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A review of computational and mathematical modeling contributions to our understanding of *Mycobacterium tuberculosis* within-host infection and treatment

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Abstract

Tuberculosis (TB) is an ancient and deadly disease characterized by complex host-pathogen dynamics playing out over multiple time and length scales and physiological compartments. Mathematical and computational modeling can be used to integrate various types of experimental data and suggest new hypotheses, mechanisms, and therapeutic approaches to TB. Here, we offer a first-time comprehensive review of work on within-host TB models that describe the immune response to infection, including the formation of lung granulomas. The models include systems of ordinary and partial differential equations and agent-based models as well as hybrid and multi-scale models that are combinations of these. Many aspects of *Mycobacterium tuberculosis* infection, including host dynamics in the lung (typical site of infection for TB), granuloma formation, roles of cytokine and chemokine dynamics, and bacterial nutrient availability have been explored. Finally, we survey applications of these within-host models to TB therapy and prevention and suggest future directions to impact this global disease.

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Introduction

Tuberculosis (TB) is a disease caused by infection with *Mycobacterium tuberculosis* (Mtb). An estimated one fourth of the world population has latent Mtb infection, and in 2014 TB was responsible for 1.5 million deaths [1,2]. There is no broadly efficacious vaccine, and drug treatment is complicated by a necessarily long course of multiple antibiotics (at least 6 months of chemotherapy) in part to prevent development of resistance. This long time course contributes to toxicity and patient non-compliance, which can lead to relapse. The infection process typically occurs after long and repeated exposure to infected individuals via inhalation of bacteria into lungs [3]. Once infection is established in the lung, macrophages take up bacteria and a complex and dynamic process follows that leads to granuloma formation. Granulomas are spherical collections of cells, bacteria and necrotic tissue that serve to both immunologically contain and physically constrain Mtb. However, granulomas also provide an environment that allows bacteria to persist, in some cases for the lifetime of the host. As granulomas are the battleground for host-pathogen interactions during infection, understanding these structures is key to developing intervention strategies [4–6].

A long-standing view of TB describes it as latent, asymptomatic infection or active TB disease. Patients with latent infection are known to sometimes progress to active TB disease, in some cases decades after the initial infection [7]. The challenge with this dichotomous view is that it does not help identify which patients are at highest risk of progression to active TB disease [8]. However, Mtb infection is now understood to result in a spectrum of patient outcomes ranging from natural cure by innate immune mechanisms to active TB disease [9]. Patients can move along this spectrum throughout their lives. Overall, approximately 10% of individuals infected with Mtb progress to active TB at some point in their lifetime, driven by a number of factors including aging, co-morbidities or immune-suppression [10]. If left untreated, active TB leads to death in about half of those infected in an average of 3 years [11]. There are ongoing efforts to find biomarkers that can identify patients at highest risk of developing active TB disease for preventive therapy [12–14].

Systems biology approaches can be critical to advance our understanding and treatment of TB [15–22]. There is a need to integrate data across multiple time and

length scales, incorporating, for example, knowledge about how bacteria can alter infected host cells, how trafficking of immune cells to lungs influences granuloma formation, how infection can spread to lymph nodes, and how vaccines and antibiotics impact disease progression [23–29]. Mathematical and computational models can be used to integrate these different types of data, as well as to bridge between experimental measurements, better understand hypothesized mechanisms, run virtual experiments (e.g. virtual clinical trials, virtual deletions/depletions) when animal experiments are too expensive or difficult, interpret data, and offer new explanations for observed phenomena.

There have been three main foci of computational models relevant to TB. First, early and continuing extensive mathematical modeling centered on the epidemiology of TB. A comprehensive review of this literature by the TB Modelling Alliance Consortium can be found at [http://tb-mac.org/Resources/Resource/4]. These models describe the population-level dynamics of TB under different scenarios. Second, models were developed to explore mycobacterium growth, drug-resistance development, metabolism, and adaptive response to stress conditions such as hypoxia, nutrient starvation and intracellular survival [18–22,30–33]. Finally, we and others have performed extensive modeling that describes within-host interactions in Mtb infection. This is the first review on this topic, and thus it focuses solely on this latter body of literature, exploring within-host dynamics of TB infection (Table 1). Much of this work was born out of the authors' studies, so the majority of references represent our efforts. In addition, the search protocol for all other references and relevant authors working in this area were found by PubMed and ScienceDirect search term "(mathematical model OR computational OR *in silico* OR systems biology) AND mycobacterium tuberculosis AND within host AND host-pathogen NOT epidemiology NOT metabolic". The resulting list of papers was manually filtered to exclude experimental, –omics (big data), epidemiology and structural biology papers. The goal of this review is to stimulate more work in this area and provide a comprehensive resource for both education and research purposes. Efforts at this within-host level, which include necessary biological detail and a range of relevant length (molecular to host) and time (minutes to lifetime) scales, may be especially useful in understanding both immune mechanisms and interventions to treat disease [34,35].

