Predicting the Within-Host Dynamics of Tuberculosis

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Abstract

We present a within-host model for tuberculosis (TB) infections, which directly models the bacterial load over the course of the infection. This allows for a future multi-scale model which can make use of the link between pathogen load and transmission potential of an infected host. By modelling the interactions between the host immune system, the invading bacteria and granulomas which are characteristic of TB, we were able to reproduce some of the major traits of the disease. The model recreates the distribution of latent and active infections and maintains an accurate dose dependence.

1 Introduction

Mycobacterium tuberculosis (Mtb) is the causative agent of Tuberculosis (TB), which affects one third of the population worldwide and is a leading cause of death. In 2014 there were 9.6 million new cases and 1.5 million deaths as a result of TB infection [1]. TB predominantly affects developing countries as shown in figure 1, but can also affect the homeless community [2] or lower income areas of developed countries [3].

Antibiotic treatments such as isoniazid and rifampicin are available, however the regimens are usually long and have unpleasant side effects. This leads to non-compliance from patients, which in turn leads to the emergence of drug resistant strains of Mtb [5]. Multi-drug-resistant tuberculosis (MDR-TB) is the name given to any strain that is resistant to both isoniazid and rifampicin. An estimated 5% of TB cases are MDR-TB which has a 50% survival rate, even with treatment [6].

Humans and Mtb have co-evolved for millennia; the oldest confirmed case comes from a 17,000 year old Bison in Wyoming and skeletal remains of Egyptian mummies dating back to 3000 BC have shown evidence of tubercular decay [7]. As a result the Mtb bacteria are well adapted to survival within a human host. A hallmark of the TB infection is the occurrence of granulomas in the lungs. Mtb has the ability to survive within these granulomas for many year before spreading further [8]. This has lead to TB infections being defined by two states; active and latent. Only 10% of infected individuals will develop active TB however if left untreated, active TB has about a 70% mortality rate [9].

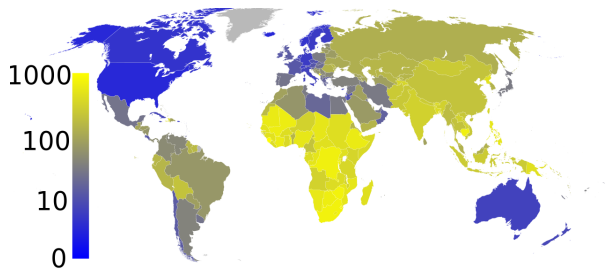


Fig 1. Prevalence of TB worldwide in 2009, number of cases per 100,000 [4].

Upon infection, Mtb predominantly attacks the lungs, although can be spread elsewhere in the body. The classic symptoms of TB are a chronic cough, fever, night sweats and weight loss [10]. Due to the pulmonary effects of TB, bacteria are easily disseminated when infected individuals cough, sneeze, speak or spit [1]. In the later stages of a TB infection, granulomas in the lungs grow and can spread to other areas of the body causing further complications. These advancements of TB are collectively referred to as extrapulmonary TB and occur in about 20% of active cases [11].

There are many challenges in studying the within host dynamics of a TB infection. First and foremost is the fact that the dynamics all occur within the lungs and are therefore unobservable without killing the host to extract the levels of bacteria in the granulomas and surrounding lung tissue. Non-human primates such as macaques, however, can be used to study TB and provide very coarse time series data on granulomas and bacteria due to their similar reaction to Mtb [12, 13].

1.1 Host response to Mtb

The first immune cell Mtb encounters upon entering the lungs of the host is the alveolar macrophage. The macrophage recognises the bacteria as a foreign cell and attempts to phagocytose the bacterium whilst releasing various cytokines (messaging proteins). Since the macrophage is only part of the innate immune system, the bacterium is able to survive phagocytosis and infect the macrophage by interfering with the phagosome-lysosome fusion [14]. The now infected macrophage continues to expel cytokines, which recruit the active immune response to the site of infection, in the form of other macrophages

as well as various lymphocytes and dendritic cells [15]. The immune cells contain the infection by encapsulating the infected macrophages in a spherical structure: the granuloma. Granulomas are made up of macrophages, that have either fused to form multinucleated giant cells or differentiated into lipid-rich foamy cells, and T and B lymphocytes (T and B cells) [16].

The purpose of these granulomas is to provide a micro-environment in which the immune system can take care of the infection, however Mtb has evolved to be able to survive for extended periods of time in these such an environment. In the early 20^{th} century Corper et al. [8] sealed several hundred strains of both human and bovine cultures of Mtb and placed them in an incubator at 37°C for 12 years between 1920 and 1932. As a result, 24 out of 56 bottles yielded culturable organisms. The survivability of Mtb in these sealed conditions for such a long time provides an analogy for the survivability of Mtb in granulomas within humans.

