Within-host dynamics model for persistence and drug resistance of M. Tuberculosis

Daniel Girardi[1], Thadeu J. P. Penna[1,2], Aquino L. Espíndola[2], Chris Bauch [3]
girardi@if.uff.br

[1]NIST-CS - Brazil, [2] ICEX - UFF - Brazil, [3] University of Guelph - Canada

NIST Complex System

Introduction

Tuberculosis (TB) is world-wide problem and one-third of the world's population is infected with TB. In specialized literature, one can find many mathematical models that deal with bacterial resistance or persistence due the use of antibiotics, separately. Then we developed a model in which resistance and persistence takes place in the within-host dynamics simultaneously.

Resistance

Due to mutations during the reproduction process, bacteria may change their genes and then become resistant to some antibiotics. Thus, the efficacy of these drugs to treat such resistant strains is reduced.

Persistence

For some unknown reason, a fraction of bacteria go into a dormancy state for some time, consequently they do not reproduce. During the dormancy state these pathogens are not detected by the immune system and they can not be affected by the antibiotics.

Mathematical Model

- Sensitive (S) and Resistant(R) Bacteria :

$$\frac{dS}{dt} = (1-q)\nu S - \gamma SI - fS + gS_d - \alpha S \quad (1)$$

$$\frac{dR}{dt} = q\nu S + \omega\nu R - \gamma RI - fR + gR_d - \delta\alpha R \quad (2)$$

- State of Dormancy (S_d and R_d):

$$\frac{dS_d}{dt} = fS - gS_d \quad (3)$$

$$\frac{dR_d}{dt} = fR - gR_d \quad (4)$$

- Immune System (I):

$$\frac{di_0}{dt} = a(S,R) - \epsilon i_0\left(\frac{S+R}{\kappa+S+R}\right) - \mu i_0 \quad (5)$$

$$\frac{di_j}{dt} = 2\epsilon i_0\left(\frac{S+R}{\kappa+S+R}\right) - \epsilon i_j\left(\frac{S+R}{\kappa+S+R}\right) - \mu i_j \quad (6)$$

where

$$I = \sum_{j=0}^{n} i_j \quad (7)$$

and

$$a(S,R) = a_1\left(2 - \frac{S^m}{a_2^m + S^m} - \frac{R^m}{a_2^m + R^m}\right) \quad (8)$$

The immune system dynamics is described by a set of n equations. Each equation represents a stage of the T cell reproductive process.

Initial Conditions

To solve a set of $n+4$ equations, the initial conditions are $S = i_0 = 1$ and $R = S_d = R_d = 0$. The fourth order Runge-Kutta method has been used to solve these equations. Parameters description and values used in simulations are in the Table below.

Parameter	Value ($days^{-1}$)	Definition
ν	0.4	reproduction rate of S type bacteria
ω	0.9	cost evolution of R type bacteria
q	10^{-3}	mutation rate
γ	0.1	immune system efficacy
f	0.0 - 0.5	conversion rate to dormant state
g	0.1	conversion to active state
α	0.0 - 0.8	annihilation rate due to antibiotiocs
δ	0.0 - 0.8	antibiotics relative efficacy
ϵ	1.0	reproductive stimulus of T cells
κ	1000	reproduction limit of T cells
m	3	shape of the recruitment function
μ	0.1	death rate of T cells
a_1	0.0 - 0, 5	recruitment rate of T cells
a_2	200	limit of recruitment rate
n	3	Hayflick limit

We have used three different threshold to the equations: **1)** Bacterial Upper Limit: the maximum amount of bacteria is 10^3. **2)** Bacterial Lower Limit: the minimum amount of bacteria is 5×10^{-3}. **3)** Immune System Lower Limit: the minimum value to the immune system is 1.

