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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]	