Journal of Statistical Mechanics: Theory and Experiment
An IOP and SISSA journal

An agent-based computational model of the spread of tuberculosis

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Received 3 November 2010
Accepted 2 April 2011
Published 4 May 2011

Online at stacks.iop.org/JSTAT/2011/P05003
doi:10.1088/1742-5468/2011/05/P05003

Abstract. In this work we propose an alternative model of the spread of tuberculosis (TB) and the emergence of drug resistance due to the treatment with antibiotics. We implement the simulations by an agent-based model computational approach where the spatial structure is taken into account. The spread of tuberculosis occurs according to probabilities defined by the interactions among individuals. The model was validated by reproducing results already known from the literature in which different treatment regimes yield the emergence of drug resistance. The different patterns of TB spread can be visualized at any time of the system evolution. The implementation details as well as some results of this alternative approach are discussed.

Keywords: population dynamics (theory), epidemic modelling

1742-5468/11/P05003+17$33.00

Contents

1. Introduction

Mathematical models have been used to study the dynamics of epidemics as an attempt to predict their behavior and control it through vaccination and public health programs. Most of these models describe the behavior of a given disease by means of ordinary differential equations (ODEs) and the transitions among the states of the considered disease are governed by rates [1]. These mathematical and computational approaches have been applied to understand one huge public health problem: tuberculosis.

According to the World Health Organization, more than two billion people are infected with *M. tuberculosis* [2], the bacteria that causes tuberculosis (TB). This disease is responsible for more deaths of adults than all other infections combined [3, 4]. Thus, effective programs for the global control of tuberculosis are necessary.

In order to help to develop public health policies, some mathematical models to study TB have been implemented. By using ODEs, computational scenarios have been used to understand the dynamics of the spread of tuberculosis [5]–[8] as well as to check the prevalence and emergence of drug resistance due to treatment with antibiotics [4], [9]–[12]. In [4], [9]–[11], Blower and collaborators have studied the prevalence of TB under different regimes of antibiotics treatment. Besides the treatment, a preventive therapy, called chemoprophylaxis, is also studied to which latent people are subjected to avoid them progressing to the active state of the disease. Moreover, and maybe the most important, these models take into account the emergence of drug resistance due to antibiotics treatment.

Taking this ODE-based model as a reference, we propose an alternative computational agent-based model to study TB dynamics and the emergence of drug resistance. Our approach offers the possibility to explicitly represent heterogeneities at an individual level and it also allows us to visualize the spatial patterns of the spread of TB [13].

This paper is organized as follows. In section 2, we present the reference model. Section 3 is devoted to the explanation of the agent-based model for TB and its subsections

J. Stat. Mech. (2011) P05003

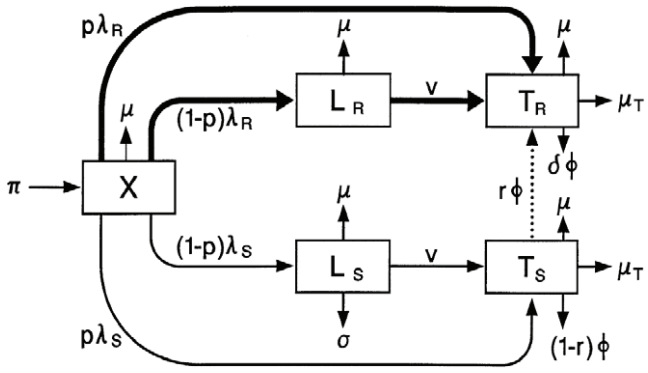


Figure 1. Schematic model for tuberculosis transmission (source: [11]). $\lambda_S = \beta_S T_S$ and $\lambda_R = \beta_R T_R$.

explain in detail each step of the model. The implementation of the computational model as well as some results obtained are discussed in section 4. Concluding remarks and possible extensions of this model are presented in section 5.