The Hayflick limit is the average number of times that a cell can reproduce before dying. For T cells, this limit is ~ 23. In order to reduce computational time we have implemented the simulation with a Hayflick limit $n = 3$, which results are the same as $n = 23$

Results:

Our model predicts three expected behaviors during a TB infection without antibiotics treatment:

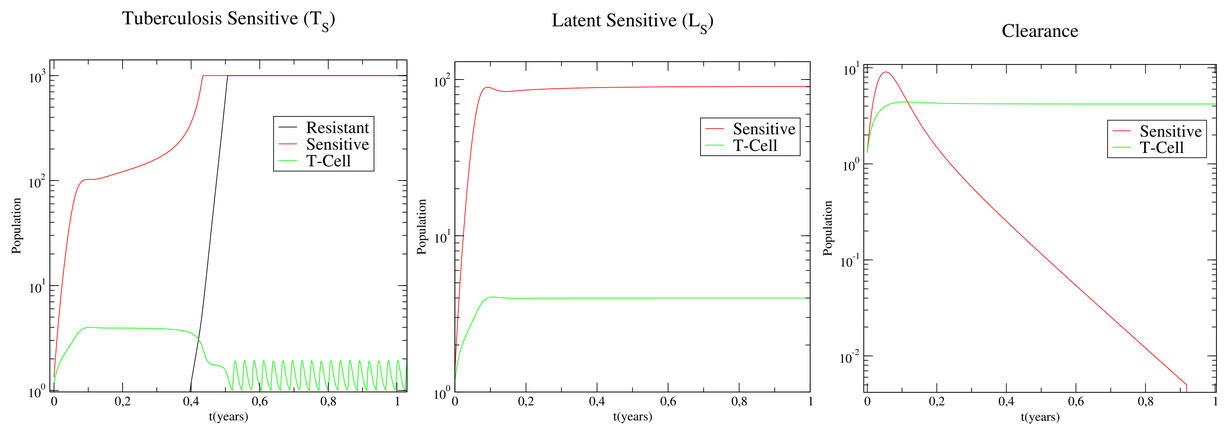

Figure 1: Bacterial population S and R as function of time for three stages of TB: Active tuberculosis ($a_1 = 0.11$), Latency ($a_1 = 0.14$) and clearance ($a_1 = 0.21$). Vertical axis is plotted in a logarithmic scale.

From now on, we use the notation: L_S and L_R for individuals in latent state with type S and type R bacteria, respectively; T_S and T_R for individuals in active state (ill) of TB. Even though both type of bacteria may be present in an individual, the subscript S or R means the predominance of such type of pathogen.

Experimental data show that after being infected, about $\sim 5\%$ of this population will progress to the active state of TB during the next 2 years. As we can see in Figure 1, after the infection ($t = 0$), the total population of bacteria ($S + R$) became smaller than 10^2. We define that number as the threshold to enter the active state. We call latency time as the period from the beginning of the infection until individual enter the active state of the disease.

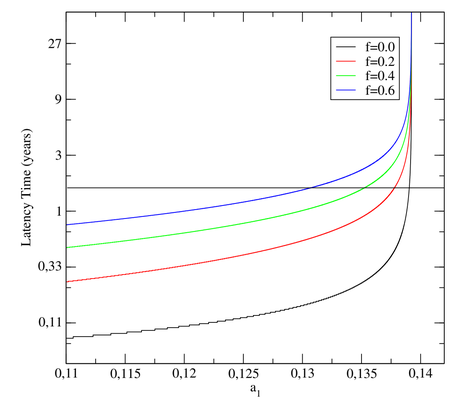

Figure 2: Latency time as function of a_1 to different values of f. Vertical axis is plotted in a logarithmic scale.

In Figure 2, it is plotted latency time as function of the recruitment rate (a_1) for different values of f. For $a_1 > 0.139$, we only have the latent state, so the latency time diverges. In particular, for $a_1 < 0.139$ and $f = 0$ almost all activation occurs before the end of the second year (horizontal black line). For the others values of f only a small range of a_1 present activation after the second year.

When treatment is employed, beyond the possibilities to be cured or not, there are also two more states. In order to reach the steady state, in Figure 3, we let the system evolve during 10 years without treatment ($\alpha = 0$) . After this period, treatment is applied during 180 days and then stopped.