In an effort to slow bacteria reproduction, the body reduces iron content in the plasma by drawing it into macrophages [17]. However, since Mtb is able to survive within the macrophage, this extra iron facilitates growth inside the immune cell [18]. Once the pathogen has infected the macrophage, it is sheltered from the immune system and able to safely replicate.

While drug resistance has a role in the prevalence of TB within humans, it also has an interesting interaction with granulomas. Vandiviere et al. were able to culture bacilli from 9 out of 22 closed granulomas in treated patients, and 7 out of these 9 were fully drug sensitive [19]. Although the patients were treated, the bacteria within the granulomas had no interaction with the antibiotics and thus neither died, nor developed drug resistance. A postulated theory to explain this is that the reduced oxygen levels and other bacteriostatic agents reduce the metabolic rates of the bacteria which renders them refractory to drugs [20].

1.2 Previous work

By modelling sites in the lungs and lymph nodes as healthy and unhealthy, Gong et al. [21] provide a model of the dynamics of granulomas in these two organs. Their model sheds light on the heterogeneity of TB infections and suggests that latency comes about as a spectrum of various states of TB that are progressing towards active TB. Through sensitivity analysis the model suggests that inducing low level tissue damage early on to kill off the granulomas could help to avoid a more serious infection later on. One problem with this model, is that there is no way to correlate counts of granulomas with infection status and disease progression [22]. Another issue is that very few TB infections result in extrapulmonary infection in the lymph nodes. Extrapulmonary TB only occurs in 15-20% of active TB cases and of those, only 20% result in infection in the lymph nodes [23, 24]. Gong et al. include the lymph nodes because they are the site at which adaptive immune responses are initiated, however the model results in high levels of infection in the lymph nodes.

Wigginton and Kirschner [15] model the cellular and cytokine control network in an effort to identify the regulatory elements in the host response. The 11 ordinary differential equation (ODE) model predicts that even if latency is achieved, an unregulated immune response may result in tissue damage. Since the model has such high dimensionality, it is difficult to understand the effects of any individual terms. By understanding the effects of parameters on the system, it is possible to develop policies or drugs that specifically effect the more important parameters thus diseases can be more efficiently controlled.

Pedruzzi et al. [25] include the effect of other chemicals such as iron lipids and nitric oxide on the dynamics within macrophages in order to determine the fate of intracellular bacteria. By modelling the early phase of macrophage infection, it was found that the pathogen interferes with mechanisms within the host cell to reach a non-zero equilibrium. However if this equilibrium is perturbed the system produces oscillatory dynamics for disease progression.

Hao et al. [26] develop a very high dimensional set of partial differential equations describing interactions between multiple types of macrophages, bacteria and cytokines within a granuloma. This leads to a complex system of equations which focuses on the evolution of the granuloma once it has already formed. The effects of drugs that inhibit specific cytokines (IL-10 and IL13) are also evaluated. It is shown that a more rapid recruitment of T cells and macrophages to the granuloma results in a lower switching time (the time at which infected macrophages outnumber healthy macrophages).

2 Methods

In this work we will develop a within host model for TB. In particular we would like to specifically model the bacterial load within the host. With this type of model it would be possible to predict infection dynamics, such as time of activation or length of infection. Furthermore, there is evidence to suggest bacterial load affects onward transmission [27], hence having a model that explicitly gives the bacterial load will make it much easier to extend to multiple scales of within-hosts and between-hosts.

How the host immune system interacts with the pathogen will determine the within-host dynamics, and ultimately the infection status of the host. These interactions, however, are pathogen specific, so a good understanding of the key mechanisms of the immune system and pathogen dynamics is required to construct a biologically realistic and mathematically reasonable

model.

2.1 Macrophages

Once a pathogen bypasses the physical barriers such as the skin and chemical barriers such as gastric acid, the innate immune response will try to clear the infection. Pathogens are removed through a process called phagocytosis. This mechanism is carried out by a class of immune cells called phagocytes, which includes macrophages. The phagocytes engulf the pathogen, trapping it in an intracellular vesicle, where it is digested by enzymes.

The innate immune response is also responsible for activating the pathogen specific response of the adaptive immune response. The adaptive immune response is predominantly composed of two cells: T cells and B cells. On the surface of the pathogen there are molecules called antigens, which allow the immune cells to identify the pathogen as foreign. When a phagocyte digests a pathogen it presents the antigen of the pathogen on its cell surface. It is this antigen presentation that activates the T and B cells. The activated T and B cells are then more efficient at killing the pathogen and removing it from the host.