Multiple physiological compartments are relevant to TB (Figure 1). Antigen-presenting cells from the lungs travel to lymph nodes (LNs), ultimately resulting in recruitment of T cells to lungs where formation of granulomas occurs. Granulomas have a characteristic composition, typically with a central core of caseous necrosis surrounded by a ring of macrophages, neutrophils, giant cells, and an outer ring of lymphocytes including T and B cells. Bacteria are either trapped inside the caseous center (non-replicating bacteria), within macrophages (intracellular bacteria) or in extracellular spaces. Multiple granulomas form in the lungs following infection in adults and granulomas have independent trajectories leading to outcomes ranging from sterilizing to controlled bacteria growth without clearance to uncontrolled bacteria growth [36]. The collective outcome of all granulomas likely determines whether the host's disease trajectory (e.g. active disease).

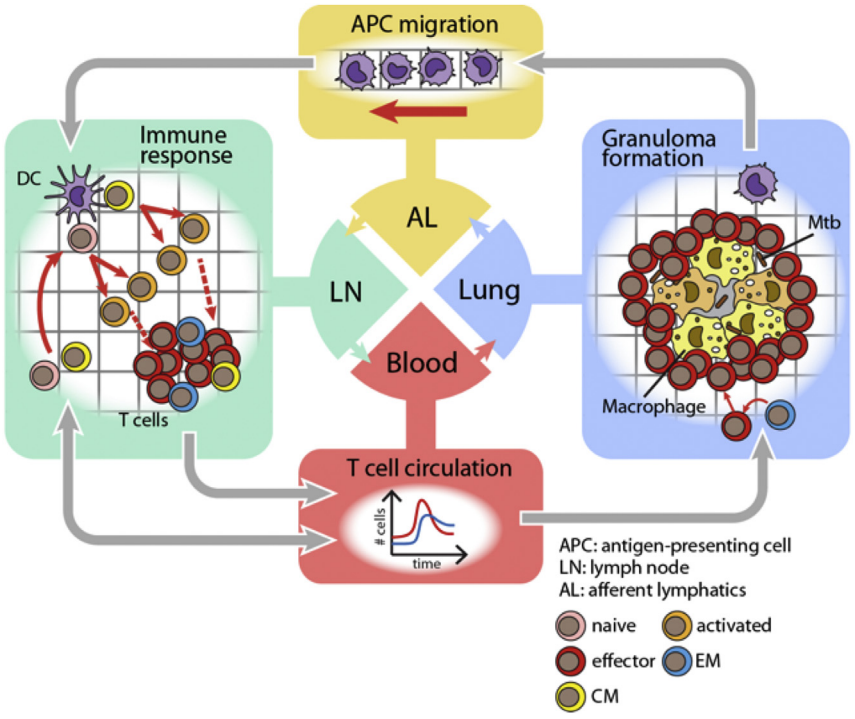
Despite much experimental research on TB over the past century (Leeuwenhoek identified Mtb using the first microscope in the 1700s), there are many features of infection that are not well understood and we still lack a broadly efficacious vaccine [28]. Antibiotics are an effective treatment for drug sensitive disease, but drug-resistant TB is more difficult, and in some cases not possible, to treat [90]. Mathematical and computational modeling can assist in better understanding this complex system, and a systems biology approach affords the pairing of multiple modalities, such as *in vitro* and *in vivo*

Table 1

Mathematical and computational models describing aspects of within-host infection dynamics during Mtb infection. Models can be classified by physiological scales (rows) and applications (columns).

