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# A Mathematical Model of in-Host Tuberculous Granuloma*

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**Abstract** Tuberculosis is the second biggest infectious disease killer after coronavirus. In this paper, we analyze a mathematical model of in-host tuberculous granuloma, obtaining the basic reproduction number, as well as the existence and stability of equilibrium points. The sensitivity analysis provides parameters that have a significant effect on model dynamics. Finally, changes in the number of immune cells, infected macrophages and Mycobacterium tuberculosis are analyzed by numerical simulation of three disease states: clearance, latent infection and active tuberculosis. The results suggest that the immune mechanism determing whether an infected individual will suffer from active or latent tuberculosis is the ability of activated infected macrophages to kill Mycobacterium tuberculosis.

**Keywords** Tuberculous granuloma, immune cell, the sensitivity analysis, stability

**MSC(2010)** 37N25, 92D30.

## 1. Introduction

Tuberculosis (TB) is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide. Until the coronavirus (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS [1]. Therefore, the study of the dynamics of the immune response within the granuloma is crucial for the prevention and treatment of TB.

About a quarter of the global population is estimated to have been infected with TB, but most people will not go on to develop TB. They either clear the infection, or experience latent infection [1]. These latent infection are neither sick nor contagious, but they are at greater risk of developing TB, especially those with weakened immune systems. Without treatment, the death rate from TB disease is high (about 50%) [1]. Providing them with TB prevention and treatment measures not only protects them from the disease, but also reduces the risk of transmission in the community. Understanding the dynamics of the immune response is critical to elucidating the differences between infected individuals and those with active disease.

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Nowadays, mathematical models are widely used to study the factors that influence the progression of TB infection [2–8]. We assume that:

1) As soon as Mycobacterium tuberculosis(Mtb) invades, macrophages are activated, that is, only activated and infected macrophages are considered;

2) Mtb is phagocytosed by macrophages and is either cleared or infects the macrophages. When the number of Mtb inside the macrophage reaches its limit, it explodes and releases Mtb outside the macrophage. Mtb outside macrophages grows in a linear manner;

3) in the event of a non-specific immune response, T cells are activated in a logistic manner induced by infected macrophages;

4) the role of cytokines in the immune response is expressed only through immune T cells and is not considered separately.

Based on the above assumptions and [3, 9], we study a four-dimensional ODE in-host TB granuloma model (1.1) that includes linear growth of Mtb. Model (1.1) includes activated infected macrophages($\bar{M}_U$), infected macrophages ($\bar{M}_I$), extracellular Mtb($\bar{B}$) and immune T cells($\bar{T}$). Activation, infection and death of activated infected macrophages($\bar{M}_U$) are tagged with $\Lambda_U$, $\bar{\beta}$ and $\mu_U$. Infected macrophages($\bar{M}_I$) are cleared by T cells at the rate $\bar{\alpha}_T$. The death rate of infected macrophages($\bar{M}_I$) is $\mu_I$. Recruitment of extracellular Mtb($\bar{B}$) resulting cell division or release by apoptosis of infected macrophages. The bacteria division is modelled in a linear manner, at a constant growth rate($\Lambda_B$). The average number of bacteria released by apoptosis of infected macrophages is $\bar{r}$. The death rate of immune T cells($\bar{T}$) is expressed as $\mu_T$. Infected macrophages($\bar{M}_I$) can activate T cells($\bar{T}$), expressed as $(1-\frac{\bar{T}}{T_{max}})\bar{k}_I\bar{M}_I$, where $\bar{k}_I$ is the growth rate of T cells, and $T_{max}$ is the maximum population level of T cells. Our mathematical model of in-host TB granuloma is written like this:

$$\begin{cases} \dfrac{\mathrm{d}\bar{M}_U}{\mathrm{d}t} = \Lambda_U - \mu_U\bar{M}_U - \bar{\beta}\bar{B}\bar{M}_U, \\ \dfrac{\mathrm{d}\bar{M}_I}{\mathrm{d}t} = \bar{\beta}\bar{B}\bar{M}_U - \bar{\alpha}_T\bar{M}_I\bar{T} - \mu_I\bar{M}_I, \\ \dfrac{\mathrm{d}\bar{B}}{\mathrm{d}t} = \Lambda_B\bar{B} + \bar{r}\mu_I\bar{M}_I - \bar{\gamma}_U\bar{M}_U\bar{B} - \mu_B\bar{B}, \\ \dfrac{\mathrm{d}\bar{T}}{\mathrm{d}t} = (1-\dfrac{\bar{T}}{T_{max}})\bar{k}_I\bar{M}_I - \mu_T\bar{T}, \end{cases} \tag{1.1}$$

In order to reduce the number of parameters, we introduce the following variables

$$M_U = \frac{\bar{M}_U}{\Lambda_U/\mu_U},\ M_I = \frac{\bar{M}_I}{\Lambda_U/\mu_U},\ B = \frac{\bar{B}}{\mu_U^2/\Lambda_B^2},\ T = \frac{\bar{T}}{T_{max}}.$$

The system(1.1) becomes

$$\begin{cases} \dfrac{\mathrm{d}M_U}{\mathrm{d}t} = \mu_U - \mu_U M_U - \beta B M_U, \\ \dfrac{\mathrm{d}M_I}{\mathrm{d}t} = \beta B M_U - \alpha_T M_I T - \mu_I M_I, \\ \dfrac{\mathrm{d}B}{\mathrm{d}t} = \Lambda_B B + r M_I - \gamma_U M_U B - \mu_B B, \\ \dfrac{\mathrm{d}T}{\mathrm{d}t} = (1-T)k_I M_I - \mu_T T, \end{cases} \tag{1.2}$$

where