In the interest of simplicity of the model we will use the term 'Macrophage' to encompass all immune cells and we will treat the immune system as a system of cells of a single homogeneous type. Macrophages are produced in the lymph nodes and migrate to the lungs at some rate r_0. They also have a lifespan and die at some fixed rate δ_M. This gives a basic dynamic for the number of macrophages M

$$\frac{\mathrm{d}M}{\mathrm{d}t} = r_0 - \delta_M M. \tag{1}$$

The steady state of this system is $M^\star = {}^{r_0}/_{\delta_M}$, but the number of macrophages in disease free equilibrium sits at around 10^9 [28,29]. This implies that r_0 needs to be 9 orders of magnitude larger than δ_M. The literature, however, yields $r_0 = 1.34$ and $\delta_M = 0.02$ [26], hence an extra mechanic is needed for a realistic equilibrium value of M.

Macrophages are able to reproduce and grow at some rate r_1 [30] which gives

$$\frac{\mathrm{d}M}{\mathrm{d}t} = r_0 + r_1 M - \delta_M M. \tag{2}$$

This leads to an equilibrium of $M^\star = {}^{r_0}/_{\delta_M - r_1}$. Given the above values of r_0 and δ_M, r_1 would need to satisfy $|r_1 - \delta_M| \approx 10^{-9}$. Not only does this disagree with the literature, but it also makes the model very unstable. Reformulating the growth of macrophages as logistic with some carrying capacity yields the required order of equilibrium

$$\frac{\mathrm{d}M}{\mathrm{d}t} = r_0 + r_1 M\left(1 - \frac{M}{K_M}\right) - \delta_M M. \tag{3}$$

A carrying capacity of $K_M = 10^9$ [28,29] and a growth rate of $r_1 = 0.03$ [30] results in $M^\star \approx 10^8$.

2.2 Extracellular bacteria

When a macrophage phagocytoses an extracellular bacteria, the two combine to become an infected macrophage

$$\frac{\mathrm{d}M}{\mathrm{d}t} = r_0 + r_1 M\left(1 - \frac{M}{K_M}\right) - \gamma MB - \delta_M M, \tag{4}$$

where B is the number of extracellular bacteria. Extracellular bacteria also have a reproduction rate [15,31]. For similar reasons to macrophages, the bacteria grow logistically

$$\frac{\mathrm{d}B}{\mathrm{d}t} = \alpha B\left(1 - \frac{B}{K_B}\right) - \gamma MB. \tag{5}$$

In early time, when $M \gg 1$ and $B \ll K_B$, ${}^{\mathrm{d}B}/_{\mathrm{d}t} \approx (\alpha - \gamma M)\, B \ll 0$ hence B rapidly goes to zero. This corresponds to the all of the initial bacteria being phagocytosed. In order for the infection to persist, the infected macrophages require a mechanism by which granulomas are produced.

2.3 Granulomas

When bacteria are phagocytosed three events can occur. The bacteria can be successfully killed, in which case both bacteria and macrophage are removed from the system. Alternatively, the bacteria can survive the phagocytosis and initiate the formation of a granuloma. In order to capture active and latent TB, we make the assumption that granulomas are in one of two states: active or dormant. Furthermore, the ODEs will not give a count of granulomas but rather a level of affected area in the lungs and will therefore be referred to as levels of lesion.

Infected macrophages can develop into either dormant or active lesions or heal and be removed from the system. Thus L_D and L_A will grow proportionally to γMB

$$\frac{\mathrm{d}L_{D,A}}{\mathrm{d}t} = \Theta_{D,A}\gamma MB, \tag{6}$$

where $\Theta_{D,A}$ is the probability that a dormant (or active) lesion forms.

The bacteria within the dormant lesions will be in a dormant state and thus not replicating or moving, however dormant lesions can reactivate and become active lesions. Furthermore since the bacteria within active lesions are reproducing and active, there will be some dissemination of bacteria back into the lung space [21]

$$\frac{\mathrm{d}L_D}{\mathrm{d}t} = \Theta_D\gamma MB - aL_D \tag{7}$$

$$\frac{\mathrm{d}L_A}{\mathrm{d}t} = \Theta_A\gamma MB + aL_D \tag{8}$$

$$\frac{\mathrm{d}B}{\mathrm{d}t} = \alpha B\left(1 - \frac{B}{K_B}\right) + \beta L_A - \gamma MB. \tag{9}$$