	Antibiotic treatment	Vaccines	Biomarker discovery	Drug target identification	Molecular mechanisms	Cellular mechanisms	Pathogen mechanisms	Other immune mechanisms	Virtual clinical trials
Whole host models	[37]		[38]		[39]	[39,40]		[41]	
Whole lung models	[42–44]				[45]	[44,46–50]	[45,50]	[41,51]	
Granuloma models	[52–55]			[56,57]	[56,58–63]	[64–71]	[57,72,73]	[74]	[63]
Lung/Lymph node models			[38]		[75,76]	[76–81]	[77]		
Lymph node/Blood models		[82]							
Single cell models					[83–87]		[88]	[89]	

Figure 1



Physiological compartments involved in Mtb infection dynamics. Infection begins when Mtb are inhaled into the lung, taken up by macrophages, and begin multiplying. Antigen-presenting cells (including dendritic cells, DCs) travel through afferent lymphatics (AF) to lung-draining lymph nodes (LNs) where priming of naïve T cells occurs. This process initiates the Mtb-specific immune response generating both CD4+ and CD8+ T cells. These T cells have phenotypes that include activated, effector, effector memory (EM), and central memory (CM). Effector and memory T cells flow out of the LN into blood to traffic to the lung to participate in granuloma formation and function. Multiple cytokines also play a role in granuloma formation and infection control. Granulomas are dynamic, can last the lifetime of a host, and fall into major categories of solid cellular, caseous (a central core of necrotic material), fibrotic (a cuff of fibrosis surrounds the granuloma) and disseminating (increasing in both size and bacteria). Orally administered antibiotics are absorbed into the blood and distribute to lungs (pharmacokinetics). Most human data reflects the blood compartment, as it is the most easily sampled compartment, in the hope that blood data may be useful for predicting disease progression.

studies together with modeling and computation. Many of the modeling concepts, approaches and tools are summarized in BOX.

Overview of in-host computational models

In-host computational models for Mtb infection focus on events occurring in specific host locations – the lung, lymph nodes, and blood. At first, data were available only at higher levels of resolution (e.g. health of host, total bacteria and immune cells in the lung), and early models reflected that. More detailed data, including lung PET/CT, cytokine concentrations, and activation of signaling networks, are now increasingly available. Table 2 gives an overview of the types of data now available to build, validate, and calibrate in-host computational models. The data presented are not exhaustive, but emphasize the types and quality that are available. We only show data derived for the lung compartment, but other datasets in TB from both blood (humans and non-human primates-NHPs) and lymph nodes (from NHPs) are available as well [12,13,38,91–96]. Here we give a brief overview of model evolution, including approaches that were developed to capture dynamics at the molecular, cellular/multicellular, and organ/tissue scales. Model formulations include continuous models, discrete models, and hybrid models that combine both (BOX). These models provide the platforms on which to examine both disease mechanisms but also, ultimately, disease therapy and prevention.

Models that capture the immune response to Mtb infection in the whole lung

Modeling host-immune infection dynamics of TB began with models bridging the rich literature of modeling HIV-1 infection to co-infection with Mtb [44,49]. TB is a primarily lung-localized infection, whereas HIV-1 is a systemic infection. The first host immune response models of TB were ODE-based virtual human models of the lung that qualitatively and quantitatively characterized the cellular and cytokine network known to occur during TB infection [46,48,50]. It was appropriate to start with ODEs (BOX) as the calibration data were derived from humans and also whole lungs isolated from mice, as no granuloma spatial data were yet available.

BOX. Computational model concepts, approaches and tools.

Agent-based model (ABM): A class of computational models that allows simulation of stochastic actions and interactions of discrete agents, with a view to identify system behavior. The TB ABMs described here incorporate spatial and temporal aspects of granuloma formation and function. Incorporation of stochastic elements in TB models allows for variability in outcomes, as seen in biology.

Continuous models: Mathematical models, including ordinary differential equations (ODEs) and partial differential equations (PDEs), formulated to capture average behaviors of collections of items (e.g. populations) over time. In TB, overall lung dynamics and receptor-ligand binding and signaling have been described with ODEs, while antibiotic diffusion within a granuloma has been described by PDEs.

Diffusion: Random motion of molecules. In TB models, cytokines and antibiotics are examples of molecules that diffuse in tissue.

Discrete models: In contrast to continuous models, discrete models track the behavior of individual elements over time. Model types that capture these include agent-based models and Markov models. In TB, ABMs are used to track granuloma formation in lungs.

