An Investigation of Tuberculosis Progression Revealing the Role of Macrophages Apoptosis via Sensitivity and Bifurcation Analysis

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The TB Model and Parameter Table

M_u, M_i, B, and T denote uninfected, infected macrophages, Mtb bacteria and T lymphocytes.

$$\begin{aligned}
\frac{dM_u}{dt} &= s_M - \mu_M M_u - \beta M_u B \\
&= \text{recruitment} - \text{death} - \text{infection} \\
\frac{dM_i}{dt} &= \beta M_u B - bM_i - \gamma M_i \frac{T/M_i}{T/M_i + c} \\
&= \text{infection} - \text{loss} - \text{killed by cell-mediated immunity} \\
\frac{dB}{dt} &= \delta B\left(1 - \frac{B}{K}\right) + M_i\left(N_1 b + N_2 \gamma \frac{T/M_i}{T/M_i + c}\right) - M_u B(\eta + N_3\beta) \\
&= \text{proliferation} + \text{released from} M_i \text{apoptosis} + \text{released from T-cell killing} - \text{killed by} M_u \\
&\quad - \text{become intracellular by infection} \\
\frac{dT}{dt} &= s_T + \frac{c_M M_i T}{e_M T + 1} + \frac{c_B B T}{e_B T + 1} - \mu_T T \\
&= \text{recruitment} + \text{activation} - \text{death}.
\end{aligned}$$

Sym.	Definition	Unites	Mean value (Range)
s_M	Uninfected macrophages' recruitment rate	$\text{ml}^{-1}\,\text{day}^{-1}$	$5000\,(3300,\ 7000)$
s_T	T-cell recruitment rate	$\text{ml}^{-1}\,\text{day}^{-1}$	$6.6\,(0.33,\ 33)$
μ_M	Uninfected macrophages' death rate	day^{-1}	$0.01\,(0.01,\ 0.011)$
b	Infected macrophages' clearance rate	day^{-1}	$0.11\,(0.05,\ 0.5)$
μ_T	T-cell death rate	day^{-1}	$0.33\,(0.05,\ 0.33)$
β	Mtb infection rate	day^{-1}	$5\times10^{-6}\,(10^{-8},\ 10^{-5})$
η	Mtb death rate by uninfected macrophages' killing	$\text{ml}^{-1}\,\text{day}^{-1}$	$1.25\times10^{-9}\,(1.25\times10^{-9},\ 1.25\times10^{-7})$
γ	T-cell mediated immunity rate	day^{-1}	$1.5\,(0.1,\ 2)$
δ	Mtb proliferation rate	day^{-1}	$5\times10^{-4}\,(0,\ 0.26)$
c_M	T-cell proliferation rate induced by infected macrophages	day^{-1}	$10^{-3}\,(10^{-8},\ 1)$
c_B	T-cell proliferation rate induced by Mtb	day^{-1}	$5\times10^{-3}\,(10^{-8},\ 1)$
e_M	Saturating factor for T-cell proliferation rate induced by infected macrophages	–	$10^{-4}\,(10^{-6},\ 10^{-2})$
e_B	Saturating factor for T-cell proliferation rate induced by Mtb	–	$10^{-4}\,(10^{-6},\ 10^{-2})$
c	$\frac{\text{T cells}}{\text{uninfected macrophages}}$ half-saturation ratio for uninfected macrophages lysis	$\frac{T}{M_i}$	$3\,(0.3,\ 30)$
K	Mtb carrying capacity	ml^{-1}	$10^8\,(10^6,\ 10^{10})$
N_1	Average number of Mtb released by one macrophage	$\frac{B}{M_i}$	$50\,(50,\ 100)$
N_2	Maximum number of Mtb released by one macrophage lysis	$\frac{T}{M_i}$	$20\,(20,\ 30)$
N_3	Average number of Mtb carried by one macrophage	$\frac{B}{M_i}$	$25\,(25,\ 50)$

Table 1. Source: Du Y, Wu J, Heffernan JM (2017) A simple in-host model for Mycobacterium tuberculosis that captures all infection outcomes. Mathematical Population Studies

Our Goal and How to Achieve It

Our goal: Mycobacterium tuberculosis infection features various disease outcomes: clearance, latency, active disease, and latent tuberculosis infection (LTBI) reactivation. Identifying the decisive factors for disease outcomes and progression is crucial to elucidate the macrophages-tuberculosis interaction and provide insights into therapeutic strategies.
To achieve this goal, we **first** model the disease progression as a dynamical shift among different disease outcomes, which are characterized by various steady states of bacterial concentration. The causal mechanisms of steady-state transitions can be the occurrence of transcritical and saddle-node bifurcations, which are induced by slowly changing parameters. Transcritical bifurcation, occurring when the basic reproduction number equals to one, determines whether the infection clears or spreads. Saddle-node bifurcation is the key mechanism to create and destroy steady states. Based on these two steady-state transition mechanisms, we carry out two sample-based sensitivity analyses on transcritical bifurcation (R_0) and saddle-node bifurcation conditions.

