggering T cell recruitment. The resulting cytotoxic activity led to eventual clearance at 47.8 h. This case highlights a scenario in which the innate immune response alone was insufficient, and clearance required an adaptive immune response. The remaining four simulations were non-cleared by 96 h, exhibiting varying mycobacterial dynamics. In three of the non-cleared simulations, T cells were triggered between 7 and 15 times, indicating frequent oscillations in mycobacterial burden. In these cases, the burden briefly decreased below the recruitment threshold before rising again, leading to repeated T cell activation with minimal overall impact. The final mycobacterial burdens for seeds 92, 93, and 94 were 7768.27, 9920.00, and 9886.77, respectively, at 96 h. The fourth non-cleared case exhibited a different pattern. Following initial T cell recruitment at 16 h, the mycobacterial burden decreased to 2451.29 by 38 h, before increasing again and triggering a second recruitment event at 84.6 h. The final burden reached 8469.97 mycobacteria at 96 h, and the infection remained non-cleared.

Furthermore, we summarise the outcomes of both the continuum model and the IBM across matched configurations in [Table 10](#). For each configuration, stochastic IBM realisations exhibit variability due to intrinsic randomness. Among the six PDE simulations that cleared by 96 h, the corresponding IBM realisations showed varying levels of agreement: seed 91 showed complete agreement (4/4), seed 90 showed strong agreement (3/4), seed 96 showed partial agreement (2/4), seed 95 showed weak agreement (1/4), and seeds 97 and 99 showed complete disagreement (0/4). However, for the PDE simulations that were non-cleared by 96 h, agreement was generally higher: seed 92 showed complete agreement (4/4), seeds 94 and 98 strong agreement (3/4), while seed 93 showed complete disagreement (0/4).

Moreover, in IBM realisations where T cell recruitment occurred, the difference between peak and final mycobacterial burden reflects the impact of T cell-mediated cytotoxicity. Seed 93 is particularly notable: although T cells were triggered at 10 different times in the PDE simulation, the infection remained non-cleared by 96 h. In contrast, all four IBM realisations cleared without any T cell recruitment, indicating effective control by resting macrophages alone. Additionally, seeds 97 and 99 also show notable reverse disagreement from seed 93. For seed 97, the PDE simulation cleared with T cell involvement, whereas all IBM realisations failed to clear, despite T cell recruitment in three out of four runs. Similarly, for seed 99, the PDE cleared without T cell involvement, yet all IBM realisations failed to clear, again with T cell recruitment in three out of four runs. These results suggest that,

for these configurations, T cell cytotoxicity in the IBM is not sufficient to achieve mycobacterial clearance.

Table 10: Qualitative outcomes and T cell responses for the ten closely matched PDE–IBM configurations. Four stochastic IBM realisations were generated for each configuration.

Seed	PDE outcome	PDE T cell recruitment	IBM C/NC (out of 4)	Outcome agreement	IBM T cell recruitment	Burden reduction after recruitment
90	Clearance	No	3/1	3/4	0/4	–
91	Clearance	No	4/0	4/4	0/4	–
92	Non-clearance	Yes	0/4	4/4	3/4	3/3
93	Non-clearance	Yes	4/0	0/4	0/4	–
94	Non-clearance	Yes	1/3	3/4	1/4	1/1
95	Clearance	No	1/3	1/4	1/4	1/1
96	Clearance	No	2/2	2/4	2/4	2/2
97	Clearance	Yes	0/4	0/4	3/4	3/3
98	Non-clearance	Yes	1/3	3/4	3/4	3/3
99	Clearance	No	0/4	0/4	3/4	3/3

Notes. C and NC denote the numbers of IBM realisations classified as cleared and non-cleared, respectively, by 96 h. Outcome agreement is the number of the four IBM realisations that reproduced the clearance or non-clearance outcome of the corresponding PDE simulation. Stochastic IBM T cell recruitment is reported as the number of realisations in which active T cells were recruited out of the four realisations performed. Burden reduction after recruitment is reported only among the realisations in which T cells were recruited and denotes a final mycobacterial burden lower than the peak mycobacterial burden. A dash indicates that no IBM realisation recruited T cells.

To further analyse these relationships, we present five representative plots of temporal dynamics in § 5.2, showing proliferating extracellular mycobacteria, resting macrophages, infected macrophages, T cells, and chemokine concentration. The selected configurations include: total clearance agreement (seed 91), strong clearance agreement (seed 90), total non-clearance agreement (seed 92), strong non-clearance agreement (seed 98), and complete model disagreement (seed 93). All four IBM realisations are shown for each case. The remaining configurations (seeds 94–99) are provided in Appendix C.

5.2 Representative Temporal Dynamics

5.2.1 Clearance Cases with High Outcome Agreement (Seeds 91 and 90)

Of the five representative configurations, among configurations where both models ultimately lead to mycobacterial clearance by 96 h, the IBM realisations generally achieve clearance later than the continuum model. This shows that agreement in qualitative outcome does not necessarily imply similar temporal dynamics. We illustrate these behaviours in Figure 2 and Figure 3. In the PDE simulations, we observe smooth, monotonic downward clearance trajectories, with the extracellular mycobacterial burden beginning to decline very early in both figures. In contrast, all four IBM realisations in Figure 2 exhibit stepwise increases and decreases in mycobacterial burden, before eventually clearing, consistent with discrete events of resting macrophage phagocytosis. Similar observation is seen in Figure 3, with three realisations clearing within a similar time window while one remains non-cleared with an increasing mycobacterial burden trajectory at 96 h.

Resting macrophage dynamics are broadly comparable with population number, remaining close to the initial deposit number between the two models, i.e. in the clearance PDE results and the seven cleared realisations in

Figure 2 and Figure 3, hence, emphasising the qualitative agreement in outcome. However, in the non-cleared IBM realisation in Figure 3, resting macrophages population are significantly reduced by 96 h, which is consistent with the increasing mycobacterial burden for that realisation (IBM realisation 2). Moreover, infected macrophage populations tend to be higher in IBM than in the PDE, corresponding to later mycobacterial clearance. This supports the higher chemokine concentrations observed for IBM realisations driven by infected macrophages contributions when compared to the PDE counterparts in Figure 2 and Figure 3.

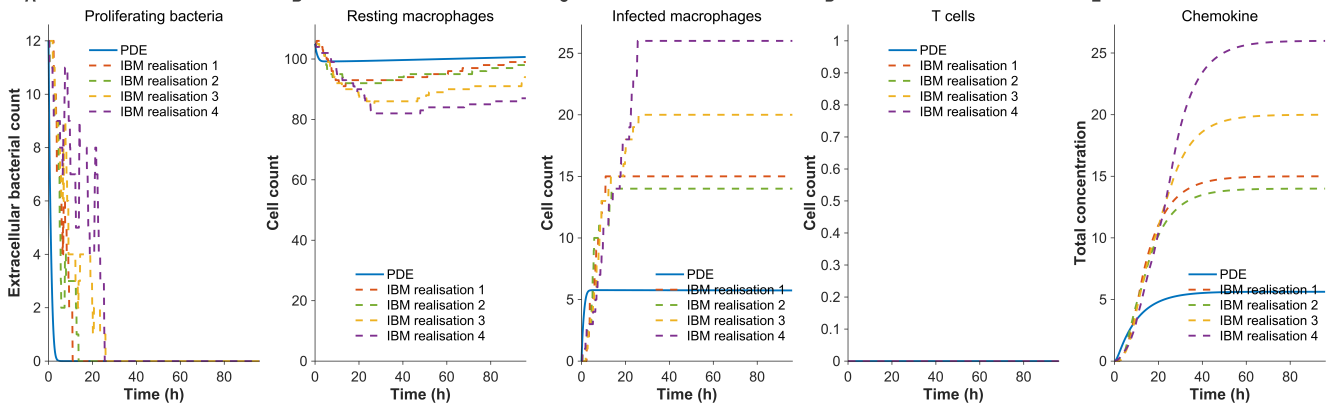


Figure 2: Temporal dynamics comparison of the reduced PDE and four stochastic IBM realisations for PDE seed 91 by 96 h.

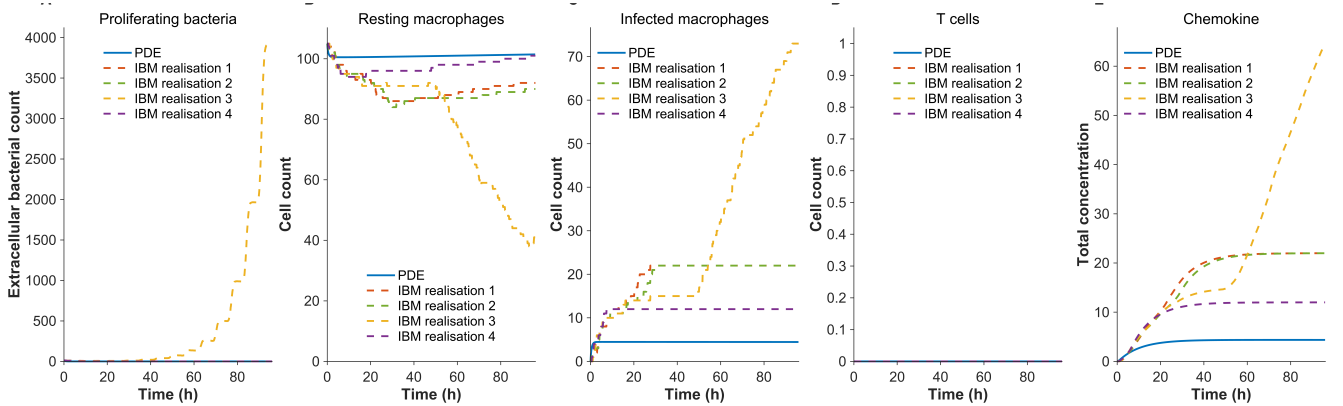


Figure 3: Temporal dynamics comparison of the reduced PDE and four stochastic IBM realisations for PDE seed 90 by 96 h.

5.2.2 Non-clearance Cases with High Outcome Agreement (Seeds 92 and 98)

In the representative configurations where both models lead to mycobacterial non-clearance by 96 h, the continuum model typically exhibits earlier but fewer recruited T cells and more pronounced oscillations in extracellular mycobacterial burden. The mycobacterial burden increases smoothly and triggers T cell recruitment very early in the simulation, usually before 15 h. In Figure 4, the proliferating extracellular mycobacterial population then undergoes repeated cycles of increase and partial, non-substantial reduction, after which a downward trajectory is observed, yet clearance is still not achieved by 96 h. In Figure 5, the mycobacterial population displays two cycles, with a more substantial reduction following the first cycle before increasing again, and then a downward trajectory, but clearance is also not achieved by 96 h. In contrast, the three IBM realisations in both Figure 4 and Figure 5 show stepwise

increases in mycobacterial burden, with T cell recruitment occurring later, typically after 75 h, and involving larger numbers of T cells. The resulting oscillations are fewer, but the downward trend in mycobacterial burden is more pronounced, reflecting stronger T cell-mediated cytotoxic effects on mycobacteria than in the continuum models.

The cytotoxic effect on infected macrophages is qualitatively comparable between the models. In the PDE, infected macrophage numbers fall to low levels (fewer than 7 cells) by 96 h, consistent with their lower peak values. In the IBM, infected macrophages remain higher, typically in the range of 16–46 cells, which is expected given their larger peak burdens, yet their trajectories still show substantial cytotoxic impact. These higher infected macrophage levels in the IBM also translate into higher chemokine concentrations compared with the PDE. A notable difference in Figure 4 and Figure 5, however, is that resting macrophages are more strongly depleted in the PDE by 96 h, whereas IBM realisations retain a reduced but clearly non-zero resting macrophage population.

Finally, Figure 4 and Figure 5 each have IBM realisation 2 that behaves differently from the others. In Figure 4, IBM realisation 2 shows a steadily increasing mycobacterial burden that does not yet reach the T cell recruitment threshold by 96 h, whereas in Figure 5, the corresponding realisation clears by 38 h without requiring T cell recruitment.

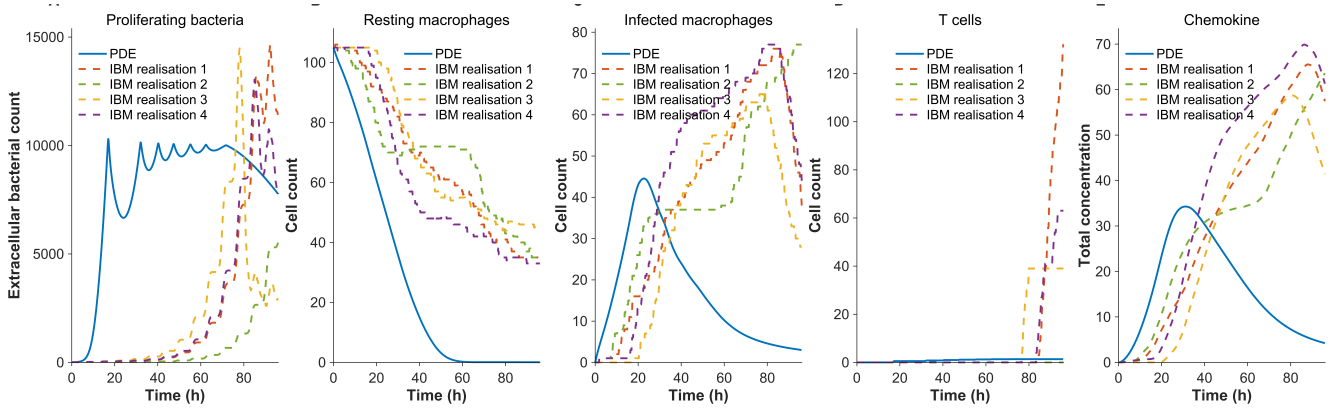


Figure 4: Temporal dynamics comparison of the reduced PDE and four stochastic IBM realisations for PDE seed 92 by 96 h.

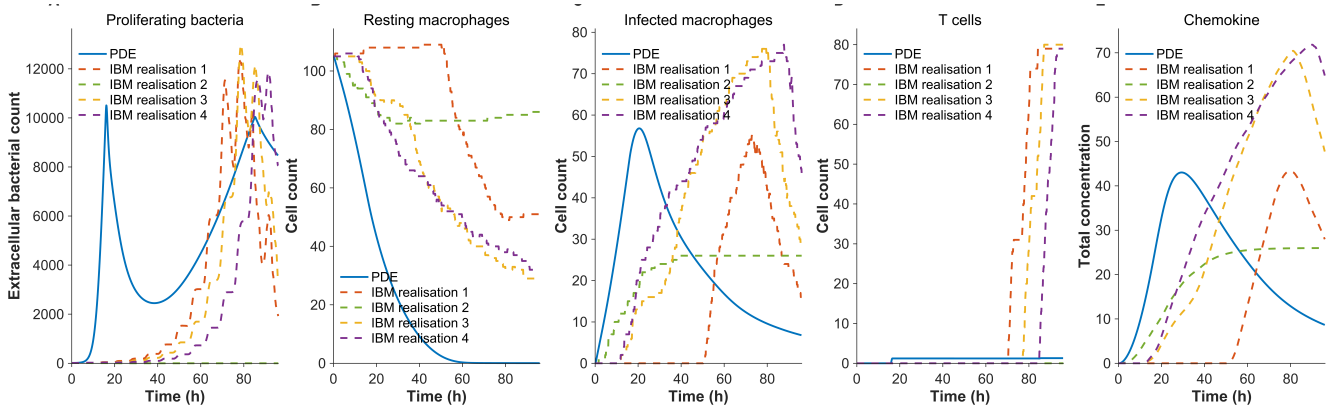


Figure 5: Temporal dynamics comparison of the reduced PDE and four stochastic IBM realisations for PDE seed 98 by 96 h.

5.2.3 Model Disagreement (Seed 93)

In the representative model disagreement case shown in Figure 6, the continuum model maintains a high proliferating extracellular mycobacterial burden and remains non-cleared by 96 h, despite repeated T cell recruitment that drives frequent oscillations in mycobacterial burden. In contrast, all IBM realisations for the same initial configurations achieve clearance between 11.9 h and 20 h without any T cell recruitment, thus, indicating effective phagocytosis by resting macrophages.

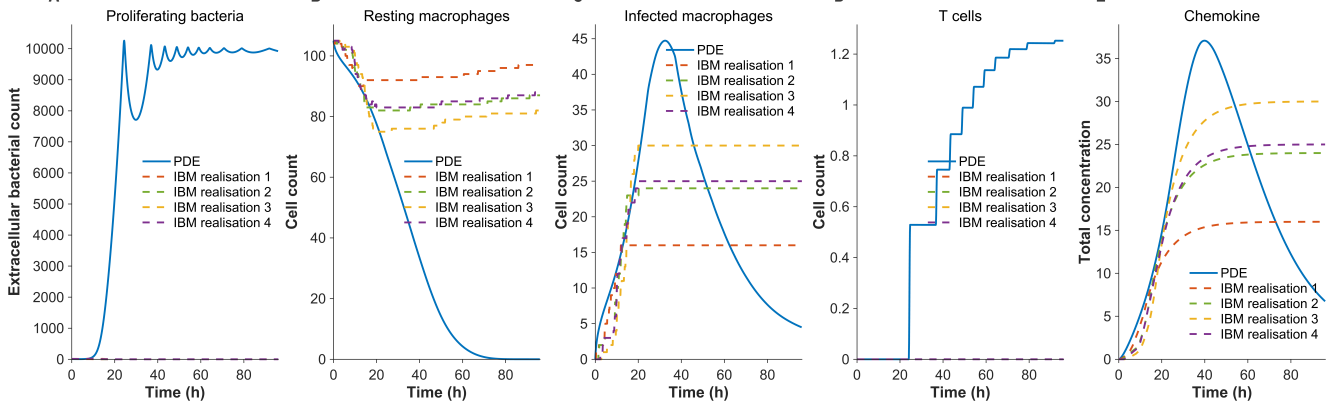


Figure 6: Temporal dynamics comparison of the reduced PDE and four stochastic IBM realisations for PDE seed 93 by 96 h.