Emergent behavior: Interactions of entities may produce a system-wide behavior that is not readily predictable. The formation of a granuloma from immune cell and bacterial interactions in lungs is an emergent phenomenon.

Hybrid model: Mathematical or computational model that is composed of at least two model formulations, e.g. differential equations and difference equations. Many of the TB models incorporate both differential equations to track diffusion of molecules and ABM components to track cellular interactions.

Model calibration: The process of using data to identify parameter values in a model to yield outputs that align with biological data. For TB, model outputs may be compared to, for example, mouse, non-human primate and human data to calibrate a model.

Model validation: Performing studies to test whether model outputs align with unique biological data or known behaviors. Data used to calibrate and validate models must be distinct. In TB, model validation may test whether model output agrees with data from primate systems, for example.

Multi-compartment model: A model that is comprised of linked sub-models representing different physiological compartments. TB models may include lung, lymph node, lymphatics and blood compartments.

Multi-scale model: A model that is comprised of linked sub-models representing different physiological scales in space or time. TB models may include molecular, cellular, and tissue level interactions across minutes to years.

Parameter estimation: Identifying model parameter values using a variety of techniques, including deriving values directly from data, using uncertainty analysis, or using model calibration to estimate them.

Pharmacokinetic/pharmacodynamic (PK/PD) modeling: PK refers to quantifying the movement of drugs throughout body compartments. PD refers to the actions of drugs in the body. TB models that describe antibiotic delivery and action include PK/PD equations.

Uncertainty and sensitivity analysis: Uncertainty analysis (UA) is performed to investigate uncertainty in model outputs that is generated from uncertainty in parameter inputs. Sensitivity analysis (SA) assesses how variations in model outputs can be apportioned, qualitatively or quantitatively, to different input sources. In TB modeling, these techniques guide parameter estimation, identification of critical mechanisms and drug targets, and model fine- and coarse-graining.

Tuneable resolution: Tuneable resolution proposes that multi-scale models should be built with multiple levels of resolution, so that a fine- or coarse-grained version can be employed with user discretion, allowing adjustment of the level(s) of resolution specific to a question, an experiment, a particular use, or a change in perspective or scale of interest. In our TB models, for example, the level of detail around tumor-necrosis factor (TNF) interactions can be adjusted according the question being asked.

Virtual clinical trial (VCT): *In silico* simulation of a clinical trial, including patient variability as well as treatment protocols. VCTs in TB have included anti-TNF treatment of a population to predict outcomes.

Virtual Deletion/Depletions: *In silico* simulation of a gene knockout or system-wide depletion of a molecule or cell. Multiple simultaneous virtual deletions or depletions, although difficult to perform in animal studies, are easily performed *in silico*.

Table 2

A sampling of experimental datasets on immune responses to Mtb in lungs are listed. Key components of the TB mathematical models have been determined in animal models (mouse, guinea pigs, rabbits, zebrafish, non-human primates) and with human data where available. The type of data derived for each component is listed. Experiments in mouse (knockouts), monkey and human (depletion by antibody or natural mutations) are indicated and can be performed *in silico* for model validation. Experimental techniques used to generate and validate data on each component are listed.

Immune factor	Animal model (mouse, guinea pig, rabbit, zebrafish) data	Monkey data (and human where available)	Knockouts or depletions	References and techniques used in experiments
CD4 T cells, CD8 T cells	Numbers Phenotypes Mtb specific Dynamics	Numbers Phenotypes Mtb specific Dynamics Spatial	Mouse Monkey	[97–114] Flow cytometry, ELISPOT, IHC, ISH, *in vivo* and *in vitro* cytotoxicity assays
Macrophages	Numbers Phenotypes Spatial	Numbers Phenotypes	Mouse, Monkey	[99,112,115–118] Flow cytometry, IHC, ISH
Dendritic cells	Numbers	Numbers	Mouse, Monkey	[119–122] Flow cytometry, ISH
Regulatory T cells	Numbers	Numbers Dynamics	Mouse Monkey Human	[123–127] Flow cytometry, IHC
Cytokines, e.g. IFN-γ, TNF, IL-12, TGF-B, IL-10	Cellular source Levels	Cellular source Levels	Mouse Monkey	[97,99,113–115,128–132] Flow cytometry, ELISPOT, Luminex, IHC, ISH
Chemokines	Cellular source Levels	Cellular source Levels Spatial expression	Mouse, Monkey	[99,115,116,133–140] Flow cytometry, IHC, ISH, Luminex
Mtb bacilli	Numbers Spatial Dynamics	Numbers Sites	Mouse Monkey Human	[99] Culture, IHC, AFB, ISH
Granuloma	Morphology Composition Formation (ZF) Dynamics	Morphology Composition Dynamics		[4,99,112,135,141–145] Histology, IHC, ISH, flow cytometry, live imaging, PET/CT imaging