Whilst the lesions are damaging the lung tissue, the immune system is also attempting to heal the lungs and removing lesions from the system [21]

$$\frac{\mathrm{d}L_D}{\mathrm{d}t} = \Theta_D \gamma MB - aL_D - \delta_D L_D \tag{10}$$

$$\frac{\mathrm{d}L_A}{\mathrm{d}t} = \Theta_A \gamma MB + aL_D - \delta_A L_A. \tag{11}$$

2.4 Adaptive immune response

The number of different cytokines and immune cells makes modelling the immune system very complicated. Instead of modelling each individually we will make an analogy of the immune response as a whole. Since the adaptive immune response is triggered by antigen presentation upon successful phagocytation from the innate immune response, the adaptive response should grow as bacteria are destroyed

$$\frac{\mathrm{d}R}{\mathrm{d}t} = g_R \left(1 - \Theta_D - \Theta_A\right) \gamma MB, \tag{12}$$

where g_R is the constant of proportionality for the growth of R. The immune response also has memory, thus R should have some degradation term [32]

$$\frac{\mathrm{d}R}{\mathrm{d}t} = g_R \left(1 - \Theta_D - \Theta_A\right) \gamma MB - \delta_R R. \tag{13}$$

The last part of the model is how the adaptive immune response changes the dynamics. Biologically, as the disease progresses, immune cells differentiate and specialise to become better at killing the specific bacteria that is infecting the host. To incorporate this into the current mechanics of the model, we assume that as R increases the probabilities Θ_D and Θ_A decrease.

2.5 Final model

Since the macrophages, extracellular bacteria and lesions are all growing within the lung space, the logistic growth rates of the macrophages and bacteria have been modified to take space into account

$$\begin{aligned}\frac{\mathrm{d}M}{\mathrm{d}t} &= r_0 + r_1 M \left(1 - \frac{C}{K_M}\right) \\ &\quad - \gamma BM - \delta_M M\end{aligned} \tag{14}$$

$$\begin{aligned}\frac{\mathrm{d}B}{\mathrm{d}t} &= \alpha B \left(1 - \frac{C}{K_B}\right) \\ &\quad + \beta L_A - \gamma BM\end{aligned} \tag{15}$$

$$\frac{\mathrm{d}L_D}{\mathrm{d}t} = \Theta_D e^{-\rho R} \gamma BM - aL_D - \delta_D L_D \tag{16}$$

$$\frac{\mathrm{d}L_A}{\mathrm{d}t} = \Theta_A e^{-\rho R} \gamma BM + aL_D - \delta_A L_A \tag{17}$$

$$\begin{aligned}\frac{\mathrm{d}R}{\mathrm{d}t} &= g_R \left(1 - \left(\Theta_D + \Theta_A\right) e^{-\rho R}\right) \gamma BM \\ &\quad - \delta_R R\end{aligned} \tag{18}$$

where

$$C = M + B + L_D + L_A.$$

The probability that either type of granuloma is formed is now dependent of the current level of R: $\Theta_{D,A}(R) = \Theta_{D,A} e^{-\rho R}$. A schematic of the model can be found in appendix A.

The final model now satisfies the basic requirements set out: disease free equilibrium and carrying capacities within the lungs. Due to the very non-linear nature of the model brought about by the response term R a full steady state analysis is very complicated and unlikely to shed any light on the model. However, it is clear that for a steady state with non-zero values of dormant lesions, we require a non-zero level of extracellular bacteria. If $B^\star \neq 0$ and $\mathrm{d}M/\mathrm{d}t = 0$ then noting that $1 - C/K_M < 1$ it is required that

$$B^\star < \frac{r_0 + \left(r_1 - \delta_M\right) M^\star}{\gamma M^\star}. \tag{19}$$

B and M are both countable values, and thus it is safe to assume that $B^\star$ should be greater than or equal to 1, however, this is only possible if $M^\star$ is less than 5 and is bounded itself by 5 when $M^\star = 1$. It is then possible to bound the other equilibrium values resulting in