As expected, the mycobacterial burden in the PDE result translates to the depletion of resting macrophages and a high peak in infected macrophages, whereas the IBM realisations retain a comparable resting macrophage population that subsequently begins to recover and steadily trend upward toward the initial number deposited in the system. Although relatively few T cells are recruited in the PDE, their cytotoxic effect on infected macrophages is substantial, producing a marked decline in infected macrophage numbers and an associated reduction in chemokine concentration. Following mycobacterial clearance, infected macrophages population stabilise in all IBM realisations, accompanied by more stable chemokine concentrations with less decay.

The total disagreement between the two models indicates that the two formulations translated the same initial spatial configuration into different mycobacteria-immune cell interaction dynamics. Figure 11, presented in Appendix C, demonstrates the reverse relationship, where the PDE cleared while all four IBM realisations remain non-cleared by 96 h.

The remaining five configurations are presented in Appendix C, where we have an additional example of mixed stochastic outcome of a clearance case with partial outcome agreement (Figure 7), a clearance case with weak outcome agreement (Figure 8), a non-clearance case with strong outcome agreement (Figure 9), a reverse-direction model disagreement relative to Figure 6, where the PDE cleared with and without T cell recruitment, respectively, while all four IBM realisations remained non-cleared even in realisations with T cell recruitments (Figure 10 and Figure 11).

6 Discussion, Conclusions, and Future Work

6.1 Discussion and Conclusions

In this study, we developed an idealised stochastic individual-based formulation based on Bowness et al. (2018) and formally derived a mechanistically related deterministic continuum counterpart from its probabilistic rules.

Relative to the published [Bowness et al. \(2018\)](#) model, the stochastic formulation incorporates several extensions and modifications. In particular, multiple occupancy of lattice sites is introduced to provide a more realistic representation of cellular interactions, allowing, for example, offspring mycobacteria to remain close to their parent mycobacterium and immune cells to migrate to lattice sites occupied by target cells in order to perform specific immune functions. We also modify aspects of cell movement and interaction, including the radius of interaction between cells. Furthermore, T cells are allowed to perform unbiased random movement in addition to chemotactic migration, enabling them to survey the local tissue environment even when chemokine concentrations are low while retaining chemokine-directed migration in the presence of a signal. Collectively, these modifications define the stochastic formulation used in this study and provide the basis for the formal continuum derivation.

The continuum counterpart comprises a system of coupled PDEs describing the spatial and temporal dynamics of mycobacterial and immune cell densities, together with oxygen and chemokine concentrations. The complete stochastic formulation represents multiple mycobacterial phenotypes, distinct macrophage states and active T cells. It incorporates chemotactic and unbiased cell migration, immune cell recruitment from blood vessels, phagocytosis, cytotoxic killing, oxygen-dependent mycobacterial phenotype switching, and changes in mycobacterial state driven by local crowding, which limits replication. It also represents macrophage state transitions arising from interactions with mycobacteria or active T cells.

For computational feasibility, we analysed closely matched reduced continuum and stochastic formulations that omit oxygen-driven mycobacterial phenotypic switching, thus retaining only proliferating extracellular mycobacteria. The reduced model further omits active macrophages, and replaces their killing of extracellular mycobacteria with a modelling assumption that T cells mediate effective mycobacterial killing. The reduced continuum model and the corresponding stochastic IBM are then compared for early TB infection dynamics (up to 96 h) under closely matched initial spatial configurations of proliferating extracellular mycobacteria, resting macrophages, and blood vessel locations (see [Table 8](#)). Outcomes were classified as cleared by 96 h based on an extracellular mycobacterial burden below one, and otherwise classified as non-cleared by 96 h. Across ten continuum model simulations, six resulted in clearance, five of which were as a result of an effective innate response modelled through phagocytosis of mycobacteria by resting macrophages, and one requiring an adaptive response in the form of T cell recruitment. The other four continuum model simulations remained non-cleared with high mycobacterial burdens at 96 h. Although the reduced continuum model and the corresponding IBM frequently agreed on qualitative outcomes, their temporal and cellular-level dynamics often differed. In particular, for configurations where both models cleared by 96 h, the continuum model typically exhibited rapid, smooth reductions in extracellular mycobacterial burden, whereas IBM realisations displayed more heterogeneous, stepwise trajectories and generally slower clearance. This reflects the influence of discrete phagocytic events and stochastic variation in resting macrophage–mycobacterium interactions in the IBM. Furthermore, for configurations that remained non-cleared by 96 h, the continuum model tended to recruit T cells earlier and produced more pronounced oscillations in mycobacterial burden, while IBM realisations often triggered T cell recruitment at later times with fewer oscillatory cycles but more pronounced T cell–mediated reductions in mycobacterial burden.

Outcome agreement was generally higher for non-clearance than for clearance cases under the fixed parameter regime considered here, suggesting that the two formulations show greater agreement under conditions in which early innate and adaptive responses are insufficient to control TB infection within the simulation time window of 96 h. This pattern is consistent with observations in other studies comparing individual-based models and continuum approximations, where closer agreement is observed in regimes with large population sizes and discrepancies become more likely when population numbers are low ([Macfarlane et al., 2022](#); [Bubba et al., 2020](#)). In our simulations, high-burden non-clearance configurations maintain large mycobacterial populations up to 96 h, whereas clearance cases typically involve low mycobacterial burdens, except for an outlier case seen in [Figure 10](#), where a high mycobacterial

burden was observed before eventual clearance by 96 h. Moreover, due to stochasticity inherent in the IBM, model realisations can diverge from the single deterministic PDE trajectory, as observed for [Figure 6](#), [Figure 10](#) and [Figure 11](#) in Appendix C. Hence, partial or total disagreement highlights regimes in which stochastic effects and model structure can substantially alter predicted infection trajectories and outcomes.

More broadly, our results show that, although the continuum model is deterministic, variation in the initial spatial distribution of mycobacteria leads to markedly different infection outcomes, ranging from early clearance to late clearance and sustained high mycobacterial burden. In the stochastic IBM, the same initial configuration can produce realisations that differ in clearance time, peak burden, and the level of T cell involvement, highlighting the impact of stochastic effects at the individual level. Differences among IBM realisations from the same configuration may arise from intrinsic stochastic variability, while discrepancies between matched PDE and IBM simulations likely reflect both stochasticity and differences in the underlying mathematical formulations. These findings are consistent with the modelling framework that served as a basis for our work, in which the spatial distribution of mycobacteria strongly influences infection outcomes ([Bowness et al., 2018](#)).

Representative spatial outputs with strong non-clearance outcome agreement from the continuum model and IBM are presented in Appendix C, [Figure 12](#) and [Figure 13](#), respectively. The PDE panels display continuous population densities, whereas the stochastic IBM panels show the locations of individual agents on the lattice. In both models, mycobacterial and immune cell populations remain concentrated around the initial infection region, indicating broad qualitative agreement in infection localisation. However, the PDE populations are generally more spatially diffuse, while the IBM agents remain more locally clustered and vary among stochastic realisations. These plots therefore allow qualitative comparison of population localisation and spread, but not a quantitative assessment of spatial agreement because the two models represent spatial populations using different quantities.

Despite these insights, we acknowledge several limitations in our work. In the complete formulation, T cells are involved in both macrophage activation and cytotoxic killing, while in the reduced model they are also assumed to directly kill extracellular mycobacteria. Representing T cells as a single population rather than as distinct functional sub-populations therefore reduces the biological detail of the model and should be considered when interpreting T cell-mediated effects. Furthermore, both reduced formulations used in the numerical comparison focus on early infection over a relatively short time window (96, h) and do not capture longer-term granuloma formation or relapse reported in human studies and animal experimental models ([Colangeli et al., 2018](#); [Consortium et al., 2002](#); [Li et al., 2015](#)). In particular, T cell recruitment in both models is triggered by high mycobacterial burdens on a short timescale, whereas studies have shown that it typically takes about 7–14 days in murine models ([Urdahl et al., 2011](#); [Reiley et al., 2008](#); [Gallegos et al., 2008](#)) and 4–6 weeks in humans and non-human primates before an adaptive response is observed ([Capuano III et al., 2003](#)), which falls beyond our simulated time window.

Although we closely matched the simulation setups and initial conditions in the two formulations (see [Table 8](#)), a one-to-one correspondence of all parameter values is not possible. Some parameters required calibration, reciprocal transformations, or other model-specific alignment ([Table 9](#)), which may have contributed to quantitative differences between the formulations. In particular, model-specific differences in resting macrophage migration and recruitment may influence their spatial distribution and interactions with extracellular mycobacteria, and therefore contribute to differences in the observed infection dynamics. Moreover, because the continuum formulation is a population-level approximation rather than an exact event-level representation of the stochastic IBM, some discrepancies may arise from differences in model structure. In particular, mycobacterial replication and offspring placement remain discrete events in the IBM, alongside stochastic event scheduling. Spatial occupancy and crowding are also represented differently between the two reduced formulations. In the IBM, finite-capacity constraints are imposed at lattice sites during mycobacterial proliferation and during immune cell migration. In the reduced continuum model, spatial spread arising from mycobacterial offspring placement and the undirected movement of resting macrophages

and T cells are captured through linear diffusion. Crowding effects are incorporated separately, through the local proliferating mycobacterial density n_P in bacterial growth and through the total cell density n in chemotactic movement. Thus, the two formulations differ not only in how spatial occupancy is imposed, but also in how crowding and spatial spread are represented. These structural differences should be considered when interpreting quantitative disagreement between the models.

Furthermore, our comparison is restricted to a relatively small finite set of initial configurations, which may not represent the full range of spatial differences that could occur in TB infection. Finally, because the IBM is stochastic, we expect that repeated simulations with identical inputs may lead to different outcomes. Hence, while we ran four IBM realisations per configuration to mitigate uncertainty from intrinsic stochasticity, this may not fully characterise the range of possible behaviours, particularly near the boundary between clearance and non-clearance.

Overall, our comparison of the reduced deterministic continuum and stochastic individual-based formulations of early TB infection shows that qualitative agreement in infection outcome does not necessarily imply similar temporal dynamics or underlying cellular behaviour. The continuum formulation captures broad population-level clearance and non-clearance behaviour, whereas the stochastic IBM reveals variability in infection trajectories, recruitment timing, and local interactions between mycobacteria and immune cells. Model disagreement in specific configurations underscores the importance of spatial structure and stochasticity in shaping early infection outcomes. However, the present comparison does not establish general agreement between the two formulations beyond the parameter regime and initial spatial configurations considered here.

These findings highlight the complementary roles of the two approaches: the continuum formulation is well suited to population-level analysis and systematic parameter exploration, whereas the stochastic IBM is valuable when individual-level variability, discrete interactions, and fine-scale spatial heterogeneity are important. Used together, the two formulations can therefore provide complementary insight into early within-host TB dynamics.

6.2 Future Work

Future work would extend this comparison to the full stochastic formulation by incorporating mycobacterial phenotypic switching and active macrophages into the IBM and comparing its behaviour with the coupled PDE system in Eq. (48). This would allow us to assess whether the qualitative relationships identified in the reduced models persist when additional biological mechanisms are included. The implementation of resting macrophage recruitment could also be more closely aligned between the two formulations. In particular, recruitment in the stochastic IBM could be made dependent on local chemokine signalling at vascular sources while retaining its stochastic event-based implementation, consistent with previous IBMs of TB infection (Fallahi-Sichani et al., 2011; Cilfone et al., 2013). This would help determine whether the current differences in recruitment mechanisms contribute to disagreement between the continuum model and the IBM.

Extending the simulations beyond the literature-reported timescale for adaptive immune recruitment would allow longer-term granuloma development to be examined and would help determine whether early agreement or disagreement between the models predicts subsequent containment, progression, reactivation, or relapse. Such extensions could also help clarify the respective roles of spatial heterogeneity and stochasticity in TB infection. Moreover, modelling distinct T cell subsets according to their functions, such as macrophage activation and cytotoxic activity, would provide a more biologically detailed representation of the adaptive immune response.

Finally, systematic parameter sensitivity, calibration, and uncertainty analyses could be performed in both models to determine which biological processes most strongly influence agreement or divergence between the continuum model and the IBM. Extending the comparison to a larger set of initial spatial configurations and additional IBM realisations would also provide a more comprehensive characterisation of heterogeneity, particularly near the boundary between clearance and non-clearance.

Statements and Declarations

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Competing Interests

The authors declare no competing interests.

Data and Code Availability

The C++ model code used in this study is hosted in a private GitHub repository and will be made publicly available upon publication at <https://github.com/Ruth-Bowness-Group/within-host-tb-ibm-model/releases/tag/paper-v1.0>. The analysis and simulation scripts, together with the associated simulation data, have been deposited in Zenodo and will be made publicly accessible upon publication at <https://doi.org/10.5281/zenodo.22737915>.

A Formal PDE Model Derivation

The continuum formulation is obtained through a formal mean-field derivation from an idealised stochastic lattice process. The derivation uses mean-field closure and Taylor expansion to obtain the corresponding continuum equations and should be interpreted as a formal population-level approximation rather than a rigorous convergence proof.

We employ the derived probabilistic rules of the stochastic formulation to construct the mass balance equations essential for the formal derivation of the deterministic continuum counterpart. For simplicity, the derivation is presented in one spatial dimension (1D), which reduces the notational and algebraic complexity while retaining the mechanisms needed to obtain the continuum terms. The 2D operators used in the continuum model are interpreted as isotropic analogues of the 1D expressions derived here, with neighbourhood-dependent prefactors absorbed into the effective transport coefficients. Hereafter, we use the notation $\mathbf{i} \equiv i$ and $\mathbf{x}_i \equiv x_i$.

Preliminaries and Notation

We denote by $n_{S_i}^k$ the density of slow-growing mycobacteria, which is defined as the number of slow-growing mycobacteria at (t_k, x_i) , $N_{S_i}^k \in \mathbb{N}_0$, divided by the size of a lattice site, that is,

$$n_{S_i}^k \equiv n_S(t_k, x_i) = \frac{N_{S_i}^k}{\eta}. \quad (\text{A.1})$$

Similarly, we denote by $n_{F_i}^k$ the density of fast-growing mycobacteria, which is the number of fast-growing mycobacteria at position at (t_k, x_i) , $N_{F_i}^k \in \mathbb{N}_0$, divided by the size of a lattice site, that is,

$$n_{F_i}^k \equiv n_F(t_k, x_i) = \frac{N_{F_i}^k}{\eta}. \quad (\text{A.2})$$

Furthermore, $n_{Q_i}^k$ denotes the density of mycobacteria in quiescent state, such that,

$$n_{Q_i}^k \equiv n_Q(t_k, x_i) = \frac{N_{Q_i}^k}{\eta}, \quad (\text{A.3})$$

where $N_{Q_i}^k \in \mathbb{N}_0$ is the number of mycobacteria in quiescent state that occupy position x_i at time t_k . We let $m_{R_i}^k$ be the density of resting macrophages, which is the number of resting macrophages at (t_k, x_i) , $M_{R_i}^k \in \mathbb{N}_0$, divided by the size of a lattice site, that is,

$$m_{R_i}^k \equiv m_R(t_k, x_i) = \frac{M_{R_i}^k}{\eta}. \quad (\text{A.4})$$

In a similar way, $m_{A_i}^k$ denotes the density of active macrophages, such that

$$m_{A_i}^k \equiv m_A(t_k, x_i) = \frac{M_{A_i}^k}{\eta}, \quad (\text{A.5})$$

where $M_{A_i}^k \in \mathbb{N}_0$ is the number of active macrophages that can occupy position x_i at time t_k . Also, we let $m_{I_i}^k$ be the number of infected macrophages that can occupy position x_i at time t_k . Thus, the density of infected macrophages $m_{I_i}^k$ is defined as

$$m_{I_i}^k \equiv m_I(t_k, x_i) = \frac{M_{I_i}^k}{\eta}. \quad (\text{A.6})$$

Finally, e_i^k denotes the density of T cells, which is the number of T cells at (t_k, x_i) , $E_i^k \in \mathbb{N}_0$, divided by the size of a lattice site, i.e.

$$e_i^k \equiv e(t_k, x_i) = \frac{E_i^k}{\eta}. \quad (\text{A.7})$$

Similar to the 2D domain, we use the functions: $\Psi(N_i^k)$ for mycobacterial proliferation and growth, and $\Phi(N_i^k)$ for immune cell migration, with

$$N_i^k = N_{S_i}^k + N_{F_i}^k + N_{Q_i}^k + M_{R_i}^k + M_{A_i}^k + M_{I_i}^k + E_i^k, \quad (\text{A.8})$$

where N_i^k is the total number of cells (mycobacterial or immune) at site i at time t_k .