The known dynamics of human immune responses in lungs were included. For example, in mice TH2 cells make IL-10, but in humans many cell types produce it and this was included in the model. These original models predicted specific cell and cytokine factors that determine the ability of a host to control infection. Interestingly, the model indicated that even if infection is controlled a balance of pro- and anti-inflammatory signals is required to prevent excessive tissue damage. These models did not include the role of CD8+ T cells; however, the models predicted that a cell type that added to cytotoxicity of infected cells and was a producer of mediators was missing. Later data showed that indeed CD8+ T cells are important in TB, and a number of models emerged to understand their role [47,48].

Computational models of granulomas in Mtb-infected lungs

Although most early datasets were derived from whole lungs of mice, cellular and molecular interactions within individual lung granulomas became increasingly understood as key to understanding TB infection. Granulomas are structures that evolve in both space and time, and so ODEs would not suffice to represent them. Concomitantly, new spatial data on granulomas were beginning to emerge from an NHP system, allowing us to visualize 2-D slices of granulomas at disease endpoints (see Table 2). We tried multiple mathematical formulations to capture the spatial evolution of granulomas in lungs. The first spatial model of granulomas developed was an agent-based model (ABM) [64,69]; formation of the granuloma was an emergent behavior in the model. PDE models [58,68,71] and other formulations such as metapopulation models [70] were also used and compared [146]. One model examined early events in mice, including neutrophils and the role they play in granuloma formation [66], while others examined the role of the bacterial burst size on granulomas [67]. The influence of lung structure also indicated an important role for neutrophils [74].

Receptor-ligand dynamics (described by ODEs) [147] and molecular diffusion (PDEs) were next integrated into the ABM framework to form a hybrid single granuloma model, and thus the granuloma models became explicitly multi-scale (BOX) [59,61]. The general

computational framework is reviewed in Ref. [148] and may sometimes rely on development of individual level models, e.g. single cell models [58,83,86,87,149], for incorporation into a multi-scale framework. These models were supported and spurred by novel NHP data, including data on individual granulomas, as well as questions from the experimental literature surrounding the roles of specific pro- and anti-inflammatory factors. In particular, TNF and IL-10 dynamics were captured by including cell secretion, diffusion within the granuloma, receptor/ligand binding and internalization, and signaling leading to particular cellular outcomes [59–62]. The observation that some anti-TNF therapies (for unrelated autoimmune disease) were more likely to cause TB reactivation was interpreted as the result of differences in TNF/drug binding kinetics and permeabilities, both in an ODE setting [63] and in an ABM platform [56,150]. IL-10 was predicted to play an important role in controlling the early immune response to Mtb at the granuloma scale, limiting host-inflammation-induced caseation and preventing granuloma sterilization [61].

Two studies [65,151] address regulation of macrophage microenvironment-specific polarization (as pro- or anti-inflammatory, often termed M1 and M2 respectively) and effects on granuloma outcome. A new metric, the macrophage polarization ratio, captures how cytokine signaling translates into polarization of individual macrophages and collectively drives the emergence of an inflammation phenotype at the granuloma scale. Results suggest that the NF-κB signaling pathway is a viable therapeutic target to promote M1 polarization early during infection and to improve outcome. Dynamics of M1 and M2 macrophages have also been modeled using ODEs to understand how switching time (e.g. from an M2 to an M1-dominated environment) can impact infection outcome (measured as total CFU in the whole lung) [75,81]. Finally, a PDE model exploring host-directed therapies in the context of M1/M2 was recently explored [71]. Taken together, these more detailed models further support the view that there is a complex balance of pro- and anti-inflammatory mechanisms that attempt to "tune" each granuloma to contain infection but prevent its elimination.