$$M^\star < 5, \quad B^\star < 5, \quad L_D^\star < 4334$$

$$L_A^\star < 34, \quad R^\star < 3.3 \times 10^{-7}.$$

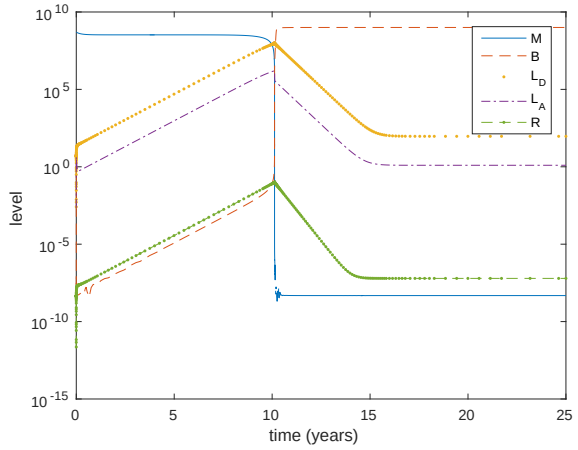
Biologically, this equilibrium does not make much sense, and in fact the large number of dormant lesions will develop into active lesions which in turn will produce more bacteria, so this equilibrium must be an unstable equilibrium. Hence the only remaining equilibriums are when either $B^\star = 0$ or when $M^\star = 0$, that is, in disease free or in active TB.

Latent TB may come about from a quasi steady state within the system. If the dynamics slow down for long enough, the individual could be classed as latent, before the disease becomes activated, which agrees with the results of Gong et al. [21].

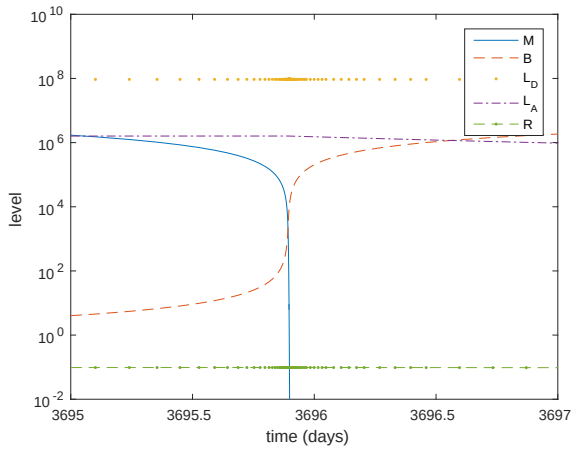
2.6 Parameters

When developing mathematical and computational models of biological systems there is often a level of uncertainty in the choice of parameter values. Time series data on bacterial load and levels of granulomas in the lungs over the course of an infection is very limited so parameter values have to be estimated. They are estimated to be biologically reasonable by observing the trends in the model and checking they are within the range observed in biological experiments and in keeping with the literature.

A future consideration to reduce the uncertainty in the parameters would be to use Latin hypercube sampling [33] and partial rank correlation coefficients [34].



(a) Full simulation.



(b) Fragment of (a) showing the switch from latent to active TB.

Fig 2. Numerical solution of the deterministic model with $B_0 = 10$. The host develops active TB after roughly 10 years.

However in order to perform these techniques more work is required to improve the efficiency of running the model.

Table 2 in appendix B gives the values of the parameters of the model. Out of the 16 parameters 12 had a basis in the literature on which to form a value. The remaining 4 pertain to the value of R which relates to multiple real-world elements, so parameters that are associated with R are difficult to measure or define within the host. As such, the assigned values were based purely on the output of the model and knowledge of the disease such as incubation period, counts of granulomas and the infectious dose.

3 Results and discussion

3.1 Recovered, latent and active

In reality, inhaling Mtb can result in one of 3 outcomes. Either the individual will recover or they will develop latent or active TB. In a deterministic model, heterogeneity comes from varying initial conditions and parameters, whilst a stochastic model will produce heterogeneity from the inherent stochasticity of the model. Definitions of the various infection statuses are as follows:

Recovered An individual is labelled as recovered if the infection does not fully take hold. There may still be bacteria within the host for a couple of years, but their immune system is able to clear the infection by itself.

Active In within-host modelling there is the idea of a switching time [28] which is the time at which the number of infected macrophages outnumber the number of healthy macrophages. With this in mind, it is reasonable to label an individual as having active TB if the bacteria (since infected macrophages are not explicitly modelled) outnumber the immune cells.

Latent If after 25 years, the individual has neither recovered nor developed active TB they are labelled as latent.

3.2 Deterministic model

Figure 2a shows the numerical solution to the ODEs with an initial dose of $B_0 = 10$. The infected host remains in the latent stage of the disease for about 10 years before developing active TB, however this switch occurs almost instantaneously, as shown in figure 2b. Figure 3 shows the contribution to extracellular bacteria from active lesions over time, found by integrating βL_A over the duration of the infection. At the time of the switch there is a large spike in the number of bacteria being produced