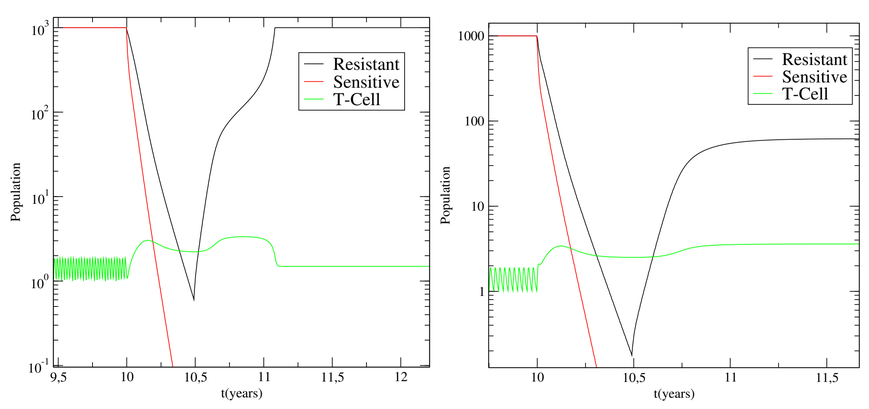

Figure 3: Bacterial population S, R and T cells population as function of time after the period 180 days with antibiotics treatment. Vertical axis is plotted in a logarithmic scale.

Phase Diagram

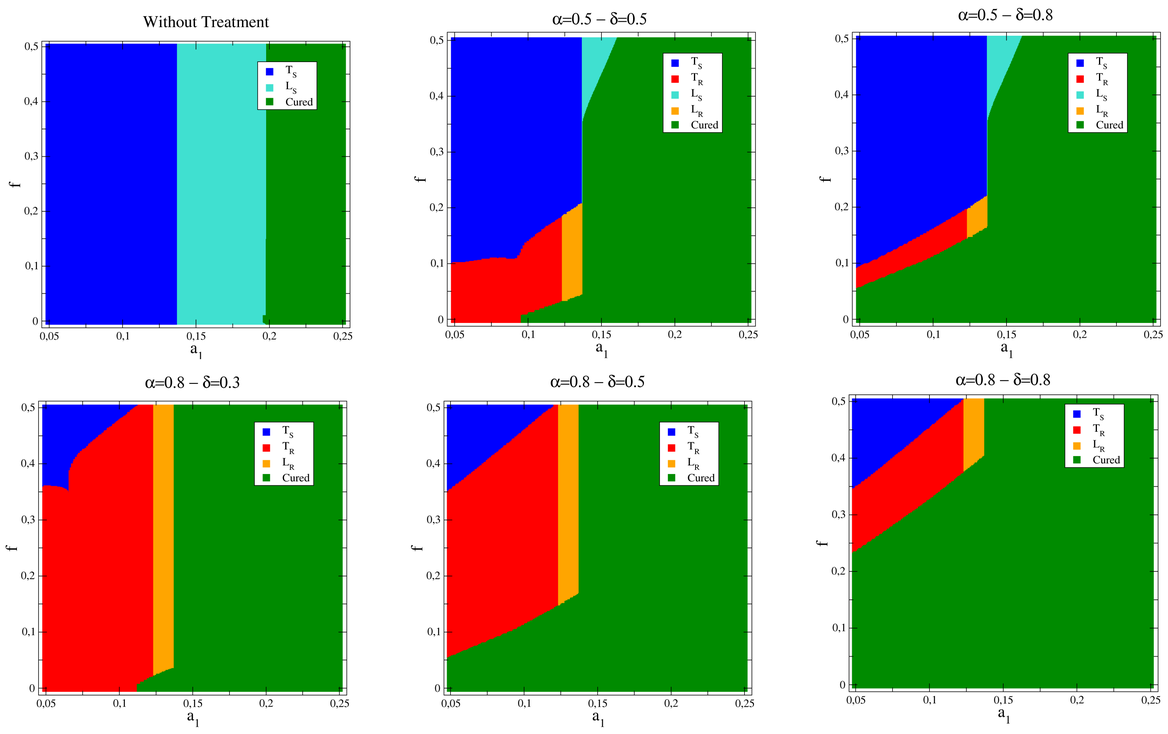

Figure 4: Phase diagram of f *versus* a_1 to treatment with different efficacies. The system evolves during 150 years. Treatment starts at 75th year and it lasts for 180 days.

Next Steps

Include the within-host dynamics in an agent-based simulation. Thus, a nested model for tuberculosis that will help to understand the impact of different treatment protocols.

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