Mtb utilize oxygen and carbon sources such as lipids. Nutrient availability can be predicted within single granuloma models, with various levels of complexity in how bacteria are described [57,72,73]. These models predict a continuous fluctuation in bacterial numbers, bacterial phenotypes and host responses throughout years of persistent infection [57]. They also address the contribution of granuloma structure to hypoxia [73] and bacterial phenotypic changes [72]. The bacterial focus of these models illuminates the constant feedback between bacterial adaptation and host immune responses that result in persistent infection.

Two compartment (lung and lymph node) models

Because cells move between lymph nodes and the lung, models also connect these compartments mathematically. Several 2-compartment ODE models capture cellular activation and priming in the lung-draining LN as well as trafficking between lungs and LN [76–78,80]. Additional models examined the link between lung granulomas and LNs [75,79]. These studies identified that mechanisms relevant to CD4+ T cell priming and trafficking might be manipulated to prevent establishment of Mtb infection or to clear bacteria from an established granuloma.

Attempting to scale in-host models to the whole host

Modeling an entire host can help bridge understanding from data and models derived at a smaller scale (e.g. single granulomas) to data derived from the host scale, including disease manifestations. Such models may also be critical to identifying new therapeutic interventions and predicting results of clinical trials. These models can be challenging from both the perspective of computational cost and capturing all relevant mechanisms. Approaches vary using either a whole lung scaling of granulomas to a whole host level model. A Boolean network model representing a whole host integrated multiple cellular and molecular mechanisms. They identified the importance of specific cytokines and phagosome functions [39]. In other work, multiple independently-evolving granulomas were linked together [38,152], created virtual NHPs that matched NHP datasets. A 3-compartment model (lung, LN and blood) captured formation of independent granulomas in lungs as well as T cell profiles in blood, and potential biomarkers that can predict infection outcome were identified. Rather than match datasets, multiple granulomas were tracked and an improved representation of DC trafficking was implemented [40]. Early events after Mtb infection were shown to be critical to establishing a timely and effective response. Finally, in a coarse-grained model, granulomas (population I, infected) were considered as variables that could spread to multiple lymph nodes (population S, susceptible) leading to infection there, with each tissue having the chance to resolve and clear infection (population R, recovered) using an SIR formalism [41]. This work showed that in early phases of infection granulomas suppress infection by providing additional antigens to the site of immune priming (in LNs); however, this induces a more rapid reactivation at later stages by disrupting immune responses.

Computational and mathematical modeling applications to TB

The mathematical and computational models described above have helped us better understand the bacterial and immune dynamics relevant to TB. They have begun to elucidate a critical aspect of infection, namely why some individuals develop clinically active disease and others latent disease. Confirmed by further wetlab

studies, we now understand containment of infection with a granuloma from the perspective of an appropriate balance of pro- and anti-inflammatory factors. Models can also help improve and direct how to prevent, treat, and monitor (via biomarkers) TB.

Within-host antibiotic treatment dynamics of TB

Sufficient exposure of bacteria to antibiotics is required for effective TB treatment [42,153]. Many studies investigate the pharmacokinetics (PK) and pharmacodynamics (PD) of anti-bacterial drugs for TB, focusing on blood and patient status (c.f. [25,154–161]). The spatial complexity of the granuloma, with Mtb within and external to cells that are located in this structure, complicates treatment, as antibiotic penetration into granulomas is often spatially heterogeneous [162–165] and bacteria develop phenotypic tolerance to antibiotics inside granulomas. To assess antibiotic efficacy within a granuloma, a single granuloma model (described above) is integrated with two additional elements [52,54]. First, ODE and PDE models are used to describe plasma and tissue pharmacokinetics (PK) following oral antibiotic administration, capturing antibiotic concentrations available to the granuloma as a function of time. Second, drug pharmacodynamics (PD) is described by ODEs that capture the mechanisms by which extracellular, intracellular replicating, and non-replicating bacteria are killed. Direct efficacy comparisons between drugs and dosing regimens (e.g. daily vs. weekly dosing) are possible, as one can examine the same simulated granulomas under different conditions. Thus far, two first line antibiotics, isoniazid (INH) and rifampin (RIF), have been examined within granulomas, with more antibiotics currently being incorporated [54,166]. This work demonstrates that antibiotic penetration into a granuloma limits treatment efficacy, particularly for intermittent dosing regimens as compared to daily regimens. It also demonstrates that intracellular bacteria present the main reservoir of bacteria at risk for developing resistance to RIF, one of the main first-line anti-TB antibiotics. In other work, the possibility of inhaled or orally dosed nanoparticle antibiotic delivery formulations was tested [53,55]. Both models highlight that the PK of released antibiotics influence the feasibility of nanoparticle delivery systems. While one drug (INH) was deemed suitable for inhaled delivery, the other (RIF) appeared less promising [53]. Overall, these *in silico* systems pharmacology approaches to examining the design space for antibiotic treatment may facilitate the identification of new treatment regimens for TB.