2. Tuberculosis modeling with ODEs

Blower *et al* developed a compartmental model for the spread of tuberculosis in a population [4], [9]–[11] where each one of the disease states is identified as a compartment. Individuals that are in the same state belong to the same compartment, namely: susceptible (X), latent (L_i), latently infected that effectively received chemoprophylaxis (C_S), infectious (T_i) and effectively treated individuals (E_i). The subscripts i define if the pathogen is sensitive (S) or resistant (R) to antibiotics.

This compartmental model consists of eight ordinary differential equations (ODEs) that represent the dynamics between compartments (see [4], [9]–[11] for more details). The transitions between the compartments of this model can be seen in figure 1.

As outlined in [14], modeling based on deterministic ODEs used by Blower and collaborators presents some limitations, such as: the constant population size, i.e. no births, deaths and migration occur, and the populations are well mixed, i.e. there is homogeneous movement between subpopulations. Also in [14], the author mentions that 'changes in the density of localized populations, changes in immunity, susceptibility and incubation time, are natural attributes of epidemics, but are omitted in simulations with ODE's'.

3. Agent-based model for TB

Let I_{ij}, with $(i, j) = \{1, 2, \ldots, L\}$, represent one individual placed on one site of a square lattice of side L. The quantity I_{ij} belongs to a population of size $N = L \times L$ and it can have one of five possible states: $I_{ij} \in \{X, L_S, L_R, T_S, T_R\}$. If $I_{ij} = X$, the individual is susceptible to tuberculosis, i.e. not exposed to the pathogen that causes it. The individual $I_{ij} = L_k$, with $k = S, R$, is in a state of latency, or exposed to the bacteria that causes TB but he/she is not sick. The subscript k defines whether the pathogen is sensitive (S)

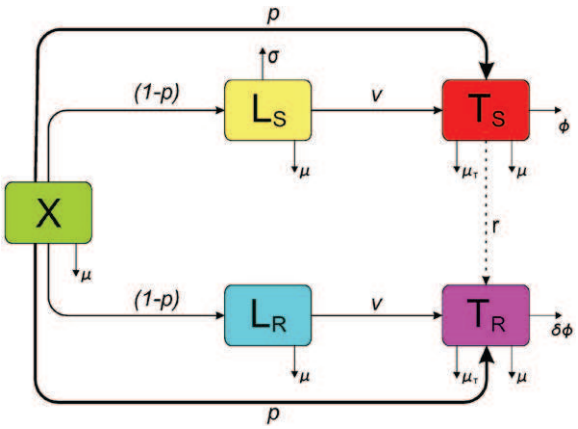


Figure 2. Schematic representation of the interaction between the five states of tuberculosis.

Table 1. Parameters of the model.

Parameter	Definition
μ	Probability of natural death
μ_T	Probability of death due to tuberculosis
p	Probability of developing active tuberculosis from X state
v	Probability of disease progression in latent individuals
σ	Probability that chemoprophylaxis therapy is effective
ϕ	Probability of effective treatment for infectious individuals
r	Probability to develop drug resistance during treatment
δ	Relative treatment efficacy
n_L	Proportion of latent individuals that receive chemoprophylaxis
n_T	Proportion of infective individuals that receive treatment

or resistant (R) to antibiotics. Finally, the individual $I_{ij} = T_k$, with $k = S, R$, is called infectious, i.e. this individual has active tuberculosis.

Individuals may undergo probabilistic transitions between the states of the system. The main parameters that drive these transitions are shown in table 1. Transitions are allowed between states and their respective probability can be seen in the scheme shown in figure 2.

In this model, we assume that cured or dead individuals are replaced in the lattice by susceptible individuals. This replacement is done in order to mimic the recruitment rate used in ODE models [4], [9]–[11]. Therefore, the states concerning cured and dead do not appear in the scheme shown in figure 2.

In the following, we describe each state of the model and the dynamics of interaction between them.