To translate the discrete variables into a continuum setting, we define corresponding continuum variables. Let $n(t, x)$ represent the continuous approximation of the number of cells at position x and time t . We denote the densities of slow-growing mycobacteria, fast-growing mycobacteria, mycobacteria in the quiescent state, resting macrophages, active macrophages, infected macrophages, and T cells by $n_S(t, x)$, $n_F(t, x)$, $n_Q(t, x)$, $m_R(t, x)$, $m_A(t, x)$, $m_I(t, x)$, and $e(t, x)$, respectively. We further denote the oxygen and chemokine concentrations by $O(t, x)$ and $c(t, x)$, respectively. The discrete quantities Ψ_i^k and Φ_i^k can then be expressed as functions of $n(t, x)$ as follows

$$\Psi_i^k \approx \psi(n(t, x)), \quad \Psi_{i\pm 1}^k \approx \psi(n(t, x \pm \eta)), \quad \Phi_i^k \approx \phi(n(t, x)), \quad \Phi_{i\pm 1}^k \approx \phi(n(t, x \pm \eta)), \quad (\text{A.9})$$

where consistent with the assumptions on ψ and ϕ given by Eqs. (2) and (3), the functions ψ and ϕ are as introduced in § 3, with η denoting the space-step size and $\bar{n} = \bar{N}/\eta$ the critical cell density in the continuum model, analogous to critical cell number $\bar{N}$ in the discrete model.

Remark A.1. *In the formal continuum limit, the lattice-site capacity is assumed to scale with the measure of the lattice site so that the corresponding critical density $\bar{n}$ remains finite as $\eta \rightarrow 0$. This is a formal scaling assumption used in deriving the continuum formulation and is distinct from the fixed physical site capacity used in the stochastic IBM numerical simulations.*

Assuming that the time-step, τ , and the space-step, η , are sufficiently small, we define $t := t_k$ and $x := x_i$. Thus, we have $t_{k+1} = t + \tau$ and $x_{i\pm 1} = x \pm \eta$. Additionally, recalling the definitions of $K_{M_R}(t_k, x_i)$, $K_{M_A}(t_k, x_i)$, and $K_E(t_k, x_i)$ as outlined in Eqs. (21), (26), and (40), respectively, along with $p(t_k, x_i)$ and $q(t_k, x_i)$ defined via Eqs. (29) and (41), we formally introduce the following continuum relations:

$$\begin{aligned} K_{M_R}(t, x) &= h_{M_R} \int_{\Omega} \Upsilon(x, x'; \theta) m_R(t, x') dx', \quad K_{M_A}(t, x) = h_{M_A} \int_{\Omega} \Upsilon(x, x'; \theta) m_A(t, x') dx', \\ K_E(t, x) &= h_E \int_{\Omega} \Upsilon(x, x'; \theta) e(t, x') dx', \quad p(t, x) = c_{\text{tot}}(t) \mathbf{1}_{\omega}(x), \quad c_{\text{tot}}(t) = \int_{\Omega} c(t, x) dx, \\ b(t, x) &= n_S(t, x) + n_F(t, x) + n_Q(t, x), \quad q(t, x) = f(b_{\text{tot}}(t)) \mathbf{1}_{\omega}(x), \quad b_{\text{tot}}(t) = \int_{\Omega} b(t, x) dx, \\ n(t, x) &= n_F(t, x) + n_S(t, x) + n_Q(t, x) + m_R(t, x) + m_A(t, x) + m_I(t, x) + e(t, x). \end{aligned} \quad (\text{A.10})$$

A.1 Formal Derivation of PDE for Extracellular Mycobacteria

A.1.1 Formal Derivation of the PDE for the Density of Slow-growing Mycobacteria

The principle mass balance gives the following difference equation for the density of slow-growing mycobacteria $n_{S_i}^k$

$$\begin{aligned} n_{S_i}^{k+1} &= n_{S_i}^k + \tau \alpha_S [n_{S_i}^k \Psi_i^k] + \frac{\beta_S}{2} \left[\Psi_i^k n_{S_{i-1}}^k + \Psi_i^k n_{S_{i+1}}^k \right] - \frac{\beta_S}{2} \left[\Psi_{i+1}^k + \Psi_{i-1}^k \right] n_{S_i}^k \\ &\quad + \tau \left[J_{F \rightarrow S}(O_i^k) n_{F_i}^k + w_{Q \rightarrow S} \Psi_i^k n_{Q_i}^k \right] \\ &\quad - \tau \left[J_{S \rightarrow F}(O_i^k) + w_{S \rightarrow Q}(1 - \Psi_i^k) + h_{N_S} K_{M_R}^k + d_{N_S, M_A} K_{M_A}^k \right] n_{S_i}^k, \end{aligned} \quad (\text{A.11})$$

where $\alpha_S \in \mathbb{R}_+^*$ represents the proliferation rate of slow-growing mycobacteria and $\beta_S \in (0, 1)$ represents probability of slow-growing mycobacteria growing into a new position due to proliferation. Using the continuum relations in

Eq. (A.10), Eq. (A.11) can be formally written in approximate form as

$$\begin{aligned}
n_S(t + \tau, x) = & n_S(t, x) + \tau \alpha_S [n_S(t, x) \psi(n(t, x))] \\
& + \frac{\beta_S}{2} \left[\psi(n(t, x)) n_S(t, x - \eta) + \psi(n(t, x)) n_S(t, x + \eta) \right] \\
& - \frac{\beta_S}{2} \left[\psi(n(t, x + \eta)) + \psi(n(t, x - \eta)) \right] n_S(t, x) \\
& + \tau \left[J_{F \rightarrow S}(O(t, x)) n_F(t, x) + w_{Q \rightarrow S} \psi(n(t, x)) n_Q(t, x) \right] \\
& - \tau \left[J_{S \rightarrow F}(O(t, x)) + w_{S \rightarrow Q} (1 - \psi(n(t, x))) \right] n_S(t, x) \\
& - \tau \left[h_{N_S} K_{M_R}(t, x) + d_{N_S, M_A} K_{M_A}(t, x) \right] n_S(t, x), \quad x \in \Omega.
\end{aligned} \tag{A.12}$$

If the function $\psi(n)$ is thrice continuously differentiable, and $n_S(t, x)$ is thrice continuously differentiable with respect to x , for sufficiently small η , using Taylor series up to second-order derivatives and grouping higher-order terms, i.e

$$n_S(t, x \pm \eta) = n_S \pm \eta \partial_x n_S + \frac{\eta^2}{2} \partial_{xx}^2 n_S + O(\eta^3), \quad \psi(n(t, x \pm \eta)) = \psi(n) \pm \eta \partial_x \psi(n) + \frac{\eta^2}{2} \partial_{xx}^2 \psi(n) + O(\eta^3),$$

expanding Eq. (A.12) and collecting like terms, we obtain

$$\begin{aligned}
n_S(t + \tau, x) - n_S(t, x) = & \tau \alpha_S [n_S \psi(n)] \\
& + \frac{\beta_S}{2} \left[(\psi(n) + \psi(n)) n_S + \eta (\psi(n) - \psi(n)) \partial_x n_S + \frac{\eta^2}{2} (\psi(n) + \psi(n)) \partial_{xx}^2 n_S \right] \\
& - \frac{\beta_S}{2} \left[(\psi(n) + \psi(n)) + \eta (\partial_x (\psi(n) - \psi(n))) + \frac{\eta^2}{2} (\partial_{xx}^2 (\psi(n) + \psi(n))) \right] n_S \\
& + \tau \left[J_{F \rightarrow S}(O) n_F + w_{Q \rightarrow S} \psi(n) n_Q \right] - \tau \left[J_{S \rightarrow F}(O) + w_{S \rightarrow Q} (1 - \psi(n)) \right] n_S \\
& - \tau \left[h_{N_S} K_{M_R} + d_{N_S, M_A} K_{M_A} \right] n_S + \mathcal{O}(\eta^3), \quad x \in \Omega.
\end{aligned} \tag{A.13}$$

Dividing both sides of Eq. (A.13) by τ and under the assumption given by Eq. (50), the balance equation reduces to

$$\begin{aligned}
\frac{n_S(t + \tau, x) - n_S(t, x)}{\tau} = & \alpha_S n_S \psi(n) \\
& + \frac{\beta_S}{\tau} \left[\psi(n) n_S + \frac{\eta^2}{2} \psi(n) \partial_{xx}^2 n_S \right] - \frac{\beta_S}{\tau} \left[\psi(n) n_S + \frac{\eta^2}{2} n_S \partial_{xx}^2 \psi(n) \right] \\
& + J_{F \rightarrow S}(O) n_F + w_{Q \rightarrow S} \psi(n) n_Q - \left[J_{S \rightarrow F}(O) + w_{S \rightarrow Q} (1 - \psi(n)) \right] n_S \\
& - \left[h_{N_S} K_{M_R} + d_{N_S, M_A} K_{M_A} \right] n_S + \mathcal{O}(\eta^3), \quad x \in \Omega.
\end{aligned} \tag{A.14}$$

Letting $\tau \rightarrow 0$ and $\eta \rightarrow 0$ in such a way that

$$\frac{\beta_S \eta^2}{2\tau} \rightarrow \gamma_{N_S} \in \mathbb{R}_*^+ \quad \text{as} \quad \tau, \eta \rightarrow 0$$

and ignoring $O(\eta^3)$, we formally obtain

$$\begin{aligned}
\partial_t n_S - \gamma_{N_S} \partial_x [\psi(n) \partial_x n_S - n_S \partial_x \psi(n)] = & \alpha_S \psi(n) n_S + J_{F \rightarrow S}(O) n_F + w_{Q \rightarrow S} \psi(n) n_Q \\
& - \left[J_{S \rightarrow F}(O) + w_{S \rightarrow Q}(1 - \psi(n)) + h_{N_S} K_{M_R} + d_{N_S, M_A} K_{M_A} \right] n_S, \quad (\text{A.15}) \\
& x \in \Omega.
\end{aligned}$$

A.1.2 Formal Derivation of the PDE for the Density of Fast-growing Mycobacteria

The principle mass balance gives the following difference equation for the density of fast-growing mycobacteria $n_{F_i}^k$

$$\begin{aligned}
n_{F_i}^{k+1} = & n_{F_i}^k + \tau \alpha_F [n_{F_i}^k \Psi_i^k] + \frac{\beta_F}{2} \left[\Psi_i^k n_{F_{i-1}}^k + \Psi_i^k n_{F_{i+1}}^k \right] - \frac{\beta_F}{2} \left[\Psi_{i+1}^k + \Psi_{i-1}^k \right] n_{F_i}^k \\
& + \tau \left[J_{S \rightarrow F}(O_i^k) n_{S_i}^k \right] - \tau \left[J_{F \rightarrow S}(O_i^k) + w_{F \rightarrow Q}(1 - \Psi_i^k) + h_{N_S} K_{M_{R_i}}^k + d_{N_S, M_A} K_{M_{A_i}}^k \right] n_{F_i}^k, \quad (\text{A.16})
\end{aligned}$$

where $\alpha_F \in \mathbb{R}_+^*$ represents the proliferation rate of fast-growing mycobacteria and $\beta_F \in (0, 1)$ represents probability of fast-growing mycobacteria growing into a new position due to proliferation. Using the continuum relations in Eq. (A.10), Eq. (A.16) can be formally written in the approximate form as

$$\begin{aligned}
n_F(x, t) = & n_F(t, x) + \tau \alpha_F [n_F(t, x) \psi(n(t, x))] \\
& + \frac{\beta_F}{2} \left[\psi(n(t, x)) n_F(t, x - \eta) + \psi(n(t, x)) n_F(t, x + \eta) \right] \\
& - \frac{\beta_F}{2} \left[\psi(n(t, x + \eta)) + \psi(n(t, x - \eta)) \right] n_F(t, x) \\
& + \tau J_{S \rightarrow F}(O(t, x)) n_S(t, x) - \tau \left[J_{F \rightarrow S}(O(t, x)) + w_{F \rightarrow Q}(1 - \psi(n(t, x))) \right] n_F(t, x) \\
& - \tau \left[h_{N_F} K_{M_R}(t, x) + d_{N_F, M_A} K_{M_A}(t, x) \right] n_F(t, x), \quad x \in \Omega. \quad (\text{A.17})
\end{aligned}$$

If the function $\psi(n)$ is thrice continuously differentiable, and $n_F(t, x)$ is thrice continuously differentiable with respect to x , for sufficiently small η , using Taylor series up to second-order derivatives and grouping higher-order terms we obtain

$$\begin{aligned}
n_F(t + \tau, x) - n_F(t, x) = & \tau \alpha_F [n_F \psi(n)] \\
& + \frac{\beta_F}{2} \left[(\psi(n) + \psi(n)) n_F + \eta (\psi(n) - \psi(n)) \partial_x n_F + \frac{\eta^2}{2} (\psi(n) + \psi(n)) \partial_{xx}^2 n_F \right] \\
& - \frac{\beta_F}{2} \left[(\psi(n) + \psi(n)) + \eta (\partial_x (\psi(n) - \psi(n))) + \frac{\eta^2}{2} (\partial_{xx}^2 (\psi(n) + \psi(n))) \right] n_F \\
& + \tau J_{S \rightarrow F}(O) n_S - \tau \left[J_{F \rightarrow S}(O) + w_{F \rightarrow Q}(1 - \psi(n)) \right] n_F \\
& - \tau \left[h_{N_F} K_{M_R} + d_{N_F, M_A} K_{M_A} \right] n_F + \mathcal{O}(\eta^3), \quad x \in \Omega. \quad (\text{A.18})
\end{aligned}$$

Dividing both sides of Eq. (A.18) by τ and under the assumption given by Eq. (50), the balance equation reduces to

$$\begin{aligned}
\frac{n_F(t+\tau, x) - n_F(t, x)}{\tau} &= \alpha_F n_F \psi(n) \\
&+ \frac{\beta_F}{\tau} \left[\psi(n) n_F + \frac{\eta^2}{2} \psi(n) \partial_{xx}^2 n_F \right] - \frac{\beta_F}{\tau} \left[\psi(n) n_F + \frac{\eta^2}{2} n_F \partial_{xx}^2 \psi(n) \right] \\
&+ J_{S \rightarrow F}(O) n_S - \left[J_{F \rightarrow S}(O) + w_{F \rightarrow Q}(1 - \psi(n)) \right] n_F \\
&- \left[h_{N_F} K_{M_R} + d_{N_F, M_A} K_{M_A} \right] n_F + \mathcal{O}(\eta^3), \quad x \in \Omega.
\end{aligned} \tag{A.19}$$

Letting $\tau \rightarrow 0$ and $\eta \rightarrow 0$ in such a way that

$$\frac{\beta_F \eta^2}{2\tau} \rightarrow \gamma_{N_F} \in \mathbb{R}_*^+ \quad \text{as} \quad \tau, \eta \rightarrow 0$$

and ignoring $\mathcal{O}(\eta^3)$, we formally obtain

$$\begin{aligned}
\partial_t n_F - \gamma_{N_F} \partial_x [\psi(n) \partial_x n_F - n_F \partial_x \psi(n)] &= \alpha_F \psi(n) n_F + J_{S \rightarrow F}(O) n_S \\
&- \left[J_{F \rightarrow S}(O) + w_{F \rightarrow Q}(1 - \psi(n)) + h_{N_F} K_{M_R} + d_{N_F, M_A} K_{M_A} \right] n_F, \\
&x \in \Omega.
\end{aligned} \tag{A.20}$$

A.1.3 Formal Derivation of the PDE for the Density of Mycobacteria in Quiescent State

The principle mass balance gives the following difference equation for the density of mycobacteria in a quiescent state $n_{Q_i}^k$

$$\begin{aligned}
n_{Q_i}^{k+1} &= n_{Q_i}^k + \tau \left[w_{S \rightarrow Q}(1 - \Psi_i^k) n_{S_i}^k + w_{F \rightarrow Q}(1 - \Psi_i^k) n_{F_i}^k \right] \\
&- \tau \left[w_{Q \rightarrow S} \Psi_i^k + h_{N_Q} K_{M_{R_i}}^k + d_{N_Q, M_A} K_{M_{A_i}}^k \right] n_{Q_i}^k.
\end{aligned} \tag{A.21}$$

Using the continuum relations in Eq. (A.10), Eq. (A.21) can be formally written in the approximate form as

$$\begin{aligned}
n_Q(t+\tau, x) &= n_Q(t, x) + \tau \left[w_{S \rightarrow Q}(1 - \psi(n(t, x))) n_S(t, x) + w_{F \rightarrow Q}(1 - \psi(n(t, x))) n_F(t, x) \right] \\
&- \tau \left[w_{Q \rightarrow S} \psi(n(t, x)) + h_{N_Q} K_{M_R}(t, x) + d_{N_Q, M_A} K_{M_A}(t, x) \right] n_Q(t, x), \quad x \in \Omega.
\end{aligned} \tag{A.22}$$

Expanding Eq. (A.22) using Taylor series up to second-order derivatives and grouping higher-order terms, we obtain

$$\begin{aligned}
n_Q(t+\tau, x) - n_Q(t, x) &= \tau \left[w_{S \rightarrow Q}(1 - \psi(n)) n_S + w_{F \rightarrow Q}(1 - \psi(n)) n_F \right] \\
&- \tau \left[w_{Q \rightarrow S} \psi(n) + h_{N_Q} K_{M_R} + d_{N_Q, M_A} K_{M_A} \right] n_Q + \mathcal{O}(\eta^3), \quad x \in \Omega.
\end{aligned} \tag{A.23}$$