Within host-immune response modeling to guide vaccine development and testing

To date there is no broadly effective vaccine for TB, although many are in various stages of clinical development [167]. These clinical trials are difficult, expensive, and time-consuming, providing incentives to take a computational systems biology approach. Computational efforts in this area are limited but hold promise. Computational models have been applied to the study of other vaccines such as those for influenza and LCMV [168–170] but have yet to be applied in the context of TB. To begin to understand the generation of vaccine immunity in lymph nodes, an ABM representing the dynamics occurring during priming in a LN was developed. This model was used to simulate the generation of effector and memory T cells in response to a vaccine [24,82,171]. In one study, a "memory design space" was postulated and explored in which various ratios of effector and memory T cells were generated and their ability to generate an appropriate response determined. Given a set of desired characteristics for antigen-specific memory populations, the model can be used as a tool to predict vaccine formulations that will generate memory cell populations as well as their effect on granuloma-scale outcomes [24,82]. Here, virtual clinical trials that allow for host-to-host variation in a population will be important to perform.

Computational modeling in biomarker discovery in TB

Biomarkers associated with the observed spectrum of TB infection have yet to be identified [9]. This gap is particularly relevant when designing and testing new treatments and vaccines and defining the correlates of protection [172–175]. Recent work partly addresses this lack of understanding in a natural immunity setting [38]. In this work, the authors generated a unique large dataset of cell and cytokine markers measured in blood samples from Mtb-infected NHPs up to 6 months post infection. The NHPs were classified as either latent or active TB cases. The experimental data were used to build and calibrate a multi-organ computational model (lung at a single granuloma scale, with *in silico* blood level readouts of T cell memory markers). The analysis of *in silico* blood measures identifies *Mtb*-specific frequencies of effector T cell phenotypes at various time points post infection as promising indicators of infection outcome. The next challenge will be to experimentally validate such biomarkers; however, more reliable experimental techniques are needed to label Mtb-specific epitopes, which is not yet possible in primates. Another direction of research will be to address the same questions but in vaccine-induced immunity scenarios.

Tools for guiding new drug formulations for TB treatment

Computational models and systems biology approaches may also suggest modifications of existing drugs to improve efficacy as well as new drug targets. Application of uncertainty and sensitivity analyses to computational models can help with this identification. For example, since antibiotic properties are parameters in the computational models, analysis of these models can identify the appropriate antibiotic properties to modify

by systematically tuning each parameter and evaluating effects on treatment outcomes in the context of complex host immunity, PK and PD [54]. Identifying good bacterial targets for new or repurposed antibiotics is challenging since growth inhibition in liquid culture or *in vitro* mammalian cell infection does not necessarily translate into infection inhibition *in vivo*. Computational models that include host immunity and bacterial metabolism are able to identify bacterial genes that will have an effect on infection progression when targeted mid-infection in an established granuloma, a realistic approximation of when antibiotics would be administered in patients [57]. Further, single granuloma computational model analyses have suggested NFκ-B-associated signaling and TNF internalization pathways as well as a variety of Mtb metabolic enzymes as promising targets [56,58,59].

Successes, limitations and future challenges

Tuberculosis is a centuries old disease that is in desperate need of new and improved strategies for treatment and prevention. Copious amounts of data are being generated on many aspects of infection and disease, and we argue that a systems biology approach can help integrate and make sense of it. Collaborations between experimental and theoretical scientists can lead to advancements in the field. Over the past 15 years as described above, mathematical and computational models of within-host dynamics of TB infection have been developed and have provided insights to advance the study of this disease. For example, initially the anti-inflammatory cytokine IL-10 was shown to have no importance in mouse models of TB, but our computational models indicated that this negative regulator was a key determinant of infection outcome [46,61,62]. Later and ongoing studies in NHPs driven by our findings have supported this role and suggest that it can potentially be harnessed for immunotherapy [[75,176] and unpublished data]. It is this close connection between theory and experiment that may have the largest impacts on therapy development as well.