3.1. Contagion of susceptible individuals (X)

Individuals in X state may be infected by individuals in T_S and/or T_R states. These individuals can be infected with TB due to the presence of:

(i) infectious neighbors T_S and/or T_R (infection of local origin); and
(ii) infectious individuals T_S and/or T_R in the rest of the lattice (infection of global origin).

Note that, in both cases, only infectious individuals T_S or T_R without treatment can transmit the disease.

The existence of two sources of infection means that a person can be infected by a neighbor or a non-neighbor infectious individual and these events may *a priori* occur with different probabilities.

The local probability of an individual in the X state to be infected with the type S bacteria is given by [15]

$$P_{\mathcal{L}_S} = 1 - (1 - \beta_S)^{N_{T_S}}, \tag{1}$$

where β_S is the infectivity of type S bacteria and N_{T_S} is the number of infectious neighbors[5] without treatment in the T_S state. Similar to equation (1), local infection may also be caused by type R bacteria:

$$P_{\mathcal{L}_R} = 1 - (1 - \beta_R)^{N_{T_R}}, \tag{2}$$

where $\beta_R = \alpha\beta_S$ is the infectivity of type R bacteria[6] and N_{T_R} is the number of infectious individuals without treatment in the T_R state. Finally, the probability of local infection due to both types of bacteria is

$$P_{\mathcal{L}} = P_{\mathcal{L}_S} + P_{\mathcal{L}_R} - P_{\mathcal{L}_S}P_{\mathcal{L}_R}. \tag{3}$$

In equation (3), the evaluation of local probability takes into account the concurrence of events (coinfection), since they are not mutually exclusive. Anyway, if coinfection takes place, we assume that this individual is infected only by type R bacteria.

Besides the probability to be infected by the neighborhood, there is also the probability of contagion due to other individuals with TB in the lattice. Thus, the global probability to be infected by type S bacteria is

$$P_{\mathcal{G}_S} = \beta_S \frac{T_{T_S}}{N}, \tag{4}$$

where T_{T_S} is the total number of infectious individuals T_S without treatment in the lattice. Similarly, the contribution to the global probability due to infectious individuals with type R bacteria is

$$P_{\mathcal{G}_R} = \beta_R \frac{T_{T_R}}{N}, \tag{5}$$

where T_{T_R} is the total number of infectious individuals T_R without treatment in the lattice. Then, the global probability to become infected because of the two types of bacteria is given by

$$P_{\mathcal{G}} = P_{\mathcal{G}_S} + P_{\mathcal{G}_R} - P_{\mathcal{G}_S}P_{\mathcal{G}_R}. \tag{6}$$

Again, in equation (6), the evaluation of local probability takes into account the concurrence of events (coinfection).

[5] In all simulations, to calculate local probabilities we consider the Moore neighborhood (eight neighbors) around the individual in the X state.

[6] Type R bacteria have a lower transmissibility than type S, then $0 < \alpha < 1$, see [16, 17].

J. Stat. Mech. (2011) P05003

Equations (3) and (6) give us the probability that the infection is caused by local or global sources, respectively.

The intensity of these effects, local or global, can be adjusted by the parameter Λ, where $\Lambda \in [0, 1]$. The quantity Λ is the intensity of the local effects of infection and, consequently, $1 - \Lambda$ is related to its global effects. Given this parameter, we can express the total probability of infection as a linear combination of local and global probabilities of infection:

$$P = \Lambda P_{\mathcal{L}} + (1 - \Lambda) P_{\mathcal{G}}. \tag{7}$$

For a susceptible individual X in the lattice, all the probabilities of infection are calculated using equations (1)–(7). Next, a random number $rn \in [0, 1] \subset \Re$ is generated and it is compared to the total probability of infection, equation (7). If $rn < P$, the infection occurs; or it does not, otherwise, and the individual is kept in the X state.

If the infection takes place, a new random number is generated to choose whether infection will be caused by local or global sources. If $rn < \Lambda P_{\mathcal{L}}/P$, the source of infection is local, and it is global otherwise.

