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An antibiotic protocol to minimize emergence of drug-resistant tuberculosis

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HIGHLIGHTS

- A within-host model of TB assessing different antibiotic treatment protocols.
- Interactions among bacterial populations, immune system cells and drugs.
- Bacterial dormancy is also taken into account in the model.
- Three types of protocols: standard, intermittent and oscillating intermittent.

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ABSTRACT

A within-host model of the spread of tuberculosis is proposed here where the emergence of drug resistance and bacterial dormancy are simultaneously combined. We consider both sensitive and resistant strains of tuberculosis pathogens as well as a dormant state of these bacteria. The dynamics of the within-host system is modeled by a set of coupled differential equations which are numerically solved to find a relation between the within-host bacterial populations and the host health states. The values of the parameters were taken from the current literature when available; a sensitivity analysis was performed for the others. Antibiotic treatment for standard, intermittent and oscillating intermittent protocols is analyzed for different conditions. Our results suggest that the oscillating protocol is the most effective one, that would imply a lower treatment cost.

1. Introduction

Tuberculosis (TB) is a world-wide [1] problem and it is estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis* [2]. It is also the leading cause of death due to a single infectious disease [3]. TB is an airborne disease and can be transmitted from one person to another by cough, sneeze, speak, etc. [4,5].

Many mathematical models have been created to describe the dynamics of this illness and many others [6,7]. Most of these models deal with the problem of transmission dynamics with emergence of drug resistance [8–15], impact of other

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infections on TB [16,17] and the role of dormancy in the persistence of the infection [18]. In contrast, within-host models have received little attention [15,18–21].

Within-host models have several advantages for studying the evolution and spread of a disease [22–26]. One of these advantages is that the host's health state is defined according to his/her internal population of pathogens. In transmission models, transitions among states are fixed parameters determined only by external factors. In contrast, in within-host models, transitions among host's health states emerge naturally from changes in the host's pathogen populations.

The possibility of defining a different set of parameters for each host is another important feature of these kinds of models. Immune response, initial load of pathogens, bacterial rate of dormancy and other parameters allow the creation of heterogeneous populations [18,27–31]. Within-host heterogeneity parameters (governed by the individual's biological characteristics) are useful to study TB spread because it is possible to simulate a large spectrum of virtual populations.

In principle, models of disease transmission from one individual to another can also be augmented by combining them with within-host models. Contagion no longer occurs because of some fixed probability, but it also depends on the amount of pathogens involved in the process. Thus, the transmission of the disease among individuals in a population can be informed by monitoring host parameters.

In previous models, resistant strains [15] and bacterial dormancy [18] are treated separately. We propose to combine both effects simultaneously in a within-host model. Further, in our model, there is an interplay among sensitive/resistant pathogens, immune system cells, bacterial dormancy and antibiotics as the key features of the dynamics. Additionally, the immune system is assumed to depend on T-cell migration from the thymus, with a limited reproduction cycle.

The emergence of drug resistance due to the use of antibiotics [32–34] is analyzed using three different treatment protocols. The standard, intermittent and oscillating intermittent protocols are characterized by the antibiotic doses and their periodicity. Outcomes are obtained for the within-host system with different T-cell migration rates and pathogen dormancy rates. Numerical calculations of the within-host model indicate the oscillating intermittent use of antibiotics as the most suitable protocol. It increases the susceptible number of individuals, but the number of drug-resistant individuals is small.

This paper is organized as follows. In Section 2, we describe the methods to build the within-host model of TB describing variables and parameters of the system. Also the dynamics of the within-host model is explained in detail using coupled ordinary differential equations. Model numerical solutions and results are discussed in Section 3. In this section we present the way outcomes of the within-host dynamics are related to the host health states. Concluding remarks and our perspective on future studies are discussed in the last section.

2. The model

Based on the models from Refs. [15,18], we propose a within-host model of tuberculosis. We consider two types of *M. tuberculosis* strains: sensitive type, S, which can be killed by treatment with antibiotics, and a resistant type, R, which is resistant to the treatment. The influence of bacterial dormancy on the disease prevalence is also considered including dormant sensitive and dormant resistant types of bacteria, S_d and R_d, respectively. We also model the emergence of drug resistance due to the treatment with antibiotics.

The dynamics of bacterial populations and the immune system are modeled by using differential equations. The within-host system, defined by these set of equations, is solved numerically. We note that outcomes presented in the following sections are for one host only; the process of contagion or any interaction among hosts is not considered in this work.

As mentioned above, the host health states are a consequence of the within-host dynamics. These states indicate the stage of the disease in which a host may be. In the case of TB, we define the possible health states for a host as: X, susceptible; L_i, latent; or T_i, infectious. The subscript $i = S, R$ defines the type of pathogen: sensitive or resistant to antibiotics, respectively.

Susceptible individuals, X, are those that had no contact with TB pathogens. They are healthy and their system is free of tuberculosis pathogens. Individuals previously susceptible who acquire TB pathogens may enter into a latency period. A latent state, L_i, is the stage when there are no disease symptoms. Finally, individuals in the infectious state, T_i, are in the active tuberculosis stage, i.e., the host is sick. Antibiotic treatment is applied in this stage of the disease.

M. Tuberculosis may enter mononuclear cells like the immune system cells, the T-cells [18]. A fraction of these bacteria go into a dormancy state for some time and consequently they do not reproduce [35]. During the dormancy state these pathogens are not detected by the immune system and they also cannot be affected by the antibiotics [18,36,37]. Dormant sensitive and resistant bacteria will be represented as S_d and R_d, respectively.

On one hand, population of active sensitive pathogens, S, reproduce at rate $(1-q)\nu$ and they also may be converted to a dormant state, S to S_d, at a rate f. On the other hand, the conversion back from the dormant to the active state, S_d to S, occurs at a rate g. The S type pathogens can be killed by the immune system response, I, or by the action of antibiotics with a clearance rate α. The two types of strains compete for resources; thus a competition term [15] $\nu(S+R)S/k_b$ is added to the dynamics. This competition is only by their intrinsic growth rate and efficiency in utilizing available nutrients [38]. Then, as modeled in Ref. [15], a logistic competition term mimics the competition of survival between S and R pathogens.

Due to mutations, type S pathogens may give rise to active resistant type bacteria, R, at rate $q\nu$. Reproduction of R population that already exist occurs at rate ν_1, which is lower than type S because of an evolutionary cost [39]. Conversion from active state to a dormant state, R to R_d is also possible, as well as the conversion back to activity. Rates of conversion from active to dormant and dormant to active states are f and g, respectively, as for sensitive pathogen.