Dividing through by τ and collecting like terms yields

$$\begin{aligned}
\frac{n_Q(t+\tau, x) - n_Q(t, x)}{\tau} &= w_{S \rightarrow Q}(1 - \psi(n)) n_S + w_{F \rightarrow Q}(1 - \psi(n)) n_F \\
&- \left[w_{Q \rightarrow S} \psi(n) + h_{N_Q} K_{M_R} + d_{N_Q, M_A} K_{M_A} \right] n_Q + \mathcal{O}(\eta^3), \quad x \in \Omega,
\end{aligned} \tag{A.24}$$

from which, letting $\tau \rightarrow 0$ and neglecting $\mathcal{O}(\eta^3)$ terms, we formally obtain the following PDE

$$\begin{aligned} \partial_t n_Q = & w_{S \rightarrow Q}(1 - \psi(n))n_S + w_{F \rightarrow Q}(1 - \psi(n))n_F \\ & - \left[w_{Q \rightarrow S}\psi(n) + h_{N_Q}K_{M_R} + d_{N_Q, M_A}K_{M_A} \right] n_Q, \quad x \in \Omega. \end{aligned} \quad (\text{A.25})$$

A.2 Formal Derivation of PDE for Macrophages

A.2.1 Formal Derivation of the PDE for the Density of Resting Macrophages

The principle mass balance gives the following difference equation for the density of resting macrophages $m_{R_i}^k$

$$\begin{aligned} m_{R_i}^{k+1} = & m_{R_i}^k + \tau \delta_{M_R} p_i^k - \tau \left[\lambda_{M_R} b_i^k + A_{M_R, E} K_{E_i}^k + d_{M_R} \right] m_{R_i}^k \\ & + \frac{\nu}{2} \left[\Phi_i^k m_{R_{i-1}}^k + \Phi_i^k m_{R_{i+1}}^k \right] - \frac{\nu}{2} \left[\Phi_{i+1}^k + \Phi_{i-1}^k \right] m_{R_i}^k. \end{aligned} \quad (\text{A.26})$$

Using the continuum relations in Eq. (A.10), Eq. (A.26) can be formally written in the approximate form as

$$\begin{aligned} m_R(t + \tau, x) = & m_R(t, x) + \tau \delta_{M_R} p(t, x) - \tau \left[\lambda_{M_R} b(t, x) + A_{M_R, E} K_E(t, x) + d_{M_R} \right] m_R(t, x) \\ & + \frac{\nu}{2} \left[\phi(n(t, x)) m_R(t, x - \eta) + \phi(n(t, x)) m_R(t, x + \eta) \right] \\ & - \frac{\nu}{2} \left[\phi(n(t, x + \eta)) + \phi(n(t, x - \eta)) \right] m_R(t, x). \end{aligned} \quad (\text{A.27})$$

If the function $\phi(n)$ is thrice continuously differentiable, and $m_R(t, x)$ is thrice continuously differentiable with respect to x , for sufficiently small η , using Taylor series up to second-order derivatives and grouping higher-order terms, we obtain

$$\begin{aligned} m_R(t + \tau, x) - m_R(t, x) = & \tau \delta_{M_R} p - \tau \left[\lambda_{M_R} b + A_{M_R, E} K_E + d_{M_R} \right] m_R \\ & + \frac{\nu}{2} \left[(\phi(n) + \phi(n)) m_R + \eta (\phi(n) - \phi(n)) \partial_x m_R + \frac{\eta^2}{2} (\phi(n) + \phi(n)) \partial_{xx}^2 m_R \right] \\ & - \frac{\nu}{2} \left[(\phi(n) + \phi(n)) + \eta (\partial_x (\phi(n) - \phi(n))) + \frac{\eta^2}{2} (\partial_{xx}^2 (\phi(n) + \phi(n))) \right] m_R \\ & + \mathcal{O}(\eta^3), \quad x \in \Omega. \end{aligned} \quad (\text{A.28})$$

Dividing both sides of Eq. (A.28) by τ and recalling the assumption given by Eq. (51), we obtain

$$\begin{aligned} \frac{m_R(t + \tau, x) - m_R(t, x)}{\tau} = & \delta_{M_R} p - \left[\lambda_{M_R} b + A_{M_R, E} K_E + d_{M_R} \right] m_R \\ & + \frac{\nu}{\tau} \left[\phi(n) m_R + \frac{\eta^2}{2} \phi(n) \partial_{xx}^2 m_R \right] - \frac{\nu}{\tau} \left[\phi(n) m_R + \frac{\eta^2}{2} m_R \partial_{xx}^2 \phi(n) \right] + \mathcal{O}(\eta^3), \quad x \in \Omega. \end{aligned} \quad (\text{A.29})$$

Letting $\tau \rightarrow 0$ and $\eta \rightarrow 0$ in such a way that

$$\frac{\nu \eta^2}{2\tau} \rightarrow \gamma_{M_R} \in \mathbb{R}_*^+ \quad \text{as} \quad \tau, \eta \rightarrow 0$$

and ignoring $\mathcal{O}(\eta^3)$, we formally obtain

$$\partial_t m_R - \gamma_{M_R} \partial_x [\phi(n) \partial_x m_R - m_R \partial_x \phi(n)] = \delta_{M_R} p - \left[\lambda_{M_R} b + A_{M_R, E} K_E + d_{M_R} \right] m_R, \quad x \in \Omega. \quad (\text{A.30})$$

A.2.2 Formal Derivation of the PDE for the Density of Active Macrophages

The principle mass balance gives the following difference equation for the density of active macrophages $m_{A_i}^k$

$$\begin{aligned} m_{A_i}^{k+1} = & m_{A_i}^k + \tau A_{M_R, E} K_{E_i}^k m_{R_i}^k - \tau d_{M_A} m_{A_i}^k \\ & + \frac{\varrho}{2c_{\max}} \left[\Phi_i^k (c_i^k - c_{i-1}^k)_+ m_{A_{i-1}}^k + \Phi_i^k (c_i^k - c_{i+1}^k)_+ m_{A_{i+1}}^k \right] \\ & - \frac{\varrho}{2c_{\max}} \left[\Phi_{i-1}^k (c_{i-1}^k - c_i^k)_+ + \Phi_{i+1}^k (c_{i+1}^k - c_i^k)_+ \right] m_{A_i}^k. \end{aligned} \quad (\text{A.31})$$

Using the continuum relations in Eq. (A.10), Eq. (A.31) can be formally written in the approximate form as

$$\begin{aligned} m_A(t + \tau, x) = & m_A(t, x) + \tau A_{M_R, E} K_E(t, x) m_R(t, x) - \tau d_{M_A} m_A(t, x) \\ & + \frac{\varrho}{2c_{\max}} \left[\phi(n(t, x))(c(t, x) - c(t, x - \eta))_+ m_A(t, x - \eta) + \phi(n(t, x))(c(t, x) - c(t, x + \eta))_+ m_A(t, x + \eta) \right] \\ & - \frac{\varrho}{2c_{\max}} \left[\phi(n(t, x - \eta))(c(t, x - \eta) - c(t, x))_+ + \phi(n(t, x + \eta))(c(t, x + \eta) - c(t, x))_+ \right] m_A(t, x). \end{aligned} \quad (\text{A.32})$$

If the function $\phi(n)$ is thrice continuously differentiable, and $m_A(t, x)$ is thrice continuously differentiable with respect to x , for sufficiently small η , using Taylor series up to second-order derivatives and grouping higher-order terms, we obtain

$$\begin{aligned} m_A(t + \tau, x) - m_A(t, x) = & \tau A_{M_R, E} K_E m_R - \tau d_{M_A} m_A \\ & + \frac{\varrho}{2c_{\max}} \left[(m_A - \eta \partial_x m_A + \frac{\eta^2}{2} \partial_{xx}^2 m_A) \phi(n) (c(t, x) - c(t, x - \eta))_+ \right] \\ & + \frac{\varrho}{2c_{\max}} \left[(m_A + \eta \partial_x m_A + \frac{\eta^2}{2} \partial_{xx}^2 m_A) \phi(n) (c(t, x) - c(t, x + \eta))_+ \right] \\ & - \frac{\varrho}{2c_{\max}} \left[(\phi(n) - \eta \partial_x \phi(n) + \frac{\eta^2}{2} \partial_{xx}^2 \phi(n)) m_A (c(t, x - \eta) - c(t, x))_+ \right] \\ & - \frac{\varrho}{2c_{\max}} \left[(\phi(n) + \eta \partial_x \phi(n) + \frac{\eta^2}{2} \partial_{xx}^2 \phi(n)) m_A (c(t, x + \eta) - c(t, x))_+ \right] + O(\eta^3), \quad x \in \Omega. \end{aligned} \quad (\text{A.33})$$

Expanding and collecting like terms gives

$$\begin{aligned} m_A(t + \tau, x) - m_A(t, x) = & \tau A_{M_R, E} K_E m_R - \tau d_{M_A} m_A \\ & + \frac{\varrho}{2c_{\max}} \left[\phi(n) (c(t, x) - c(t, x - \eta))_+ + \phi(n) (c(t, x) - c(t, x + \eta))_+ \right] m_A \\ & - \frac{\varrho \eta}{2c_{\max}} \left[\phi(n) (c(t, x) - c(t, x - \eta))_+ - \phi(n) (c(t, x) - c(t, x + \eta))_+ \right] \partial_x m_A \\ & + \frac{\varrho \eta^2}{4c_{\max}} \left[\phi(n) (c(t, x) - c(t, x - \eta))_+ + \phi(n) (c(t, x) - c(t, x + \eta))_+ \right] \partial_{xx}^2 m_A \\ & - \frac{\varrho}{2c_{\max}} \left[\phi(n) (c(t, x - \eta) - c(t, x))_+ + \phi(n) (c(t, x + \eta) - c(t, x))_+ \right] m_A \\ & + \frac{\varrho \eta}{2c_{\max}} \left[\partial_x \phi(n) (c(t, x - \eta) - c(t, x))_+ - \partial_x \phi(n) (c(t, x + \eta) - c(t, x))_+ \right] m_A \\ & - \frac{\varrho \eta^2}{4c_{\max}} \left[\partial_{xx}^2 \phi(n) (c(t, x - \eta) - c(t, x))_+ + \partial_{xx}^2 \phi(n) (c(t, x + \eta) - c(t, x))_+ \right] m_A \\ & + O(\eta^3), \quad x \in \Omega. \end{aligned} \quad (\text{A.34})$$

Under the assumption given by Eq. (51) and using the elementary property $(a)_+ - (-a)_+ = a$ for $a \in \mathbb{R}$, we obtain

$$\begin{aligned}
m_A(t + \tau, x) - m_A(t, x) = & \tau A_{M_R, E} K_E m_R - \tau d_{M_A} m_A \\
& + \frac{\varrho}{2c_{\max}} \phi(n) \left[2c(t, x) - c(t, x - \eta) - c(t, x + \eta) \right] m_A \\
& - \frac{\varrho \eta}{2c_{\max}} \phi(n) \left[(c(t, x) - c(t, x - \eta))_+ - (c(t, x) - c(t, x + \eta))_+ \right] \partial_x m_A \\
& + \frac{\varrho \eta^2}{4c_{\max}} \phi(n) \left[(c(t, x) - c(t, x - \eta))_+ + (c(t, x) - c(t, x + \eta))_+ \right] \partial_{xx}^2 m_A \\
& + \frac{\varrho \eta}{2c_{\max}} \partial_x \phi(n) \left[(c(t, x - \eta) - c(t, x))_+ - (c(t, x + \eta) - c(t, x))_+ \right] m_A \\
& - \frac{\varrho \eta^2}{4c_{\max}} \partial_{xx}^2 \phi(n) \left[(c(t, x - \eta) - c(t, x))_+ + (c(t, x + \eta) - c(t, x))_+ \right] m_A \\
& + O(\eta^3), \quad x \in \Omega.
\end{aligned} \tag{A.35}$$

Dividing both sides of Eq. (A.35) by τ gives

$$\begin{aligned}
\frac{m_A(t + \tau, x) - m_A(t, x)}{\tau} = & A_{M_R, E} K_E m_R - d_{M_A} m_A \\
& - \frac{\varrho \eta^2}{2\tau c_{\max}} \phi(n) \left[\frac{c(t, x - \eta) - 2c(t, x) + c(t, x + \eta)}{\eta^2} \right] m_A \\
& - \frac{\varrho \eta^2}{2\tau c_{\max}} \phi(n) \left[\left(\frac{c(t, x) - c(t, x - \eta)}{\eta} \right)_+ - \left(\frac{c(t, x) - c(t, x + \eta)}{\eta} \right)_+ \right] \partial_x m_A \\
& + \frac{\varrho \eta^3}{4\tau c_{\max}} \phi(n) \left[\left(\frac{c(t, x) - c(t, x - \eta)}{\eta} \right)_+ + \left(\frac{c(t, x) - c(t, x + \eta)}{\eta} \right)_+ \right] \partial_{xx}^2 m_A \\
& + \frac{\varrho \eta^2}{2\tau c_{\max}} \partial_x \phi(n) \left[\left(\frac{c(t, x - \eta) - c(t, x)}{\eta} \right)_+ - \left(\frac{c(t, x + \eta) - c(t, x)}{\eta} \right)_+ \right] m_A \\
& - \frac{\varrho \eta^3}{4\tau c_{\max}} \partial_{xx}^2 \phi(n) \left[\left(\frac{c(t, x - \eta) - c(t, x)}{\eta} \right)_+ + \left(\frac{c(t, x + \eta) - c(t, x)}{\eta} \right)_+ \right] m_A \\
& + O(\eta^3), \quad x \in \Omega.
\end{aligned} \tag{A.36}$$

If $c(t, x)$ is continuously differentiable with respect to x , letting $\tau \rightarrow 0$ and $\eta \rightarrow 0$ in such a way that

$$\frac{\varrho \eta^2}{2\tau c_{\max}} \rightarrow \chi_{M_A} \in \mathbb{R}_*^+ \quad \text{as } \tau, \eta \rightarrow 0,$$

we have

$$\begin{aligned}
\frac{\varrho \eta^3}{4\tau c_{\max}} \phi(n) \left[\left(\frac{c(t, x) - c(t, x - \eta)}{\eta} \right)_+ + \left(\frac{c(t, x) - c(t, x + \eta)}{\eta} \right)_+ \right] \partial_{xx}^2 m_A &= O(\eta), \quad \text{as } \tau, \eta \rightarrow 0, \\
\frac{\varrho \eta^3}{4\tau c_{\max}} \partial_{xx}^2 \phi(n) \left[\left(\frac{c(t, x - \eta) - c(t, x)}{\eta} \right)_+ + \left(\frac{c(t, x + \eta) - c(t, x)}{\eta} \right)_+ \right] m_A &= O(\eta), \quad \text{as } \tau, \eta \rightarrow 0.
\end{aligned}$$

Thus, ignoring $O(\eta^3)$, we formally obtain

$$\begin{aligned}
\partial_t m_A = & A_{M_R, E} K_E m_R - d_{M_A} m_A \\
& - \chi_{M_A} \phi(n) m_A \partial_{xx}^2 c - \chi_{M_A} \phi(n) \partial_x m_A ((\partial_x c)_+ - (-\partial_x c)_+) + \chi_{M_A} \partial_x \phi(n) m_A ((-\partial_x c)_+ - (\partial_x c)_+), \quad x \in \Omega.
\end{aligned} \tag{A.37}$$

Using again the elementary property $(a)_+ - (-a)_+ = a$ for $a \in \mathbb{R}$, we obtain

$$\partial_t m_A + \partial_x [\chi_{M_A} \phi(n) m_A \partial_x c] = A_{M_R, E} K_E m_R - d_{M_A} m_A, \quad x \in \Omega. \tag{A.38}$$

A.2.3 Formal Derivation of the PDE for the Density of Infected Macrophages

The principle mass balance gives the following difference equation for the density of infected $m_{I_i}^k$

$$\begin{aligned} m_{I_i}^{k+1} = & m_{I_i}^k + \tau \lambda_{M_R} b_i^k m_{R_i}^k - \tau \left[d_{M_I} + d_{M_I, E} K_{E_i}^k \right] m_{I_i}^k \\ & + \frac{\zeta}{2c_{\max}} \left[\Phi_i^k (c_i^k - c_{i-1}^k)_+ m_{I_{i-1}}^k + \Phi_i^k (c_i^k - c_{i+1}^k)_+ m_{I_{i+1}}^k \right] \\ & - \frac{\zeta}{2c_{\max}} \left[\Phi_{i-1}^k (c_{i-1}^k - c_i^k)_+ + \Phi_{i+1}^k (c_{i+1}^k - c_i^k)_+ \right] m_{I_i}^k. \end{aligned} \quad (\text{A.39})$$

Using the continuum relations in Eq. (A.10), Eq. (A.39) can be formally written in the approximate form as

$$\begin{aligned} m_I(t + \tau, x) = & m_I(t, x) + \tau \lambda_{M_R} b(t, x) m_R(t, x) - \tau \left[d_{M_I} + d_{M_I, E} K_E(t, x) \right] m_I(t, x) \\ & + \frac{\zeta}{2c_{\max}} \left[\phi(n(t, x)) (c(t, x) - c(t, x - \eta))_+ m_I(t, x - \eta) + \phi(n(t, x)) (c(t, x) - c(t, x + \eta))_+ m_I(t, x + \eta) \right] \\ & - \frac{\zeta}{2c_{\max}} \left[\phi(n(t, x - \eta)) (c(t, x - \eta) - c(t, x))_+ + \phi(n(t, x + \eta)) (c(t, x + \eta) - c(t, x))_+ \right] m_I(t, x). \end{aligned} \quad (\text{A.40})$$