Next, we define which type of bacteria, S or R, is the cause of infection. As mentioned before, cases of coinfection will be considered as an infection by the type R bacteria. Hence, the normalized local probability to be infected by the type S bacteria is

$$\tilde{P}_{\mathcal{L}_S} = \frac{P_{\mathcal{L}_S}(1 - P_{\mathcal{L}_R})}{P_{\mathcal{L}_S} + P_{\mathcal{L}_R} - P_{\mathcal{L}_S} P_{\mathcal{L}_R}}. \tag{8}$$

The normalized probability for the type R pathogen is simply $\tilde{P}_{\mathcal{L}_R} = 1 - \tilde{P}_{\mathcal{L}_S}$, since cases of coinfection are considered type R infection. Then, a random number is compared to the value of equation (8), i.e. if $rn < \tilde{P}_{\mathcal{L}_S}$ the infection is locally caused by the type S bacteria, otherwise it is locally caused by the R bacteria.

In a similar manner, if the infection is of global origin, the normalized probability to be infected by the type S bacteria is

$$\tilde{P}_{\mathcal{G}_S} = \frac{P_{\mathcal{G}_S}(1 - P_{\mathcal{G}_R})}{P_{\mathcal{G}_S} + P_{\mathcal{G}_R} - P_{\mathcal{G}_S} P_{\mathcal{G}_R}}, \tag{9}$$

and $\tilde{P}_{\mathcal{G}_R} = 1 - \tilde{P}_{\mathcal{G}_S}$. The value obtained in equation (9) is compared to a random number. If $rn < \tilde{P}_{\mathcal{G}_S}$ the infection is due to the type S bacteria, or type R otherwise.

There are still two possibilities for a change of state:

(i) go straight to the infectious state (active tuberculosis) T_k, with $k = S, R$ with probability p; or

(ii) enter a latent state, L_k with $k = S, R$ with probability $1 - p$.

3.2. Latent individuals (L_S and L_R)

Individuals in the latent state are only carriers of the pathogen and they do not transmit the disease. If the pathogen is detected in this state, individuals may undergo chemoprophylaxis therapy that can clear such pathogens.

In our model, a proportion of latent individuals, n_L, are randomly chosen to receive chemoprophylaxis. During the chemoprophylaxis therapy, individuals may:

J. Stat. Mech. (2011) P05003

(i) be cured with probability σ, leaving the L_S state and returning to the X state;
(ii) progress to one of the infectious states, T_S or T_R, with probability v; or
(iii) remain in the latent state.

Latent individuals that have reached the end of therapy but not cured, remain latent.

All other latent individuals, those who do not receive chemoprophylaxis, may:

(i) progress to one of the infectious states with probability v; or
(ii) remain latent with probability $1 - v$.

Note that chemoprophylaxis has no effect in latent individuals carrying the resistant type of bacteria (R). Therefore, even under treatment with chemoprophylaxis, permanence or progression of L_R individuals to other states is the same for those who are not receiving chemoprophylaxis.

3.3. Infectious individuals (T_S and T_R)

Infectious individuals are in the active state of TB and they can transmit the pathogen. There are two different states for these individuals: T_S, for those who carry the type of bacteria sensitive to antibiotics, and T_R, for those who have the type of bacteria resistant to antibiotics.

A proportion, n_T, of infectious individuals are randomly chosen to receive treatment with antibiotics. At each simulation step, individuals who are in the T_S and T_R states can die from tuberculosis with probability μ_T, regardless of being under treatment or not.