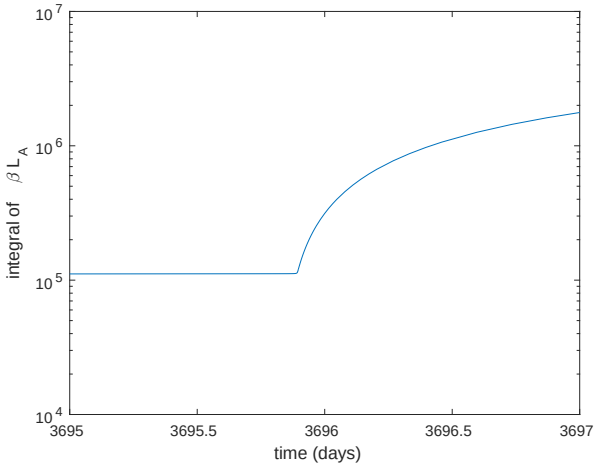
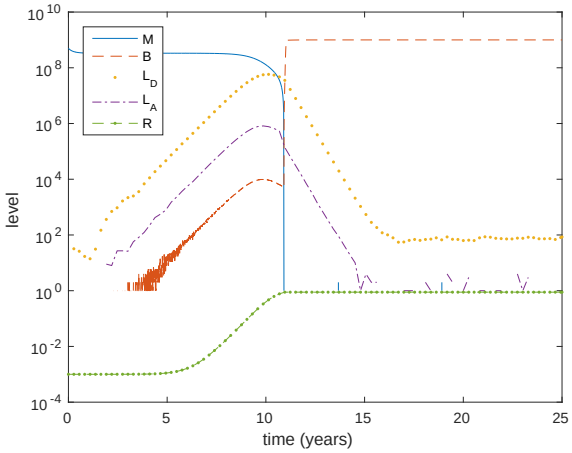
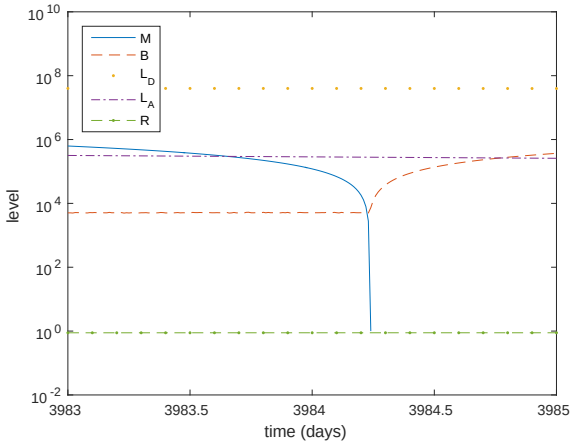


Fig 3. Contribution to extracellular bacteria from active lesions during the switch.



(a) Full simulation.



(b) Fragment of (a) showing the switch from latent to active TB.

Fig 4. A single run of the stochastic model with $B_0 = 10$. Similarly to the deterministic case the host develops active TB after roughly 10 years.

by active lesions. This spike allows the

$$\alpha B\left(1 - \frac{M + B + L_D + L_A}{K_B}\right)$$

term to move away from zero and the bacteria rapidly gain traction and explode in population. Since there is now a large number of bacteria, macrophages begin to deplete allowing further replication of bacteria.

A further artefact of the deterministic model is that the number of bacteria is never actually zero. After the initial uptake of bacteria, the level of bacteria has order 10^{-9}, but since the order of macrophages is 10^8 this gives a significant rate at which bacteria are being phagocytosed, even though there should be no bacteria present. The result of this is the production of phantom lesions which in turn produce more bacteria.

In addition to looking at the dynamics of the immune cells and bacteria within a granuloma, Hao et al. modelled the growth rate of the granuloma as a whole [26]. Their model predicted that over 50 days the radius of a granuloma grows from 0.01 cm to 0.014 cm. By naively assuming linear growth, and that a granuloma begins as a single infected macrophage, the volume of a granuloma over time (days) can be written as

$$V(t) = 4.99 \times 10^{-9} + 1.46 \times 10^{-7} t. \tag{20}$$

Assuming that macrophages and bacteria have a similar size, dividing equation 20 by the volume of a single macrophage [35] gives an estimation for the number of cells in granulomas at any time

$$N(t) = 1 + 29.3t. \tag{21}$$

Lastly computing $L_D(t)+L_A(t)/N(t)$ gives 10^2 for the order of lesions, which and agrees with the estimates of lung capacity given by Gong et al [21].

3.3 Stochastic model

To overcome the issues of the deterministic model, we convert the model to a stochastic version with transition rates as defined by the deterministic model. The standard method for this would be to use the Gillespie algorithm [36], however due to the large number ($\sim 10^9$) of macrophages during the early time of the model, there are far too many events to make this simulation feasible. A common compromise to this problem is to use the τ-leap method [37] with a variable step size τ that depends on the rates. The large differences in rates attributed to the macrophages and the other particles in the system again make this an infeasible solution. In order for the simulations to run in a reasonable amount of time, a fixed step size of $\tau = 0.01$ was used.