If the function $\phi(n)$ is thrice continuously differentiable and $m_I(t, x)$ is thrice continuously differentiable with respect to x , for sufficiently small η , expanding Eq. (A.40) using Taylor series up to second-order derivatives and collecting like terms, we obtain

$$\begin{aligned} m_I(t + \tau, x) - m_I(t, x) = & \tau \lambda_{M_R} b m_R - \tau \left[d_{M_I} + d_{M_I, E} K_E \right] m_I \\ & + \frac{\zeta}{2c_{\max}} \left[(m_I - \eta \partial_x m_I + \frac{\eta^2}{2} \partial_{xx}^2 m_I) \phi(n) (c(t, x) - c(t, x - \eta))_+ \right] \\ & + \frac{\zeta}{2c_{\max}} \left[(m_I + \eta \partial_x m_I + \frac{\eta^2}{2} \partial_{xx}^2 m_I) \phi(n) (c(t, x) - c(t, x + \eta))_+ \right] \\ & - \frac{\zeta}{2c_{\max}} \left[(\phi(n) - \eta \partial_x \phi(n) + \frac{\eta^2}{2} \partial_{xx}^2 \phi(n)) m_I (c(t, x - \eta) - c(t, x))_+ \right] \\ & - \frac{\zeta}{2c_{\max}} \left[(\phi(n) + \eta \partial_x \phi(n) + \frac{\eta^2}{2} \partial_{xx}^2 \phi(n)) m_I (c(t, x + \eta) - c(t, x))_+ \right] + O(\eta^3), \quad x \in \Omega. \end{aligned} \quad (\text{A.41})$$

Expanding and collecting like terms gives

$$\begin{aligned}
m_I(t + \tau, x) - m_I(t, x) = & \tau \lambda_{M_R} b m_R - \tau \left[d_{M_I} + d_{M_I, E} K_E \right] m_I \\
& + \frac{\zeta}{2c_{\max}} \left[\phi(n)(c(t, x) - c(t, x - \eta))_+ + \phi(n)(c(t, x) - c(t, x + \eta))_+ \right] m_I \\
& - \frac{\zeta \eta}{2c_{\max}} \left[\phi(n)(c(t, x) - c(t, x - \eta))_+ - \phi(n)(c(t, x) - c(t, x + \eta))_+ \right] \partial_x m_I \\
& + \frac{\zeta \eta^2}{4c_{\max}} \left[\phi(n)(c(t, x) - c(t, x - \eta))_+ + \phi(n)(c(t, x) - c(t, x + \eta))_+ \right] \partial_{xx}^2 m_I \\
& - \frac{\zeta}{2c_{\max}} \left[\phi(n)(c(t, x - \eta) - c(t, x))_+ + \phi(n)(c(t, x + \eta) - c(t, x))_+ \right] m_I \\
& + \frac{\zeta \eta}{2c_{\max}} \left[\partial_x \phi(n)(c(t, x - \eta) - c(t, x))_+ - \partial_x \phi(n)(c(t, x + \eta) - c(t, x))_+ \right] m_I \\
& - \frac{\zeta \eta^2}{4c_{\max}} \left[\partial_{xx}^2 \phi(n)(c(t, x - \eta) - c(t, x))_+ + \partial_{xx}^2 \phi(n)(c(t, x + \eta) - c(t, x))_+ \right] m_I \\
& + O(\eta^3), \quad x \in \Omega.
\end{aligned} \tag{A.42}$$

Under the assumption given by Eq. (51) and using the elementary property $(a)_+ - (-a)_+ = a$ for $a \in \mathbb{R}$, we obtain

$$\begin{aligned}
m_I(t + \tau, x) - m_I(t, x) = & \tau \lambda_{M_R} b m_R - \tau \left[d_{M_I} + d_{M_I, E} K_E \right] m_I \\
& + \frac{\zeta}{2c_{\max}} \phi(n) \left[2c(t, x) - c(t, x - \eta) - c(t, x + \eta) \right] m_I \\
& - \frac{\zeta \eta}{2c_{\max}} \phi(n) \left[(c(t, x) - c(t, x - \eta))_+ - (c(t, x) - c(t, x + \eta))_+ \right] \partial_x m_I \\
& + \frac{\zeta \eta^2}{4c_{\max}} \phi(n) \left[(c(t, x) - c(t, x - \eta))_+ + (c(t, x) - c(t, x + \eta))_+ \right] \partial_{xx}^2 m_I \\
& + \frac{\zeta \eta}{2c_{\max}} \partial_x \phi(n) \left[(c(t, x - \eta) - c(t, x))_+ - (c(t, x + \eta) - c(t, x))_+ \right] m_I \\
& - \frac{\zeta \eta^2}{4c_{\max}} \partial_{xx}^2 \phi(n) \left[(c(t, x - \eta) - c(t, x))_+ + (c(t, x + \eta) - c(t, x))_+ \right] m_I \\
& + O(\eta^3), \quad x \in \Omega.
\end{aligned} \tag{A.43}$$

Dividing both sides of Eq. (A.43) by τ gives

$$\begin{aligned}
\frac{m_I(t + \tau, x) - m_I(t, x)}{\tau} = & \lambda_{M_R} b m_R - \left[d_{M_I} + d_{M_I, E} K_E \right] m_I \\
& - \frac{\zeta \eta^2}{2\tau c_{\max}} \phi(n) \left[\frac{c(t, x - \eta) - 2c(t, x) + c(t, x + \eta)}{\eta^2} \right] m_I \\
& - \frac{\zeta \eta^2}{2\tau c_{\max}} \phi(n) \left[\left(\frac{c(t, x) - c(t, x - \eta)}{\eta} \right)_+ - \left(\frac{c(t, x) - c(t, x + \eta)}{\eta} \right)_+ \right] \partial_x m_I \\
& + \frac{\zeta \eta^3}{4\tau c_{\max}} \phi(n) \left[\left(\frac{c(t, x) - c(t, x - \eta)}{\eta} \right)_+ + \left(\frac{c(t, x) - c(t, x + \eta)}{\eta} \right)_+ \right] \partial_{xx}^2 m_I \\
& + \frac{\zeta \eta^2}{2\tau c_{\max}} \partial_x \phi(n) \left[\left(\frac{c(t, x - \eta) - c(t, x)}{\eta} \right)_+ - \left(\frac{c(t, x + \eta) - c(t, x)}{\eta} \right)_+ \right] m_I \\
& - \frac{\zeta \eta^3}{4\tau c_{\max}} \partial_{xx}^2 \phi(n) \left[\left(\frac{c(t, x - \eta) - c(t, x)}{\eta} \right)_+ + \left(\frac{c(t, x + \eta) - c(t, x)}{\eta} \right)_+ \right] m_I \\
& + O(\eta^3), \quad x \in \Omega.
\end{aligned} \tag{A.44}$$

If $c(t, x)$ is continuously differentiable with respect to x , letting $\tau \rightarrow 0$ and $\eta \rightarrow 0$ in such a way that

$$\frac{\zeta\eta^2}{2\tau c_{\max}} \rightarrow \chi_{M_I} \in \mathbb{R}_*^+ \quad \text{as} \quad \tau, \eta \rightarrow 0,$$

we have

$$\begin{aligned} \frac{\zeta\eta^3}{4\tau c_{\max}} \phi(n) \left[\left(\frac{c(t, x) - c(t, x - \eta)}{\eta} \right)_+ + \left(\frac{c(t, x) - c(t, x + \eta)}{\eta} \right)_+ \right] \partial_{xx}^2 m_I &= O(\eta), \quad \text{as} \quad \tau, \eta \rightarrow 0, \\ \frac{\zeta\eta^3}{4\tau c_{\max}} \partial_{xx}^2 \phi(n) \left[\left(\frac{c(t, x - \eta) - c(t, x)}{\eta} \right)_+ + \left(\frac{c(t, x + \eta) - c(t, x)}{\eta} \right)_+ \right] m_I &= O(\eta), \quad \text{as} \quad \tau, \eta \rightarrow 0. \end{aligned}$$

Thus, ignoring $O(\eta^3)$, we formally obtain

$$\begin{aligned} \partial_t m_I &= \lambda_{M_R} b m_R - \left[d_{M_I} + d_{M_I, E} K_E \right] m_I \\ &\quad - \chi_{M_I} \phi(n) m_I \partial_{xx}^2 c - \chi_{M_I} \phi(n) \partial_x m_I ((\partial_x c)_+ - (-\partial_x c)_+) + \chi_{M_I} \partial_x \phi(n) m_I ((-\partial_x c)_+ - (\partial_x c)_+), \quad x \in \Omega. \end{aligned} \quad (\text{A.45})$$

Using again the elementary property $(a)_+ - (-a)_+ = a$ for $a \in \mathbb{R}$, we find

$$\partial_t m_I + \partial_x [\chi_{M_I} \phi(n) m_I \partial_x c] = \lambda_{M_R} b m_R - \left[d_{M_I} + d_{M_I, E} K_E \right] m_I, \quad x \in \Omega. \quad (\text{A.46})$$

A.3 Formal Derivation of the PDE for the Density of T Cells

The principle mass balance gives the following difference equation for the density of T cells e_i^k

$$\begin{aligned} e_i^{k+1} &= e_i^k + \tau \delta_E q_i^k - \tau d_E e_i^k \\ &\quad + \frac{\chi}{2c_{\max}} \left[\Phi_i^k (c_i^k - c_{i-1}^k)_+ e_{i-1}^k + \Phi_i^k (c_i^k - c_{i+1}^k)_+ e_{i+1}^k \right] \\ &\quad - \frac{\chi}{2c_{\max}} \left[\Phi_{i-1}^k (c_{i-1}^k - c_i^k)_+ + \Phi_{i+1}^k (c_{i+1}^k - c_i^k)_+ \right] e_i^k \\ &\quad + \frac{\xi}{2} \left[\Phi_i^k e_{i-1}^k + \Phi_i^k e_{i+1}^k \right] - \frac{\xi}{2} \left[\Phi_{i+1}^k + \Phi_{i-1}^k \right] e_i^k. \end{aligned} \quad (\text{A.47})$$

Using the continuum relations in Eq. (A.10), Eq. (A.47) can be formally written in the approximate form as

$$\begin{aligned} e(t + \tau, x) &= e(t, x) + \tau \delta_E q(t, x) - \tau d_E e(t, x) \\ &\quad + \frac{\chi}{2c_{\max}} \left[\phi(n(t, x)) (c(t, x) - c(t, x - \eta))_+ e(t, x - \eta) + \phi(n(t, x)) (c(t, x) - c(t, x + \eta))_+ e(t, x + \eta) \right] \\ &\quad - \frac{\chi}{2c_{\max}} \left[\phi(n(t, x - \eta)) (c(t, x - \eta) - c(t, x))_+ + \phi(n(t, x + \eta)) (c(t, x + \eta) - c(t, x))_+ \right] e(t, x) \\ &\quad + \frac{\xi}{2} \left[\phi(n(t, x)) e(t, x - \eta) + \phi(n(t, x)) e(t, x + \eta) \right] - \frac{\xi}{2} \left[\phi(n(t, x + \eta)) + \phi(n(t, x - \eta)) \right] e(t, x). \end{aligned} \quad (\text{A.48})$$

If the function $\phi(n)$ is thrice continuously differentiable, and $e(t, x)$ is thrice continuously differentiable with respect to x , for sufficiently small η , using Taylor series up to second-order derivatives and grouping higher-order terms, we

obtain

$$\begin{aligned}
e(t + \tau, x) - e(t, x) = & \tau \delta_E q(t, x) - \tau d_E e(t, x) \\
& + \frac{\chi}{2c_{\max}} \left[(e - \eta \partial_x e + \frac{\eta^2}{2} \partial_{xx}^2 e) \phi(n) (c(t, x) - c(t, x - \eta))_+ \right] \\
& + \frac{\chi}{2c_{\max}} \left[(e + \eta \partial_x e + \frac{\eta^2}{2} \partial_{xx}^2 e) \phi(n) (c(t, x) - c(t, x + \eta))_+ \right] \\
& - \frac{\chi}{2c_{\max}} \left[(\phi(n) - \eta \partial_x \phi(n) + \frac{\eta^2}{2} \partial_{xx}^2 \phi(n)) e (c(t, x - \eta) - c(t, x))_+ \right] \\
& - \frac{\chi}{2c_{\max}} \left[(\phi(n) + \eta \partial_x \phi(n) + \frac{\eta^2}{2} \partial_{xx}^2 \phi(n)) e (c(t, x + \eta) - c(t, x))_+ \right], \\
& + \frac{\xi}{2} \left[(e - \eta \partial_x e + \frac{\eta^2}{2} \partial_{xx}^2 e) \phi(n) + (e + \eta \partial_x e + \frac{\eta^2}{2} \partial_{xx}^2 e) \phi(n) \right] \\
& - \frac{\xi}{2} \left[(\phi(n) + \eta \partial_x \phi(n) + \frac{\eta^2}{2} \partial_{xx}^2 \phi(n)) + (\phi(n) - \eta \partial_x \phi(n) + \frac{\eta^2}{2} \partial_{xx}^2 \phi(n)) \right] e \\
& + O(\eta^3), \quad x \in \Omega
\end{aligned} \tag{A.49}$$

Expanding and collecting like terms gives

$$\begin{aligned}
e(t + \tau, x) - e(t, x) = & \tau \delta_E q - \tau d_E e \\
& + \frac{\chi}{2c_{\max}} \left[\phi(n) (c(t, x) - c(t, x - \eta))_+ + \phi(n) (c(t, x) - c(t, x + \eta))_+ \right] e \\
& - \frac{cult \eta}{2c_{\max}} \left[\phi(n) (c(t, x) - c(t, x - \eta))_+ - \phi(n) (c(t, x) - c(t, x + \eta))_+ \right] \partial_x e \\
& + \frac{\chi \eta^2}{4c_{\max}} \left[\phi(n) (c(t, x) - c(t, x - \eta))_+ + \phi(n) (c(t, x) - c(t, x + \eta))_+ \right] \partial_{xx}^2 e \\
& - \frac{cult}{2c_{\max}} \left[\phi(n) (c(t, x - \eta) - c(t, x))_+ + \phi(n) (c(t, x + \eta) - c(t, x))_+ \right] e \\
& + \frac{cult \eta}{2c_{\max}} \left[\partial_x \phi(n) (c(t, x - \eta) - c(t, x))_+ - \partial_x \phi(n) (c(t, x + \eta) - c(t, x))_+ \right] e \\
& - \frac{\chi \eta^2}{4c_{\max}} \left[\partial_{xx}^2 \phi(n) (c(t, x - \eta) - c(t, x))_+ + \partial_{xx}^2 \phi(n) (c(t, x + \eta) - c(t, x))_+ \right] e \\
& + \frac{\xi}{2} \left[(\phi(n) + \phi(n)) e + \eta (\phi(n) - \phi(n)) \partial_x e + \frac{\eta^2}{2} (\phi(n) + \phi(n)) \partial_{xx}^2 e \right] \\
& - \frac{\xi}{2} \left[(\phi(n) + \phi(n)) + \eta (\partial_x (\phi(n) - \phi(n))) + \frac{\eta^2}{2} (\partial_{xx}^2 (\phi(n) + \phi(n))) \right] e \\
& + O(\eta^3), \quad x \in \Omega.
\end{aligned} \tag{A.50}$$

Under the assumption given by Eq. (51) and using the elementary property $(a)_+ - (-a)_+ = a$ for $a \in \mathbb{R}$, we obtain

$$\begin{aligned}
e(t + \tau, x) - e(t, x) = & \tau \delta_E q - \tau d_E e \\
& + \frac{\chi}{2c_{\max}} \phi(n) \left[2c(t, x) - c(t, x - \eta) - c(t, x + \eta) \right] e \\
& - \frac{cult\eta}{2c_{\max}} \phi(n) \left[(c(t, x) - c(t, x - \eta))_+ - (c(t, x) - c(t, x + \eta))_+ \right] \partial_x e \\
& + \frac{\chi\eta^2}{4c_{\max}} \phi(n) \left[(c(t, x) - c(t, x - \eta))_+ + (c(t, x) - c(t, x + \eta))_+ \right] \partial_{xx}^2 e \\
& + \frac{cult\eta}{2c_{\max}} \partial_x \phi(n) \left[(c(t, x - \eta) - c(t, x))_+ - (c(t, x + \eta) - c(t, x))_+ \right] e \\
& - \frac{\chi\eta^2}{4c_{\max}} \partial_{xx}^2 \phi(n) \left[(c(t, x - \eta) - c(t, x))_+ + (c(t, x + \eta) - c(t, x))_+ \right] e \\
& + \xi \left[\phi(n)e + \frac{\eta^2}{2} \phi(n) \partial_{xx}^2 e \right] - \xi \left[\phi(n)e + \frac{\eta^2}{2} e \partial_{xx}^2 \phi(n) \right] + O(\eta^3), \quad x \in \Omega.
\end{aligned} \tag{A.51}$$