T_S individuals who are under treatment may:

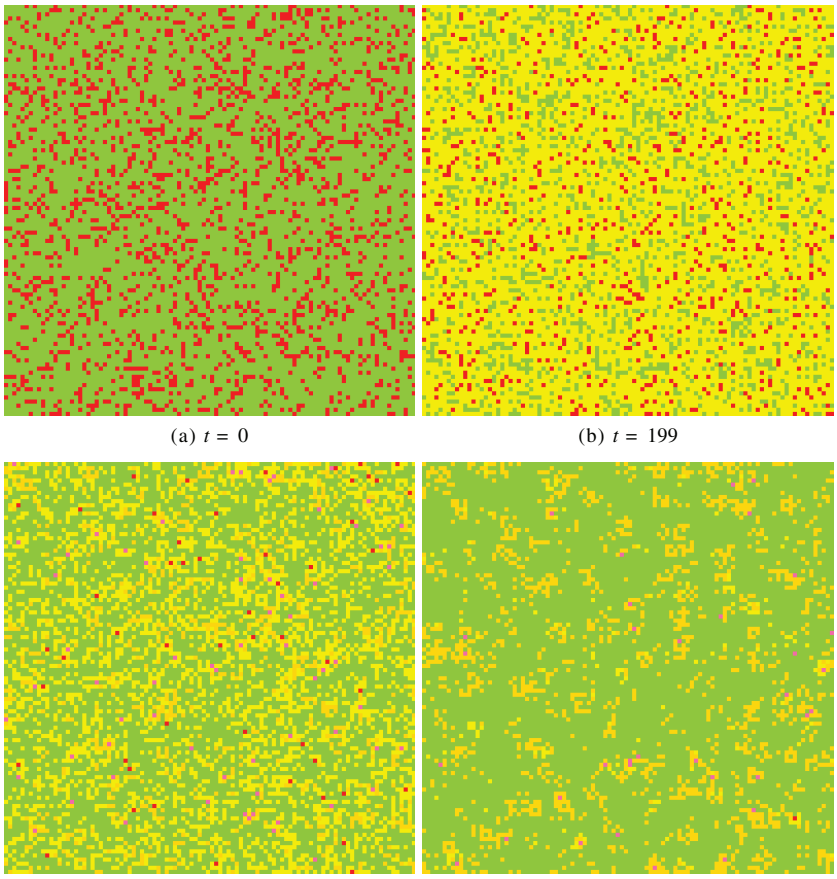
(i) be successfully treated, clearing the infection with probability[7] $(1 - r)\phi$;
(ii) develop drug resistance due to treatment failure with probability $r\phi$ [18, 19]; or
(iii) reach the end of the treatment without clearing the infection, but also without developing drug resistance, remaining in the T_S state.

For individuals in the T_R state, the procedure is the same as described above, but the treatment with antibiotics for resistant strains of bacteria have a lower efficacy in relation to those cases involving bacteria sensitive to drugs [4]. In our model, the relative efficacy is adjusted by the parameter δ, i.e. the probability of healing T_R patients will be given by the product $\delta\phi$.

4. Model implementation and results

At time $t = 0$, only susceptible, X, and infectious individuals with the sensitive type of bacteria, T_S, are present in an $L \times L$ lattice. The initial number of T_S individuals represents 20% of the total population and their distribution on the lattice is random and uniform. The lattice is updated synchronously, i.e. this update occurs at the same time for all individuals and it is done after all individuals have been tested during each simulation step (computational time interval).

[7] Note that the probability of effective treatment ϕ is altered depending on the value of the treatment failure probability r.



(a) $t = 0$ (b) $t = 199$

(c) $t = 220$ (d) $t = 300$

Figure 3. Snapshots of the lattice. Each color represents one state: green, X; yellow, L_S; orange, L_R, red, T_S; and pink, T_R. The simulation parameters are: $L = 100$, $n_T = 0.6$, $n_L = 0.1$, $\phi = 0.50$, $\sigma = 0.20$ and $r = 0.9$.