As described in Table 2, datasets to build, validate, and test in-host models are available. Different and disparate types of data are available from unique animal systems, at both different length and time scales and from different types of experiments and in different physiological compartments, including cell numbers in blood and lung, PET/CT images from NHP granulomas, as well as *in vitro* datasets (i.e. antibiotic microbicidal activity), and patient disease status and blood protein levels, etc. The computational approaches reviewed here are an excellent way to integrate various types of data into a more cohesive picture, providing better understanding of the immune factors and bacterial properties that drive and control infection.

Current and forthcoming data, together with the types of models described herein, position computational biologists to take on new challenges in TB. The first challenge is to better understand the factors that limit the efficacy of current and (forthcoming) antibiotics. The four front-line anti-TB drugs, INH, RIF, pyrazinamide, and ethambutol, as well as second-line agents used against drug-resistant strains, were implemented decades ago. More recently, broader spectrum antibiotics — aminoglycosides, fluoroquinolones and oxazolidinones — have been repurposed to treat drug-resistant TB. In addition, two representatives of new drug classes were approved for use against drug-resistant TB: Bedaquiline and Delamanid. More than a dozen drugs or drug candidates from these various classes are currently in clinical development or repositioning [177—179]. While the potential of new classes of antibiotics is promising, the "design space" for treatment regimens (combinations of antibiotics, doses, and dose frequencies) is huge. There is no standard approach to identifying treatment regimens and drugs are currently assigned in an ad hoc fashion, e.g. based on local guidelines and cost rather than comparative clinical data, which are largely missing. Exploring the design space in animal models or human clinical trials is extremely costly, lengthy, and difficult to assess. Integrating multi-scale computational models with relevant animal model data could allow rapid *in silico* testing of antibiotic therapies to predict more effective treatment regimens and accelerate clinical research.

We also need to better understand the development of antibiotic resistance. While some mathematical and computational approaches have been applied at the bacterial scale [31,180—184], including additional scales may be necessary in the multi-scale approaches described earlier. The genetic scale can capture resistance that arises due to point mutations or other genetic changes, up to the population scale, which captures the spread of drug resistance. The power of granuloma level models can be harnessed to understand how resistance can develop in the presence of antibiotics, esp. inadequate concentrations of antibiotics. These models may also require additional computational and modeling approaches to efficiently capture rare events in the context of what are computationally intensive simulations.

Challenges in the modeling approaches to study TB remain. For example, the single granuloma models described above capture in great detail the dynamics of immune cells, cytokines and chemokines, and Mtb; however the model simulations are time-consuming and costly, particularly given the large numbers of replications needed to gain meaningful statistics. In addition, on average, there are 42 granulomas in NHP lungs during TB infection [4—6]. Modeling techniques need to be developed to track the evolution of multiple granulomas. Early approaches assumed a well-mixed lung compartment; current approaches improve on this

but are still fairly simplified [38]. Further, we need computational approaches that mechanistically link to blood datasets (the most easily sampled compartment in humans) with the simultaneous evolving infection in the host lung. Such studies will advance the identification and interpretation of biomarkers of infection and correlates of protection for vaccine studies. However, given the computational demands of multi-scale modeling, especially ABMs, models should be developed with an appropriate level of complexity; techniques such as tuneable resolution (BOX) [185] and other coarse-graining tools can assist in analysis [186–188]. Developing models capturing within-host and population-scale dynamics is computationally difficult but necessary to explore the population-scale impacts of host-level factors [189–191].

While there are few applications of multi-scale modeling to infectious disease, the approaches here build on and contribute to the broader application of multi-scale modeling in biology, including many focused in cancer modeling and blood-related studies (e.g. Refs. [192–196]). In addition, there are other granulomatous diseases such as Schistosomaisis and Leishmania that would benefit from modeling, and lessons there could be applicable to TB and vice versa [197]. To advance infectious disease research further, it will likely take scientists and modelers collaborating across fields as different as HIV and TB, promoting cross-fertilization of ideas, methods, therapies and analysis techniques to gain a better understanding of how to combat and prevent infections.

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