Dividing both sides of Eq. (A.51) by τ gives

$$\begin{aligned}
\frac{e(t + \tau, x) - e(t, x)}{\tau} = & \delta_E q - d_E e \\
& - \frac{\chi\eta^2}{2\tau c_{\max}} \phi(n) \left[\frac{c(t, x - \eta) - 2c(t, x) + c(t, x + \eta)}{\eta^2} \right] e \\
& - \frac{\chi\eta^2}{2\tau c_{\max}} \phi(n) \left[\left(\frac{c(t, x) - c(t, x - \eta)}{\eta} \right)_+ - \left(\frac{c(t, x) - c(t, x + \eta)}{\eta} \right)_+ \right] \partial_x e \\
& + \frac{\chi\eta^3}{4\tau c_{\max}} \phi(n) \left[\left(\frac{c(t, x) - c(t, x - \eta)}{\eta} \right)_+ + \left(\frac{c(t, x) - c(t, x + \eta)}{\eta} \right)_+ \right] \partial_{xx}^2 e \\
& + \frac{\chi\eta^2}{2\tau c_{\max}} \partial_x \phi(n) \left[\left(\frac{c(t, x - \eta) - c(t, x)}{\eta} \right)_+ - \left(\frac{c(t, x + \eta) - c(t, x)}{\eta} \right)_+ \right] e \\
& - \frac{\chi\eta^3}{4\tau c_{\max}} \partial_{xx}^2 \phi(n) \left[\left(\frac{c(t, x - \eta) - c(t, x)}{\eta} \right)_+ + \left(\frac{c(t, x + \eta) - c(t, x)}{\eta} \right)_+ \right] e \\
& + \frac{\xi}{\tau} \left[\phi(n)e + \frac{\eta^2}{2} \phi(n) \partial_{xx}^2 e \right] - \frac{\xi}{\tau} \left[\phi(n)e + \frac{\eta^2}{2} e \partial_{xx}^2 \phi(n) \right] + O(\eta^3), \quad x \in \Omega.
\end{aligned} \tag{A.52}$$

If $c(t, x)$ is continuously differentiable with respect to x , letting $\tau \rightarrow 0$ and $\eta \rightarrow 0$ in such a way that

$$\frac{\chi\eta^2}{2\tau c_{\max}} \rightarrow \chi_E \in \mathbb{R}_*^+, \quad \frac{\xi\eta^2}{2\tau} \rightarrow \gamma_E \in \mathbb{R}_*^+ \quad \text{as} \quad \tau, \eta \rightarrow 0,$$

we have

$$\begin{aligned}
\frac{\chi\eta^3}{4\tau c_{\max}} \phi(n) \left[\left(\frac{c(t, x) - c(t, x - \eta)}{\eta} \right)_+ + \left(\frac{c(t, x) - c(t, x + \eta)}{\eta} \right)_+ \right] \partial_{xx}^2 e &= O(\eta), \quad \text{as} \quad \tau, \eta \rightarrow 0, \\
\frac{\chi\eta^3}{4\tau c_{\max}} \partial_{xx}^2 \phi(n) \left[\left(\frac{c(t, x - \eta) - c(t, x)}{\eta} \right)_+ + \left(\frac{c(t, x + \eta) - c(t, x)}{\eta} \right)_+ \right] e &= O(\eta), \quad \text{as} \quad \tau, \eta \rightarrow 0.
\end{aligned}$$

Thus, ignoring $O(\eta^3)$, we formally obtain

$$\begin{aligned}
\partial_t e = & \delta_E q - d_E e - \chi_E \phi(n) e \partial_{xx}^2 c - \chi_E \phi(n) \partial_x e ((\partial_x c)_+ - (-\partial_x c)_+) \\
& + \chi_E \partial_x \phi(n) e ((-\partial_x c)_+ - (\partial_x c)_+) + \gamma_E (\phi(n) \partial_{xx}^2 e - e \partial_{xx}^2 \phi(n)).
\end{aligned} \tag{A.53}$$

Using again the elementary property $(a)_+ - (-a)_+ = a$ for $a \in \mathbb{R}$, we obtain

$$\partial_t e + \partial_x [\chi_E \phi(n) e \partial_x c] - \gamma_E \partial_x [\phi(n) \partial_x e - e \partial_x \phi(n)] = \delta_E q - d_E e, \quad x \in \Omega. \tag{A.54}$$

A.4 Formal Derivation of the PDE for Oxygen Concentration

The dynamics O_i^k follows the discrete balance equation

$$O_i^{k+1} = O_i^k + \tau\beta_O(\mathcal{L}O^k)_i + \tau\delta_O\mathbf{1}_{\omega_i} - \tau w_i^k, \quad (\text{A.55})$$

where

$$w_i^k = O_{ns}n_{S_i}^k + O_{nf}n_{F_i}^k + O_{nq}n_{Q_i}^k + O_{mr}m_{R_i}^k + O_{ma}m_{A_i}^k + O_{mi}m_{I_i}^k + O_e e_i^k.$$

Using the continuum relations in Eq. (A.10), Eq. (A.55) can be formally written in the approximate form as

$$\frac{O(t+\tau, x) - O(t, x)}{\tau} = \beta_O \left(\frac{O(t, x-\eta) - 2O(t, x) + O(t, x+\eta)}{\eta^2} \right) + \delta_O \mathbf{1}_\omega(x) - w(t, x), \quad x \in \Omega. \quad (\text{A.56})$$

Letting $\tau \rightarrow 0$ and $\eta \rightarrow 0$, we formally obtain

$$\partial_t O - \beta_O \partial_{xx}^2 O = \delta_O \mathbf{1}_\omega(x) - w, \quad x \in \Omega. \quad (\text{A.57})$$

A.5 Formal Derivation of PDE for Chemokine Concentration

The dynamics c_i^k follows the discrete balance equation

$$c_i^{k+1} = c_i^k + \tau\beta_c(\mathcal{L}c^k)_i + \tau\delta_c a_i^k - \tau\kappa_c c_i^k, \quad a_i^k = m_{A_i}^k + m_{I_i}^k. \quad (\text{A.58})$$

Using the continuum relations in Eq. (A.10), Eq. (A.58) can be formally written in the approximate form as

$$\frac{c(t+\tau, x) - c(t, x)}{\tau} = \beta_c \left(\frac{c(t, x-\eta) - 2c(t, x) + c(t, x+\eta)}{\eta^2} \right) + \delta_c a(t, x) - \kappa_c c(t, x), \quad x \in \Omega. \quad (\text{A.59})$$

Letting $\tau \rightarrow 0$ and $\eta \rightarrow 0$, we formally obtain

$$\partial_t c - \beta_c \partial_{xx}^2 c = \delta_c a - \kappa_c c, \quad x \in \Omega. \quad (\text{A.60})$$

B Numerical Methods for the Comparison Models

We present the numerical details of the scheme used for the numerical simulation of the reduced continuum model in Appendix B.1, and the computational algorithm used for the stochastic IBM in Appendix B.2. The implementation of the reduced continuum model is done in MATLAB, while the IBM algorithm is implemented in C++, with a yaml configuration for execution. Where an adjustment has been made to the initial configurations transferred from the continuum model to the IBM, we detail the adjustments made in Appendix B.3.

B.1 Numerical Scheme for the Reduced Continuum Model

Let

$$x_i, \quad i = 1, \dots, N_x, \quad \text{and} \quad y_j, \quad j = 1, \dots, N_y,$$

denote uniformly spaced lattice sites in the x - and y -directions, respectively, where

$$N_x = N_y = 100, \quad \Delta x = x_{i+1} - x_i, \quad \Delta y = y_{j+1} - y_j,$$

with space-step size

$$\Delta x = \Delta y = \eta \approx 0.002,$$

and time-step

$$\Delta t = 10^{-5}, \text{ in relation to } t_k = k\Delta t.$$

We discretise the transport terms in the reduced continuum model using conservative fluxes and advance the solution in time using an explicit finite-difference scheme on the square domain

$$\Omega = (0, 0.2) \times (0, 0.2) \text{ cm}^2.$$

For

$$u \in \{n_P, m_R, m_I, e, c\},$$

we write

$$u_{i,j}^k \approx u(x_i, y_j, t_k).$$

Hence, the total cell density on lattice site (i, j) at time t_k is

$$n_{i,j}^k = n_{P,i,j}^k + m_{R,i,j}^k + m_{I,i,j}^k + e_{i,j}^k.$$

For any $z \in \mathbb{R}$, its positive and negative parts are defined by

$$[z]_+ := \max\{z, 0\}, \quad [z]_- := \max\{-z, 0\}.$$

In the numerical implementation, the crowding functions corresponding to ϕ_{red} and ψ_{red} are evaluated using the untruncated linear forms

$$\phi_{\text{num}}(n) = 1 - \frac{n}{\bar{n}}, \quad \psi_{\text{num}}(n_P) = 1 - \frac{n_P}{\bar{n}}.$$

Thus, ϕ_{num} is evaluated using the total cell density, whereas ψ_{num} is evaluated using the local proliferating mycobacterial density.

B.1.1 Chemokine Gradients and Diffusion

The discrete chemokine gradients between neighbouring lattice sites are

$$D_x c_{i+\frac{1}{2},j}^k = \frac{c_{i+1,j}^k - c_{i,j}^k}{\Delta x}, \quad D_y c_{i,j+\frac{1}{2}}^k = \frac{c_{i,j+1}^k - c_{i,j}^k}{\Delta y},$$

with their positive and negative parts denoted by

$$\left(D_x c_{i+\frac{1}{2},j}^k\right)^+ = \left[D_x c_{i+\frac{1}{2},j}^k\right]_+, \quad \left(D_x c_{i+\frac{1}{2},j}^k\right)^- = \left[D_x c_{i+\frac{1}{2},j}^k\right]_- ,$$

with analogous definitions in the y -direction. Furthermore, the chemokine fluxes between neighbouring lattice sites are

$$F_{i+\frac{1}{2},j}^{c,k} = \beta_c \frac{c_{i+1,j}^k - c_{i,j}^k}{\Delta x},$$

and

$$G_{i,j+\frac{1}{2}}^{c,k} = \beta_c \frac{c_{i,j+1}^k - c_{i,j}^k}{\Delta y}.$$

B.1.2 Diffusive Cell Fluxes and Chemotactic Fluxes

The proliferating mycobacterial fluxes are

$$F_{i+\frac{1}{2},j}^{P,k} = \gamma_{N_P} \frac{n_{P,i+1,j}^k - n_{P,i,j}^k}{\Delta x},$$

and

$$G_{i,j+\frac{1}{2}}^{P,k} = \gamma_{N_P} \frac{n_{P,i,j+1}^k - n_{P,i,j}^k}{\Delta y}.$$

The resting macrophage fluxes are

$$F_{i+\frac{1}{2},j}^{R,k} = \gamma_{M_R} \frac{m_{R,i+1,j}^k - m_{R,i,j}^k}{\Delta x},$$

and

$$G_{i,j+\frac{1}{2}}^{R,k} = \gamma_{M_R} \frac{m_{R,i,j+1}^k - m_{R,i,j}^k}{\Delta y}.$$

The diffusive T cell fluxes are

$$F_{i+\frac{1}{2},j}^{E,\text{diff},k} = \gamma_E \frac{e_{i+1,j}^k - e_{i,j}^k}{\Delta x},$$

and

$$G_{i,j+\frac{1}{2}}^{E,\text{diff},k} = \gamma_E \frac{e_{i,j+1}^k - e_{i,j}^k}{\Delta y}.$$

These linear diffusive fluxes are algebraically equivalent to the form used in the MATLAB implementation, for which

$$\phi_{\text{num}}(n_{\text{mid}}) + \frac{n_{\text{mid}}}{\bar{n}} = 1.$$

The chemotactic fluxes of infected macrophages and T cells are discretised using an upwind approximation determined by the sign of the local chemokine gradient. For infected macrophages, the numerical chemotactic fluxes are

$$\begin{aligned} F_{i+\frac{1}{2},j}^{I,k} = & -\chi_{M_I} \left(D_x c_{i+\frac{1}{2},j}^k \right)^+ m_{I,i,j}^k \phi_{\text{num}}(n_{i,j}^k) \\ & + \chi_{M_I} \left(D_x c_{i+\frac{1}{2},j}^k \right)^- m_{I,i+1,j}^k \phi_{\text{num}}(n_{i+1,j}^k), \end{aligned}$$

and

$$\begin{aligned} G_{i,j+\frac{1}{2}}^{I,k} = & -\chi_{M_I} \left(D_y c_{i,j+\frac{1}{2}}^k \right)^+ m_{I,i,j}^k \phi_{\text{num}}(n_{i,j}^k) \\ & + \chi_{M_I} \left(D_y c_{i,j+\frac{1}{2}}^k \right)^- m_{I,i,j+1}^k \phi_{\text{num}}(n_{i,j+1}^k). \end{aligned}$$

For T cells, the chemotactic fluxes are

$$\begin{aligned} F_{i+\frac{1}{2},j}^{E,\text{chem},k} = & -\chi_E \left(D_x c_{i+\frac{1}{2},j}^k \right)^+ e_{i,j}^k \phi_{\text{num}}(n_{i,j}^k) \\ & + \chi_E \left(D_x c_{i+\frac{1}{2},j}^k \right)^- e_{i+1,j}^k \phi_{\text{num}}(n_{i+1,j}^k), \end{aligned}$$

and

$$\begin{aligned} G_{i,j+\frac{1}{2}}^{E,\text{chem},k} = & -\chi_E \left(D_y c_{i,j+\frac{1}{2}}^k \right)^+ e_{i,j}^k \phi_{\text{num}}(n_{i,j}^k) \\ & + \chi_E \left(D_y c_{i,j+\frac{1}{2}}^k \right)^- e_{i,j+1}^k \phi_{\text{num}}(n_{i,j+1}^k). \end{aligned}$$

Hence, the total T cell fluxes are

$$F_{i+\frac{1}{2},j}^{E,k} = F_{i+\frac{1}{2},j}^{E,\text{chem},k} + F_{i+\frac{1}{2},j}^{E,\text{diff},k},$$

and

$$G_{i,j+\frac{1}{2}}^{E,k} = G_{i,j+\frac{1}{2}}^{E,\text{chem},k} + G_{i,j+\frac{1}{2}}^{E,\text{diff},k}.$$

Furthermore, for any pair of numerical fluxes F and G in the x - and y -directions, respectively, their discrete divergence is defined by

$$\mathcal{D}_h(F, G)_{i,j} = \frac{F_{i+\frac{1}{2},j} - F_{i-\frac{1}{2},j}}{\Delta x} + \frac{G_{i,j+\frac{1}{2}} - G_{i,j-\frac{1}{2}}}{\Delta y}.$$

B.1.3 Recruitment Functions

Let the total proliferating mycobacterial population be defined by

$$B^k = \Delta x \Delta y \sum_{i=1}^{N_x} \sum_{j=1}^{N_y} n_{P,i,j}^k,$$

and the spatially integrated chemokine concentration be given by

$$C^k = \Delta x \Delta y \sum_{i=1}^{N_x} \sum_{j=1}^{N_y} c_{i,j}^k.$$

For lattice position $\mathbf{x}_{i,j} = (x_i, y_j)$, the discrete random blood vessel distribution, through which immune cell recruitment occurs, is represented by

$$v_{i,j} = \mathbf{1}_\omega(\mathbf{x}_{i,j}),$$

where $v_{i,j} = 1$ at blood vessel locations and $v_{i,j} = 0$ elsewhere. Thus, the chemokine-dependent macrophage recruitment function is

$$p_{i,j}^k = C^k v_{i,j},$$

while the mycobacterial burden-dependent T cell recruitment function is

$$q_{i,j}^k = [B^k - \bar{b}]_+ v_{i,j}.$$

B.1.4 Cytotoxic Death of Proliferating Mycobacteria Induced by T Cells

We make the modelling assumption that, at each time t_k , T cells can induce the cytotoxic death of proliferating extracellular mycobacteria. In the reduced continuum formulation, this interaction is represented locally. Hence, the probability of cytotoxic death of a proliferating mycobacterium at lattice site (i, j) is given by

$$0 \leq \tau d_{NP,E} h_E e_{i,j}^k \leq 1, \tag{B.61}$$

where $d_{NP,E}$ is associated with the efficiency of T cells in killing mycobacteria and $h_E e_{i,j}^k$ represents the local T cell contribution at lattice site (i, j) .

B.1.5 Forward-Euler Updates

The proliferating mycobacterial update is

$$\begin{aligned} n_{P,i,j}^{k+1} &= n_{P,i,j}^k + \Delta t \mathcal{D}_h(F^{P,k}, G^{P,k})_{i,j} \\ &\quad + \Delta t \alpha_P \psi_{\text{num}}(n_{P,i,j}^k) n_{P,i,j}^k \\ &\quad - \Delta t [h_{NP} h_{MR} m_{R,i,j}^k + d_{NP,E} h_E e_{i,j}^k] n_{P,i,j}^k. \end{aligned}$$

The resting macrophage update is

$$\begin{aligned} m_{R,i,j}^{k+1} &= m_{R,i,j}^k + \Delta t \mathcal{D}_h(F^{R,k}, G^{R,k})_{i,j} \\ &\quad + \Delta t \delta_{M_R} p_{i,j}^k \\ &\quad - \Delta t (\lambda_{M_R} n_{P,i,j}^k + d_{M_R}) m_{R,i,j}^k. \end{aligned}$$

The infected macrophage update is

$$\begin{aligned} m_{I,i,j}^{k+1} &= m_{I,i,j}^k + \Delta t \mathcal{D}_h(F^{I,k}, G^{I,k})_{i,j} \\ &\quad + \Delta t \lambda_{M_R} n_{P,i,j}^k m_{R,i,j}^k \\ &\quad - \Delta t [d_{M_I} + d_{M_I,E} h_E e_{i,j}^k] m_{I,i,j}^k. \end{aligned}$$

The T cell update is

$$\begin{aligned} e_{i,j}^{k+1} &= e_{i,j}^k + \Delta t \mathcal{D}_h(F^{E,k}, G^{E,k})_{i,j} \\ &\quad + \Delta t \delta_E q_{i,j}^k - \Delta t d_E e_{i,j}^k. \end{aligned}$$

The chemokine update is

$$\begin{aligned} c_{i,j}^{k+1} &= c_{i,j}^k + \Delta t \mathcal{D}_h(F^{c,k}, G^{c,k})_{i,j} \\ &\quad + \Delta t \delta_c m_{I,i,j}^k - \Delta t \kappa_c c_{i,j}^k. \end{aligned}$$

Following each Forward-Euler update, any negative values of the numerical solutions at time t_{k+1} were set to zero.