The values of the parameters used in the numerical simulations are: $L = 317$, $\alpha = 0.8$, $n_L = 0.1$, $n_T = 0.6$, $\mu_T = 2.74 \times 10^{-4}$/day, $\mu = 3.65 \times 10^{-5}$/day, $p = 1.37 \times 10^{-4}$/day, $v = 3.13 \times 10^{-5}$/day, $\beta_S = 2.47 \times 10^{-3}$/day and $\delta = 0.7$. The remaining parameters, ϕ, σ, r and Λ, have specific values for each scenario and their values are assigned in each case. We stress that these values have been adjusted so that each simulation step represents one day.

In order to illustrate the spatial distribution of individuals in the lattice, as well as the time evolution of the system, we have plotted in figures 3(a)–(d) four snapshots of the lattice for $t = 0$, 199, 220 and 300 years. In figure 3(a), the system is shown at $t = 0$ where one can see only X (green) and T_S (red) individuals. As mentioned above, the amount of T_S individuals is 20% of the total population. The system evolves with no public health intervention (no treatment for TB) until the 199th year, which is plotted in figure 3(b). In this stage, three states can be seen in the lattice: X (green), L_S (yellow) and T_S (red). The reduction in the amount of T_S cases is due to the death of ill individuals, once there is no treatment with antibiotics. In the same figure, there can also be seen the large quantity of latent individuals, which can be explained by the absence of antibiotics treatment and chemoprophylaxis.

J. Stat. Mech. (2011) P05003

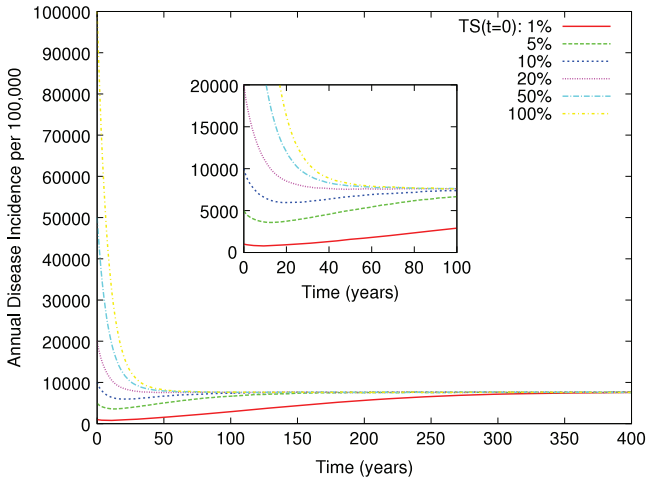


Figure 4. Evolution of tuberculosis in a lattice model representing 400 years for different initial proportions of infective individuals with type S bacteria, $T_S(t = 0)$. The system evolves with only local interactions ($\Lambda = 1.0$). Inset: a zoom for the period from 0th year to 100th year. Treatment and chemoprophylaxis are not applied during the whole evolution of the system. The simulation parameters are: $n_T = 0.0$, $n_L = 0.0$, $\phi = 0.0$ and $\sigma = 0.0$.

The treatment with antibiotics and chemoprophylaxis started on the first day of the 200th year. Then, in order to visualize the effect of this public health intervention, in figure 3(c) one can see a snapshot of the system in the 220th year, i.e. 20 years after the beginning of the intervention. As expected, the amount of T_S individuals has decreased dramatically due to treatment with 50% probability of effective cure ($\phi = 0.5$). There is also a decrease in the amount of L_S individuals because of the lower quantity of T_S people (source of infection) and the response to chemoprophylaxis. Another consequence of the antibiotics treatment is the emergence of drug resistance, i.e. the emergence of L_R (orange) and T_R (pink) individuals.

Finally, in figure 3(d), in the 300th year, the system has reached the steady state. Cases of tuberculosis caused by type S bacteria no longer exist because of the antibiotics treatment. On the other hand, the use of these drugs has caused the emergence of drug resistance. Both effects can bee seen in the figure: the amount of X individuals is higher than in the past periods, and L_R and T_R cases of tuberculosis are present in the lattice.