For terms M, B, L_D and L_A the rates at which they increase and the sizes of increase can be easily obtained by analogy with the deterministic model. R should grow every time there is a successful phagocytation of a bacteria. In the deterministic model, this growth is partially controlled by the constant of proportionality g_R. Thus, every time a bacteria is killed, R should grow by g_R.

Figure 4a shows a single run of the stochastic model. In this case, the individual developed active TB at about 10 years, which is similar to that of the deterministic model. The spike in bacteria level, however, is much less pronounced and the rapid growth, although along the same time-scale, seems much more reasonable. An expanded view of the switch from latent to active TB is shown in figure 4b.

A noticeable difference between the stochastic model and the deterministic model, is the level of B in the early stage of the model. This comes about from the fact that only integer values of B are allowed in the stochastic model. Initially $B = L_A = 0$ and L_D is very

low. Eventually some of the dormant lesions become active and can start producing bacteria. At first the bacteria only facilitate the growth of L_D and L_A, but this has a knock on effect for the extracellular population of bacteria to be able to grow on their own.

The time to activation in both models, as shown in figures 2 and 4, is roughly 10 years. In fact, running the stochastic model 45 times with $B_0 = 10$, resulted in an average activation time of 3794 days (10.4 years) with a standard deviation of 512 days (1.4 years). The similarity to the deterministic model and the lack of deviation suggests that large number of events within the stochastic model average out and end up closely approximating the deterministic version.

3.4 Epidemiology

It has already been discussed that one third of the population is infected with TB and that of that 33% that develop an infection only 10% will develop active TB. After running the stochastic model 100 times with an initial dose of $B_0 = 10$, it yielded 25 latent infections, 2 active infections and 73 recoveries.

Infection status	Epidemiology [1]	Model
Recovered	67%	73%
Active	3%	2%
Latent	30%	25%

Table 1. Epidemiological results of the stochastic model

As shown in table 1 the model closely represents this simple epidemiological data for TB. As a result, it could be used in a multi-scale model along with a model for transmission based on bacterial load. Using social interaction data this could lead to a deeper understanding of the transmission of TB through communities.

3.5 50% infectious dose

A common figure to find when modelling a dose dependent within host model of disease is the dose required to infect 50% of people. Running the stochastic simulation for 20 iterations each over a range of doses gives an estimation of the probability that a given dose will infect an individual, shown in figure 5. As in Ref. [38], it can be assumed that the bacteria each have an independent chance to cause infection, that is

$$\mathbb{P}\left[\text{infection}|\text{dose } d\right] = 1 - (1-\theta)^d \qquad (22)$$

where θ is the probability that any individual bacteria causes infection. At the start of the model, the response term R is zero, and so the probability that a bacteria survives phagocytosis is $1 - \Theta_D - \Theta_A$. A single surviving bacteria however does not guarantee infection so we would expect θ to be slightly less than this. By fitting equation 22 to the results from the model we get that $\theta = 0.0657$, which is actually slightly larger than $1 - \Theta_D - \Theta_A = 0.0460$. This will be due to error as a result of the stochastic simulation. Solving equation 22 for $0.5 = 1 - (1-\theta)^d$ gives that the required dose to infect 50% of people is approximately 10 bacteria. This agrees with the low infectious dose of TB given in the literature [39].

4 Conclusions and further work

A within-host model for TB has been developed which exhibits some of the characteristic traits observed in TB infections. The model has a dose dependence and will account for both latent and active infection states. Further work on the model would be to look at how it interacts with other infections, in particular diseases with an immunosupression effect such as HIV.

Individuals with active TB have a very high mortality rate without medical intervention. It would be interesting to investigate the processes involved in drug uptake and vaccination and see how they interact with the above model.

Additionally the model has only 2 equilibrium states; either disease free or active TB. The latent infection status comes about from individuals whose infection has either not yet activated or not yet recovered, but their bacterial load is still following an arc as in figure 4. This means that had the model been allowed to run longer, people would begin to recover by themselves without medical intervention. This disagrees with the recovery rate of TB without medical intervention and thus shows a flaw in the model.