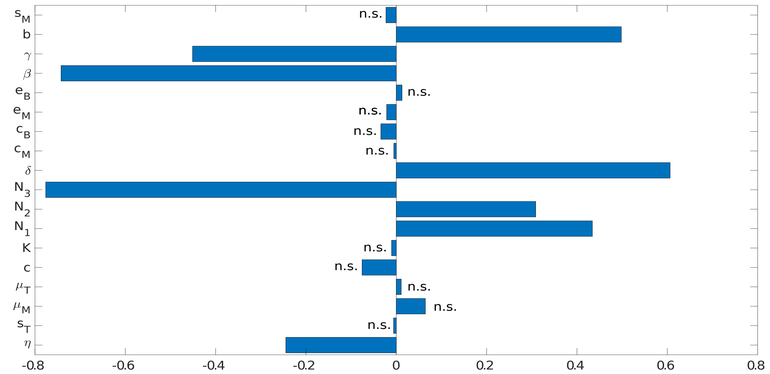


Figure 1. PRCC values for R_0 under the variations of all model parameters. n.s. denotes statistically not significant.

The above figure indicate that R_0 has

- a significantly positive relation with N_1, N_2, and N_3;
- a significantly negative relation with β because the infection process involves the loss of extracellular Mtb by macrophages phagocytosis;
- a significantly negative relation with η;
- a significant relation with the whole term $\frac{b}{b+\gamma}$, indicating that more intracellular Mtb are released from apoptosis than necrosis;
- the significant parameter set affecting R_0 is $p_v = (b, \gamma, \beta, \delta, \eta, N_1, N_2, N_3)$.

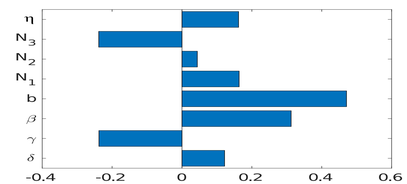
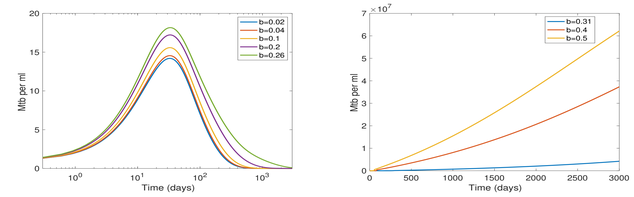


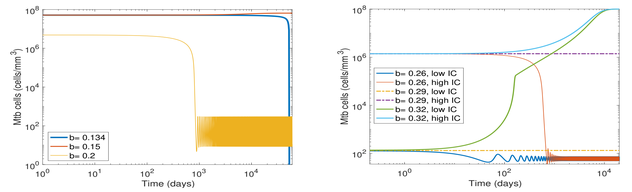
Figure 2. PRCC values for saddle-node bifurcations on the influential parameters,p_v, for disease outcomes. It suggests that the macrophage clearance rate, b, is the most significant factor affecting the transition in disease outcomes.

Roles of Macrophage Programmed Cell Death (Apoptosis)

1. In the case of low infection environment, apoptosis induces clearance (see the left figure), but fail to control the Mtb progression if b value passes LP_2 (see the right figure).



2. In low infection case, Mtb load is controllable to LTBI status. In heavy infection case, Mtb load stay in active disease status. Infection will progress to active disease if b value passes LP_2. Virulent Mtb strains manage to suppress macrophage apoptosis, then tune the value b.



3. Mtb infection can be eliminated or controlled in LTBI status if the b value on the left of LP_3 (see the right figure). Disease clearance and LTBI status can be achieved by increasing b and γ, or decreasing N_1. It means that a drug therapy that moderates the macrophage apoptosis works better with the combination of an increased killing rate of infected cells by the immune system γ or a decreased Mtb released number N_1 during programmed cell death.

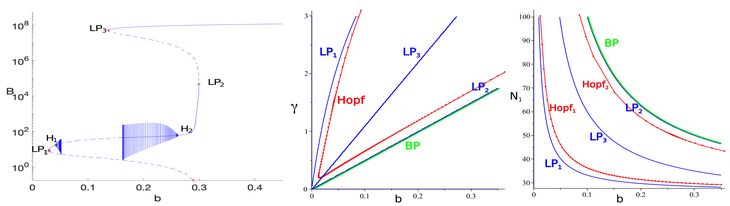


Figure 3. B: Mtb cells, LP: saddle node bifurcation, H: Hopf bifurcation, BP: transcritical bifurcation.

Conclusion

Our results agree with the discovery that the programmed cell death (apoptosis) plays a unique role in the complex microorganism-host interplay. Sensitivity analysis narrows down the parameters of interest, but cannot answer how these parameters influence the model outcomes. To do this, we employ bifurcation analysis and numerical simulation to unfold various disease outcomes induced by the variation of macrophage clearance rate. Our findings support the hypothesis that the regulation mechanism of macrophage apoptosis affects the host immunity against tuberculosis infection and tuberculosis virulence. Moreover, our mathematical results suggest that new treatments and/or vaccines that regulate macrophage apoptosis in combination with weakening bacillary viability and/or promoting adaptive immunity could have therapeutic value.