In figures 4 and 5, one can see the evolution of the system during 400 years for different initial proportions of infected individuals with type S bacteria. The values are $T_S(t = 0) = \{1\%, 5\%, 10\%, 20\%, 50\%, 100\%\}$ of a total population of 100 000 individuals. In these simulations there is no treatment ($n_T = 0.0$) and no chemoprophylaxis ($n_L = 0.0$). Therefore, the steady state curves are the endemic states of tuberculosis without the intervention of health care systems. Also in figures 4 and 5, it is clear that the endemic state does not depend upon the initial conditions of the system. Nevertheless, the transient time to reach steady states depends on the initial condition of $T_S(t = 0)$. The comparison between these figures shows that the time to reach a steady state is longer when we assume only local interactions ($\Lambda = 1.0$) in figure 4. When only local interactions are taken into account the spread of the disease is limited to the neighborhood of the susceptible

J. Stat. Mech. (2011) P05003

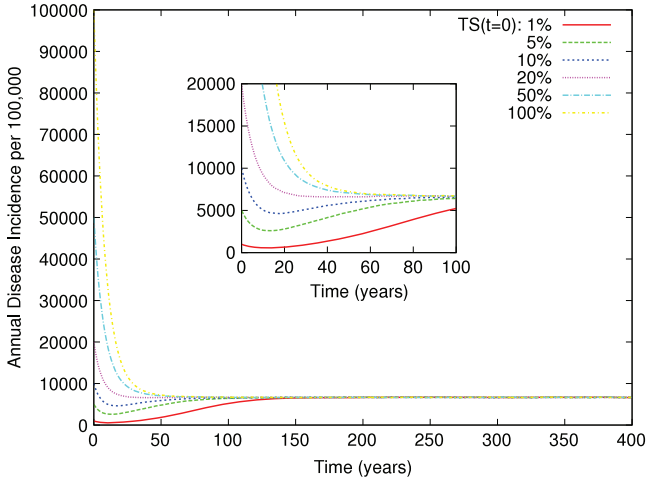


Figure 5. Evolution of tuberculosis in a lattice model representing 400 years, for different initial proportions of infective individuals with type S bacteria, $T_S(t = 0)$. The system evolves with only global interactions ($\Lambda = 0.0$). Inset: a zoom for the period from 0th year to 100th year. Treatment and chemoprophylaxis are not applied during the whole evolution of the system. The simulation parameters are: $n_T = 0.0$, $n_L = 0.0$, $\phi = 0.0$ and $\sigma = 0.0$.

individuals. On the other hand, when only global interactions are present, figure 5, the pool of susceptible individuals subjected to be infected is bigger, speeding up the spread of TB.

The evolution of tuberculosis during 500 years is shown in figure 6. From the first day of the 0th year up to the last day of the 199th year, there is no treatment ($n_T = 0.0$) and no chemoprophylaxis ($n_L = 0.0$) so that the system can go to an endemic state of tuberculosis without intervention. From the first day of the 200th year, antibiotics treatment starts with a proportion of individuals under treatment $n_T = 0.6$ and 95% efficacy ($\phi = 0.95$). There is also started chemoprophylaxis therapy with $n_L = 0.1$ and 58% efficacy ($\sigma = 0.58$). In figure 6, two effects become apparent as soon as the treatment and chemoprophylaxis start:

(i) an abrupt drop in the number of T_S individuals because of the high efficacy of the treatment;

(ii) emergence of drug resistance, due to the 10% probability of treatment failure ($r = 0.1$).