B.1.6 Initial and Boundary Conditions

Let $N_{P,i,j}^0$ and $N_{R,i,j}^0$ denote the initial numbers of proliferating extracellular mycobacteria and resting macrophages deposited onto lattice site (i, j) . The corresponding initial densities are

$$n_{P,i,j}^0 = \frac{N_{P,i,j}^0}{\Delta x \Delta y}, \quad m_{R,i,j}^0 = \frac{N_{R,i,j}^0}{\Delta x \Delta y}.$$

The domain was initialised with a total of 12 proliferating extracellular mycobacteria and 105 resting macrophages, distributed across individual lattice sites. Multiple mycobacteria could be assigned to the same lattice site, in which case their contributions to $N_{P,i,j}^0$ were added. The initial densities of infected macrophages, T cells, and chemokine concentration satisfy

$$m_{I,i,j}^0 = 0, \quad e_{i,j}^0 = 0, \quad c_{i,j}^0 = 0,$$

respectively. We impose the zero-flux boundary conditions by setting the numerical fluxes at the boundary of the computational domain to zero. Thus, for each

$$u \in \{n_P, m_R, m_I, e, c\},$$

the boundary fluxes satisfy

$$F_{\frac{1}{2},j}^{u,k} = F_{N_x+\frac{1}{2},j}^{u,k} = 0, \quad j = 1, \dots, N_y,$$

and

$$G_{i,\frac{1}{2}}^{u,k} = G_{i,N_y+\frac{1}{2}}^{u,k} = 0, \quad i = 1, \dots, N_x.$$

In the implementation, the boundary fluxes were set to zero before evaluating the discrete divergence, so that no flux entered or left the domain through $\partial\Omega$.

B.2 Computational Algorithm for the Reduced IBM

B.2.1 IBM Time-step Operations

In the stochastic IBM implementation, at each timestep, the following operations are performed:

1. Increase the ages of all agents and remove agents whose lifespans have expired, provided they are not engaged in an ongoing operation.
2. Update proliferating extracellular mycobacteria.
3. Update resting and infected macrophages.
4. Update active T cells.
5. Accumulate the chemokine source contributions from infected macrophages.
6. At each blood vessel, evaluate resting macrophage and T cell recruitment.
7. Advance the chemokine reaction–diffusion dynamics and reset the accumulated source terms.

Remark: Throughout the remainder of this section, we define an eligible agent as one who is not involved in an ongoing event and has not been marked for removal.

Lifespan-mediated Cell Death. Each agent is assigned a fixed, state-specific lifespan. At the start of each timestep, the age a_ℓ^k of agent ℓ is updated according to

$$a_\ell^{k+1} = a_\ell^k + \Delta t_W.$$

Provided that the agent is not locked in an ongoing event, it is removed when

$$a_\ell^{k+1} > T_\ell^{\text{life}},$$

where T_ℓ^{life} denotes its predefined lifespan. An agent that is locked in an ongoing event is not removed until that event has been completed.

Mycobacterial Update. Following initial mycobacterial placement, each proliferating extracellular mycobacterium ℓ is assigned an individual replication interval,

$$T_\ell^{\text{rep}} \sim \mathcal{U}(T_{\min}^{\text{rep}}, T_{\max}^{\text{rep}}).$$

Following the age update, mycobacterium ℓ attempts replication when

$$a_\ell^{k+1} \geq T_\ell^{\text{rep}},$$

provided there is an available lattice site within its Moore neighbourhood to place the offspring mycobacterium. If no site has sufficient available area, replication is postponed until the next timestep. In this case, the parent retains both its current age and its assigned replication interval. Following successful offspring placement, the age of the parent is reset to zero and a new replication interval is sampled independently. The offspring mycobacterium is created with age zero and is independently assigned its own replication interval from the same distribution.

Macrophage Update. For each macrophage, an ongoing phagocytosis event is completed before a new action is attempted. Otherwise, the macrophage first attempts migration according to its state-specific movement rule and then searches its Moore neighbourhood for an eligible extracellular mycobacterium.

Phagocytosis is evaluated using the general event rule with the configured phagocytosis rate. Following successful uptake, the extracellular mycobacterium is removed from the lattice and recorded as intracellular mycobacterial content of the macrophage. The state transition from resting to infected macrophage is subsequently evaluated from the intracellular mycobacterial content using the predefined content threshold and transition rule.

T cell Update. As in the macrophage update, for each active T cell, any ongoing cytotoxicity event is completed before migration or the initiation of a new cytotoxic activity. Otherwise, the T cell first attempts migration according to its state-specific movement rule. For T cell migration, a neighbouring site is selected with a probability that increases with its non-negative chemokine concentration. If the chemokine concentration is zero at all sites in the Moore neighbourhood, a neighbouring site is selected uniformly at random, corresponding to undirected random movement. Movement occurs only if the selected site has sufficient available area for the T cell. The T cell then searches the selected lattice site for an eligible cytotoxic target.

Eligible infected macrophages and extracellular mycobacteria at the selected lattice site are considered as cytotoxic targets using their respective target-specific event rates. Once a cytotoxicity event is successfully initiated, the T cell and its target remain locked for the duration of the interaction, and no further cytotoxic interaction is initiated by that T cell during the same update. When the interaction site differs from the T cell’s current lattice site, initiation of cytotoxicity moves the T cell directly to the target site. Upon completion of an interaction with an infected macrophage, the macrophage and its intracellular mycobacterial content are removed. Completion of an interaction with an extracellular mycobacterium also removes the mycobacterium from the system.

Chemokine Update. In the reduced IBM model, infected macrophages are the only source of chemokine production, and the contribution from each infected macrophage is accumulated at the macrophage’s lattice location.

Following all cell updates and the evaluation of immune cell recruitment through the blood vessels, the accumulated source terms are passed to the IBM reaction–diffusion solver. At the next timestep, the solver advances the existing chemokine concentration according to the predefined diffusion, production, and decay parameters. The updated chemokine concentration is carried forward to the next timestep, while the temporary source accumulator is reset to zero before new source contributions are collected.

B.2.2 Immune Cell Recruitment

In the reduced IBM configuration, immune cell recruitment is triggered by mycobacterial burden rather than by chemokine signaling. At each timestep, resting macrophage and T cell recruitment are evaluated independently at every blood vessel using the global extracellular mycobacterial population N_P^k .

Resting macrophage recruitment uses a mycobacterial threshold of zero, whereas T cell recruitment is evaluated only when N_P^k reaches the prescribed threshold $\bar{N}_P$. Conditional on the relevant threshold requirement, cell recruitment is evaluated using an event-specific factor, F , with $F = N_P^k$ and the corresponding cell-specific recruitment rate.

Following a successful recruitment event, the new immune cell is placed at an available lattice site in the immediate neighbourhood of the recruiting vessel, subject to the area-based occupancy condition. If no neighbouring site has sufficient available area, recruitment is abandoned for that vessel during the current timestep.

B.3 Adjustments to Transferred Initial Configurations

To resolve the indexing mismatch, we reconciled the one-based indexing of the MATLAB-exported PDE coordinates with the zero-based indexing of the IBM lattice. Specifically, all blood vessel, resting macrophage and mycobacterial coordinates were transformed according to

$$(x_{\text{IBM}}, y_{\text{IBM}}) = (x_{\text{PDE}} - 1, y_{\text{PDE}} - 1).$$

This indexing conversion was applied uniformly and was not regarded as a spatial adjustment. Following the indexing conversion, three exported agent positions coincided with vessel-occupied sites. To resolve the vessel-agent

conflict, each affected agent was moved to the nearest available non-vessel site with sufficient area within the Moore neighbourhood. Where an adjustment was made due to a conflict, we present information on the adjustment in Table 11.

Table 11: Adjustments made to transferred agent coordinates that coincided with vessel-occupied sites.

Seed	Agent	MATLAB PDE coordi- nate	Mapped IBM coordi- nate	Final IBM coordinate
91	Resting macrophage	(97, 73)	(96, 72)	(95, 72)
96	Proliferating mycobacterium	(30, 46)	(29, 45)	(28, 45)
99	Resting macrophage	(62, 71)	(61, 70)	(60, 70)

Note. The mapped IBM coordinate is the zero-based coordinate obtained directly from the exported MATLAB coordinate. Each affected agent was moved by one lattice site in the negative x -direction. Since one lattice spacing corresponded to 0.002 cm, each adjustment represented a displacement of 20 μm . The original population totals of 49 vessels, 105 resting macrophages, and 12 proliferating mycobacteria were preserved.

C Additional Numerical Results

This appendix presents the complete temporal dynamics comparisons for the five closely matched configurations not shown in the main text. All four stochastic IBM realisations are displayed for each configuration. A representative spatial plot for seed 92 is also included for both models.

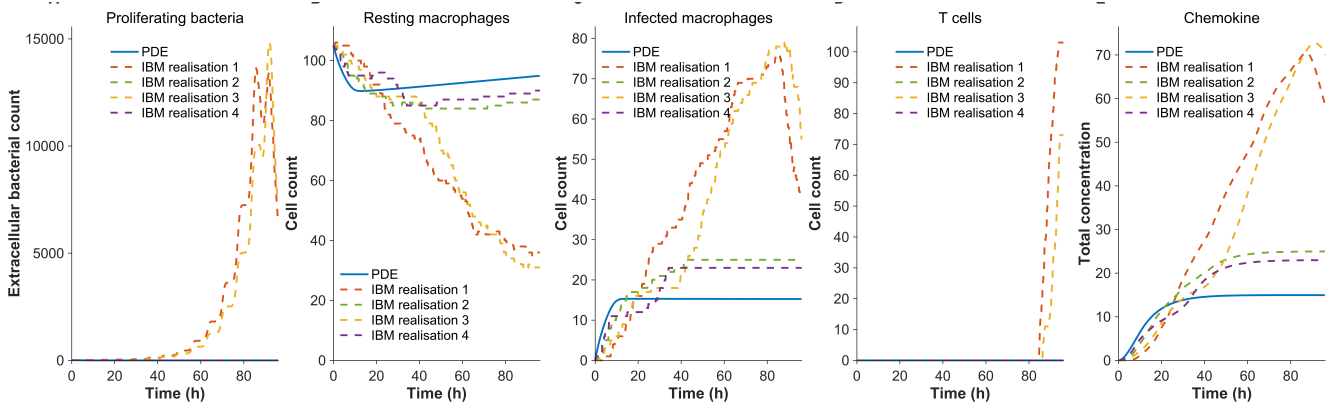


Figure 7: Temporal dynamics comparison for PDE seed 96. The PDE cleared, while two of the four IBM realisations cleared and two remained non-cleared by 96 h.

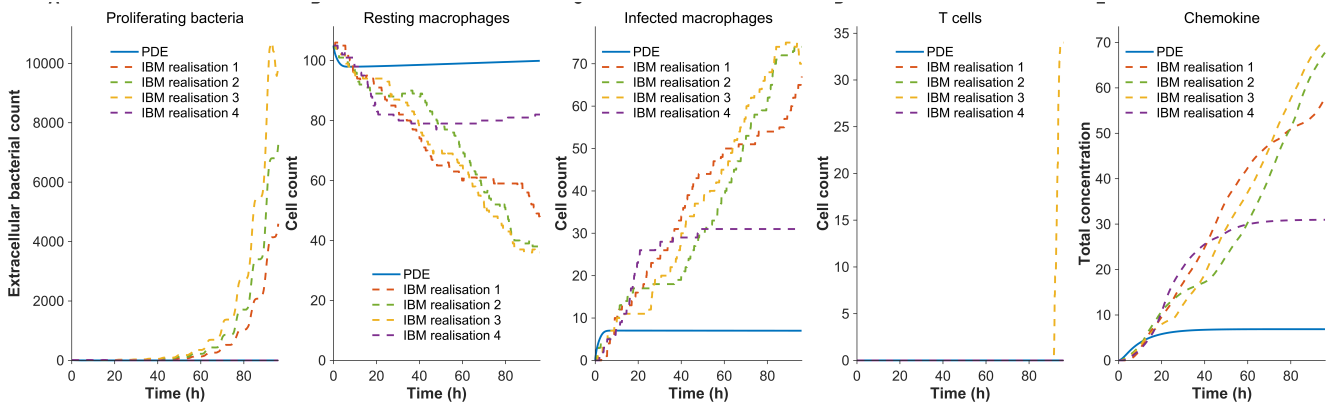


Figure 8: Temporal dynamics comparison for PDE seed 95. The PDE cleared, whereas only one of the four IBM realisations reproduced the clearance outcome by 96 h.

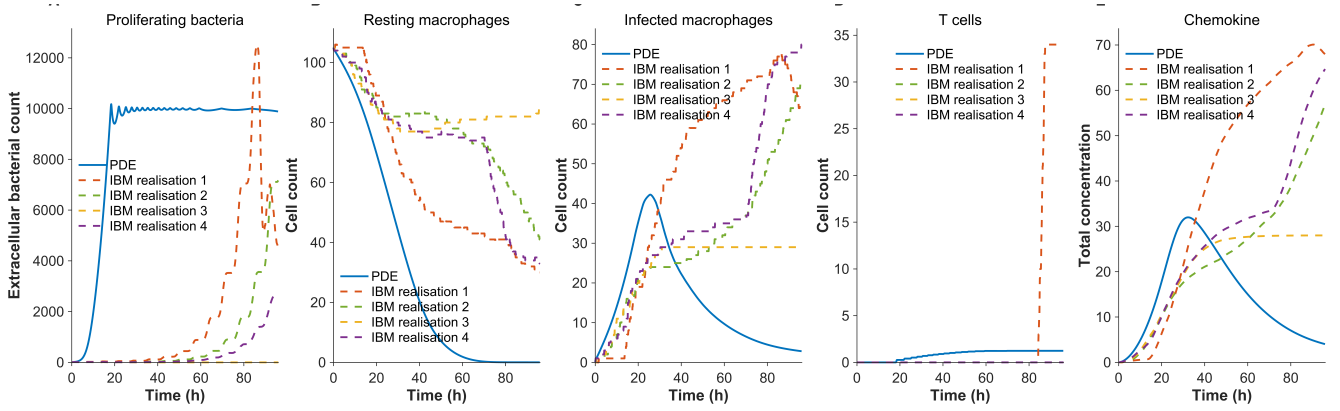


Figure 9: Temporal dynamics comparison for PDE seed 94. The PDE and three of the four IBM realisations remained non-cleared by 96 h.

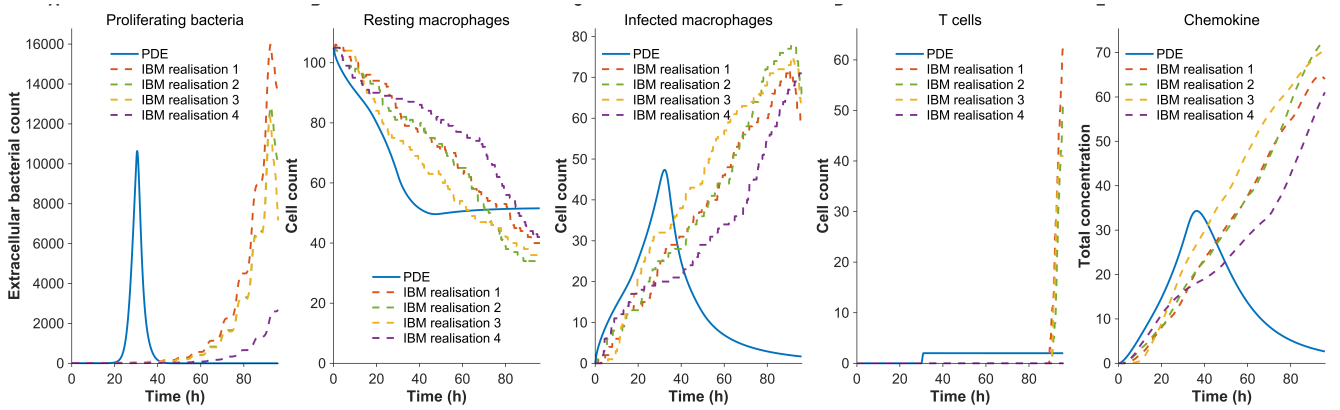


Figure 10: Temporal dynamics comparison for PDE seed 97. The PDE cleared, whereas all four IBM realisations remained non-cleared by 96 h.