Furthermore, the addition of a compartmental aspect of the model to introduce the possibility of extrapulmonary TB could allow further investigation into how TB affects other parts of the body. By incorporating some

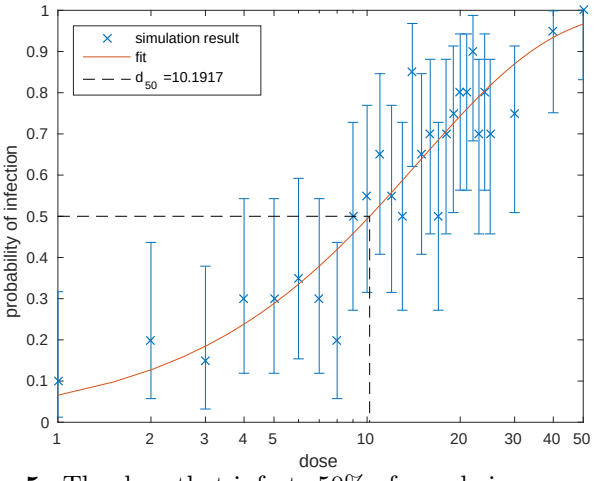


Fig 5. The dose that infects 50% of people is approximately 10.

more detailed biological dynamics, predictions could be made on whether extrapulmonary symptoms will develop based on current symptoms.

In conclusion, the model presented in this work will provide a good base to build upon in the future. The fact that the model produces biologically reasonable results and that they are along the expected time-scales means that model should be robust enough to take in additional mechanics without losing its current worth.

Appendices

A Schematic of the final model

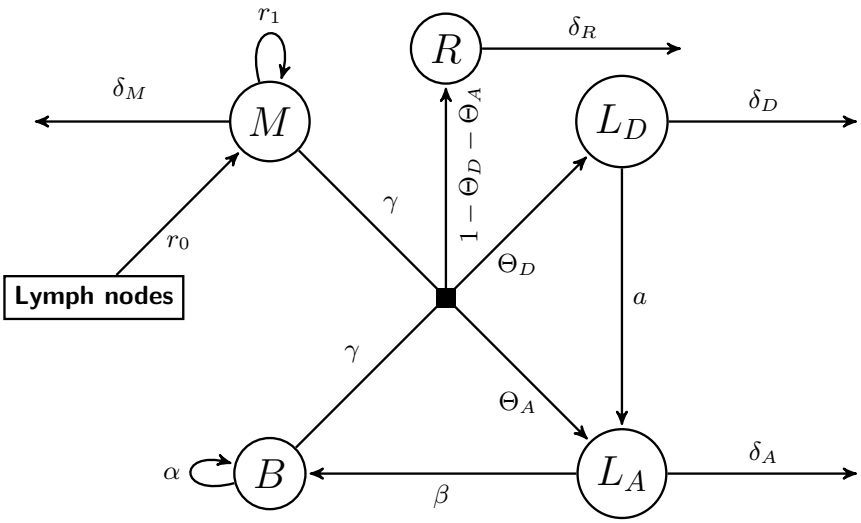


Fig 6. According to the model macrophages phagocytose bacteria. This can either be successful resulting in an increase in the immune response, or it can fail resulting in either dormant or active lesions forming. Dormant lesions can transition into active lesions, which in turn produce more bacteria.

B Parameters

Symbol	Description	Value	Unit	Source
B	Extracellular bacteria		count	
M	Macrophages		count	
L_D	Level of dormant lesions		scalar	
L_A	Level of active lesions		scalar	
R	Level of immune response		scalar	
r_0	Recruitment rate of macrophages	1.34	cell day^{-1}	[26]
r_1	Growth rate of macrophages	0.03	day^{-1}	[30], estimated
K_M	Carrying capacity of macrophages	10^9	scalar	[28, 29]
γ	Rate of phagocytosis	0.28	day^{-1}	[26]
δ_M	Death rate of macrophages	0.02	day^{-1}	[26]
α	Growth rate of extracellular bacteria	0.2	day^{-1}	[15]
K_B	Carrying capacity of bacteria	10^9	scalar	[31]
β	Rate of release of bacteria from active lesions	1.2	day^{-1}	[21]
Θ_D	Probability that phagocytosis results in a dormant lesions	0.52	scalar	estimated
Θ_A	Probability that phagocytosis results in an active lesion	0.434	scalar	estimated
δ_D	Resolution rate of dormant lesions	0.005	day^{-1}	[21]
δ_A	Resolution rate of active lesions	0.65	day^{-1}	[21]
a	Rate of activation of dormant lesions	0.0025	day^{-1}	[21]
ρ	Strength of the immune response	0.27	scalar	estimated
g_R	Growth rate of the immune response	10^{-8}	scalar	estimated
δ_R	Rate of immunological decay	0.01	scalar	[32], estimated

Table 2. The values of parameters used in the model. Most parameters have been taken from literature. Those that have been estimated were given values that seem biologically reasonable as in section 2.6.

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