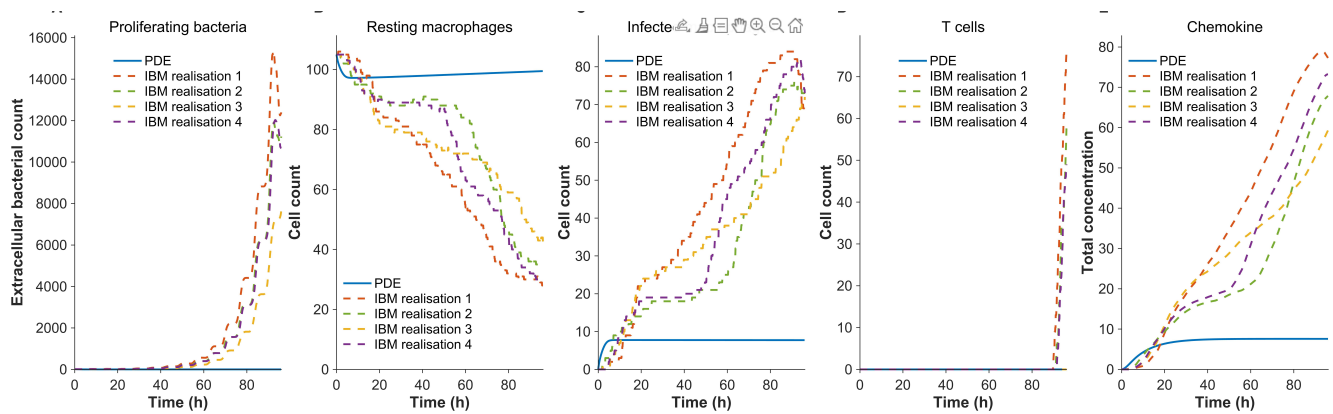


Figure 11: Temporal dynamics comparison for PDE seed 99. The PDE cleared, whereas all four IBM realisations remained non-cleared by 96 h.

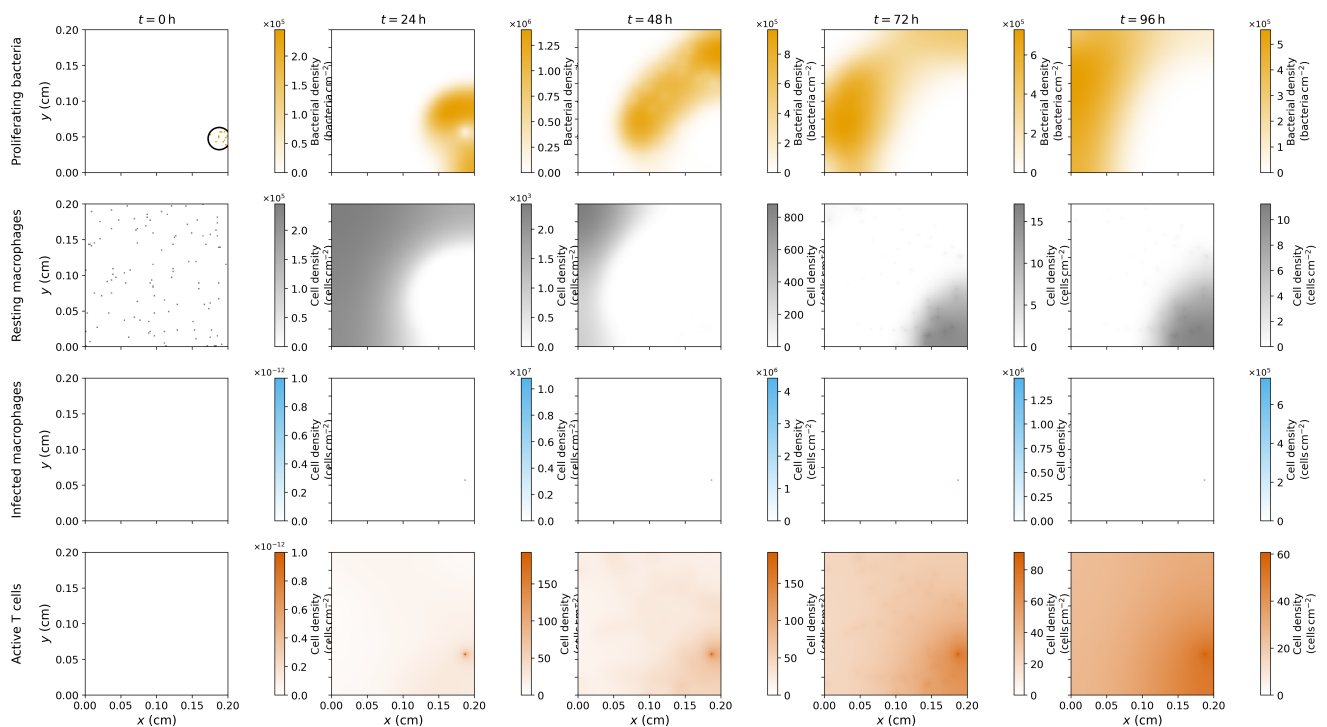


Figure 12: Spatial distributions of proliferating mycobacteria, resting macrophages, infected macrophages, and active T cells predicted by the reduced PDE model for seed 92 up to 96 h. Colours represent population density, and the black circle marks the initial mycobacterial deposition region. Each panel uses its own colour scale.

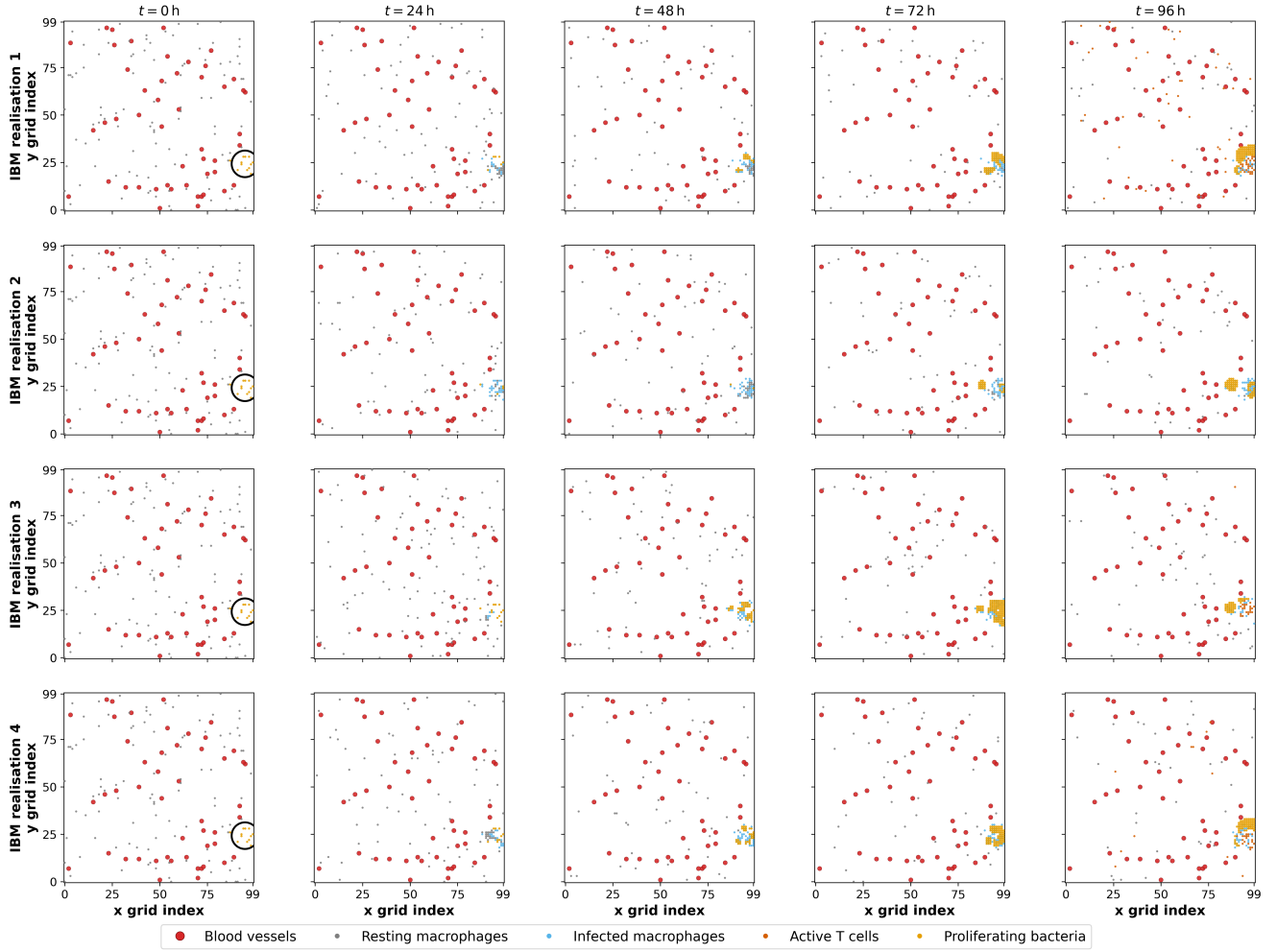


Figure 13: Spatial distributions of agents in four stochastic IBM realisations for seed 92 up to 96 h. Blood vessels are shown in red, resting macrophages in grey, infected macrophages in light blue, active T cells in orange, and proliferating mycobacteria in yellow. The black circle marks the initial mycobacterial deposition region.

Bibliography

- Holly M Scott Algood, John Chan, and JoAnne L Flynn. Chemokines and tuberculosis. *Cytokine & growth factor reviews*, 14(6):467–477, 2003.
- Luis Almeida, Chloe Audebert, Emma Leschiera, and Tommaso Lorenzi. A hybrid discrete–continuum modelling approach to explore the impact of t-cell infiltration on anti-tumour immune response. *Bulletin of Mathematical Biology*, 84(12):141, 2022.
- Aleksandra Ardaševa, Alexander RA Anderson, Robert A Gatenby, Helen M Byrne, Philip K Maini, and Tommaso Lorenzi. Comparative study between discrete and continuum models for the evolution of competing phenotype-structured cell populations in dynamical environments. *Physical Review E*, 102(4):042404, 2020.
- Ruth Bowness, Mark AJ Chaplain, Gibin G Powathil, and Stephen H Gillespie. Modelling the effects of bacterial

- cell state and spatial location on tuberculosis treatment: Insights from a hybrid multiscale cellular automaton model. *Journal of theoretical biology*, 446:87–100, 2018.
- Federica Bubba, Tommaso Lorenzi, and Fiona R Macfarlane. From a discrete model of chemotaxis with volume-filling to a generalized patlak–keller–segel model. *Proceedings of the Royal Society A*, 476(2237):20190871, 2020.
- Helen Byrne and Dirk Drasdo. Individual-based and continuum models of growing cell populations: a comparison. *Journal of mathematical biology*, 58:657–687, 2009.
- R Luz Elena Cano and H Damaris E Lopera. Introduction to t and b lymphocytes. In *Autoimmunity: from bench to bedside [Internet]*. El Rosario University Press, 2013.
- Saverio V Capuano III, Denise A Croix, Santosh Pawar, Angelica Zinovik, Amy Myers, Philana L Lin, Stephanie Bissel, Carl Fuhrman, Edwin Klein, and JoAnne L Flynn. Experimental mycobacterium tuberculosis infection of cynomolgus macaques closely resembles the various manifestations of human m. tuberculosis infection. *Infection and immunity*, 71(10):5831–5844, 2003.
- Nicholas A Cilfone, Cory R Perry, Denise E Kirschner, and Jennifer J Linderman. Multi-scale modeling predicts a balance of tumor necrosis factor- α and interleukin-10 controls the granuloma environment during mycobacterium tuberculosis infection. *PloS one*, 8(7):e68680, 2013.
- Roberto Colangeli, Hannah Jedrey, Soyeon Kim, Roy Connell, Shuyi Ma, Uma D Chippada Venkata, Soumitesh Chakravorty, Aditi Gupta, Erin E Sizemore, Lois Diem, et al. Bacterial factors that predict relapse after tuberculosis therapy. *New England Journal of Medicine*, 379(9):823–833, 2018.
- Tuberculosis Trials Consortium et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in hiv-negative patients: a randomised clinical trial. *The Lancet*, 360(9332):528–534, 2002.
- Adegbenro O Fakoya, Ahmed Naeem, and Louisdon Pierre. Histology, alveolar macrophages. In *StatPearls [Internet]*. StatPearls Publishing, 2024.
- Mohammad Fallahi-Sichani, Mohammed El-Kebir, Simeone Marino, Denise E Kirschner, and Jennifer J Linderman. Multiscale computational modeling reveals a critical role for tnf- α receptor 1 dynamics in tuberculosis granuloma formation. *The Journal of Immunology*, 186(6):3472–3483, 2011.
- Alena M Gallegos, Eric G Pamer, and Michael S Glickman. Delayed protection by esat-6-specific effector cd4+ t cells after airborne m. tuberculosis infection. *The Journal of experimental medicine*, 205(10):2359–2368, 2008.
- David Gammack, Suman Ganguli, Simeone Marino, Jose Segovia-Juarez, and Denise E Kirschner. Understanding the immune response in tuberculosis using different mathematical models and biological scales. *Multiscale Modeling & Simulation*, 3(2):312–345, 2005.
- Edith NG Houben, Liem Nguyen, and Jean Pieters. Interaction of pathogenic mycobacteria with the host immune system. *Current opinion in microbiology*, 9(1):76–85, 2006.
- Louis R Joslyn, Marissa Renardy, Caleb Weissman, Nicole L Grant, JoAnne L Flynn, J Russ Butler, and Denise E Kirschner. Temporal and spatial analyses of tb granulomas to predict long-term outcomes. In *Complex Systems and Computational Biology Approaches to Acute Inflammation*, pages 273–291. Springer, 2021.

- Fritz Krombach, Silvia Münzing, Anne-Marie Allmeling, J Tilman Gerlach, Jürgen Behr, and Martina Dörger. Cell size of alveolar macrophages: an interspecies comparison. *Environmental health perspectives*, 105(Suppl 5):1261, 1997.
- Matthew F Krummel, Frederic Bartumeus, and Audrey Gérard. T cell migration, search strategies and mechanisms. *Nature Reviews Immunology*, 16(3):193–201, 2016.
- Si-Yang Li, Scott M Irwin, Paul J Converse, Khisi E Mdluli, Anne J Lenaerts, and Eric L Nuermberger. Evaluation of moxifloxacin-containing regimens in pathologically distinct murine tuberculosis models. *Antimicrobial agents and chemotherapy*, 59(7):4026–4030, 2015.
- Fiona R. Macfarlane, Xinran Ruan, and Tommaso Lorenzi. Individual-based and continuum models of phenotypically heterogeneous growing cell populations. *AIMS Bioengineering*, 9(1):68–92, 2022.
- Simeone Marino and Denise E Kirschner. A multi-compartment hybrid computational model predicts key roles for dendritic cells in tuberculosis infection. *Computation*, 4(4):39, 2016.
- Simeone Marino, Jennifer J Linderman, and Denise E Kirschner. A multifaceted approach to modeling the immune response in tuberculosis. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*, 3(4):479–489, 2011.
- Michael J Pitcher, Ruth Bowness, Simon Dobson, and Stephen H Gillespie. A spatially heterogeneous network-based metapopulation software model applied to the simulation of a pulmonary tuberculosis infection. *Applied network science*, 3(1):1–21, 2018.
- Michael J Pitcher, Ruth Bowness, Simon Dobson, Raluca Eftimie, and Stephen H Gillespie. Modelling the effects of environmental heterogeneity within the lung on the tuberculosis life-cycle. *Journal of Theoretical Biology*, 506: 110381, 2020.
- Gibin G. Powathil, Kirsty E. Gordon, Lydia A. Hill, and Mark A.J Chaplain. Modelling the effects of cell-cycle heterogeneity on the response of a solid tumour to chemotherapy: biological insights from a hybrid multiscale cellular automaton model. *Journal of theoretical biology*, 308:1–19, 2012.
- William W Reiley, Mark D Calayag, Susan T Wittmer, Jennifer L Huntington, John E Pearl, Jeffrey J Fountain, Cynthia A Martino, Alan D Roberts, Andrea M Cooper, Gary M Winslow, et al. Esat-6-specific cd4 t cell responses to aerosol mycobacterium tuberculosis infection are initiated in the mediastinal lymph nodes. *Proceedings of the National Academy of Sciences*, 105(31):10961–10966, 2008.
- Thomas Riggs, Adrienne Walts, Nicolas Perry, Laura Bickle, Jennifer N Lynch, Amy Myers, Joanne Flynn, Jennifer J Linderman, Mark J Miller, and Denise E Kirschner. A comparison of random vs. chemotaxis-driven contacts of t cells with dendritic cells during repertoire scanning. *Journal of theoretical biology*, 250(4):732–751, 2008.
- Jose L Segovia-Juarez, Suman Ganguli, and Denise Kirschner. Identifying control mechanisms of granuloma formation during m. tuberculosis infection using an agent-based model. *Journal of theoretical biology*, 231(3):357–376, 2004.
- Cheryl L Sershen, Steven J Plimpton, and Elebeoba E May. Oxygen modulates the effectiveness of granuloma mediated host response to mycobacterium tuberculosis: a multiscale computational biology approach. *Frontiers in cellular and infection microbiology*, 6:6, 2016.
- KB Urdahl, S Shafiani, and JD Ernst. Initiation and regulation of t-cell responses in tuberculosis. *Mucosal immunology*, 4(3):288–293, 2011.

Eileen A Wong, Louis Joslyn, Nicole L Grant, Edwin Klein, Philana Ling Lin, Denise E Kirschner, and JoAnne L Flynn. Low levels of t cell exhaustion in tuberculous lung granulomas. *Infection and immunity*, 86(9):e00426–18, 2018.