The inset of figure 6 shows a zoom in the period running from the 190th to 300th year. In this inset, one sees that cases of tuberculosis sensitive to antibiotics (T_S) have vanished around 60 years after the beginning of the treatment. As soon as the treatment starts, due to the probability of treatment failure, r, the emergence of drug resistance occurs and there is a peak in the T_R cases between the 201th and 205th years. The emergence of T_R cases depends upon the treatment failure of T_S cases. Thus, initially, the amount of T_S individuals is higher, which creates a pool of T_S individuals to be converted to T_R cases. After a few years, as soon as T_S has decreased, the amount of T_R cases also decrease, and the peak shown in the figure converges to an stable endemic state. Remember that T_R

J. Stat. Mech. (2011) P05003

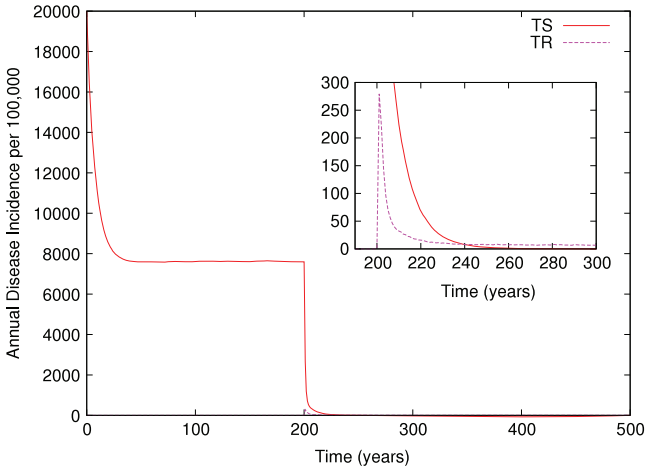


Figure 6. Evolution of tuberculosis in the lattice model, representing real 500 years. Treatment and chemoprophylaxis start at year 200. Inset: zoom of the period from 190 to 300 years. The simulation parameters are: $n_T = 0.6$, $n_L = 0.1$, $\phi = 0.95$, $\sigma = 0.58$, $r = 0.1$ and $\Lambda = 1.0$.

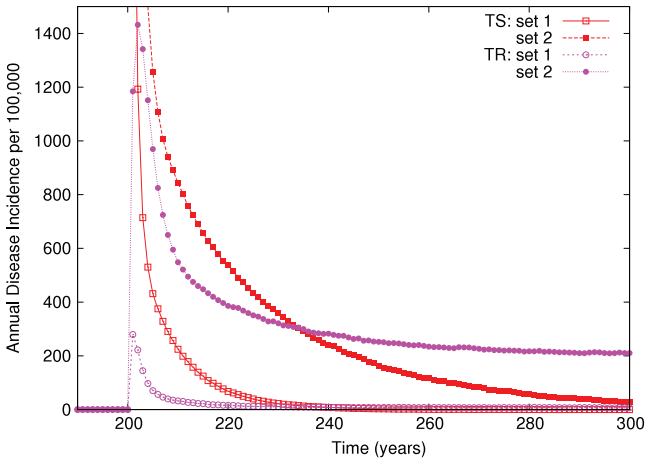


Figure 7. Evolution of tuberculosis during 300 years with treatment and chemoprophylaxis starting at year 200 for two sets of parameters. Set 1: $n_T = 0.6$, $n_L = 0.1$, $\phi = 0.95$, $\sigma = 0.58$, $r = 0.1$ and $\Lambda = 1.0$. Set 2: $n_T = 0.6$, $n_L = 0.1$, $\phi = 0.50$, $\sigma = 0.20$, $r = 0.5$ and $\Lambda = 1.0$.

cases are cured with an efficacy relative to T_S cases defined by the parameter δ. It is then expected that infective individuals T_R remain in the population, even though in the case of high efficacy treatments.

To check the impact of antibiotics use in the evolution of tuberculosis dynamics, we tested two scenarios with two sets of parameters: set $1 = \{\phi = 0.95, \sigma = 0.58, r = 0.1, \Lambda = 1.0\}$; set $2 = \{\phi = 0.50, \sigma = 0.20, r = 0.1, \Lambda = 1.0\}$. The evolution of TB for these cases is depicted in figure 7.

The first set of parameters with $\phi = 0.95$, $\sigma = 0.58$ and $r = 0.1$ represents a health care system in a developed country. The treatment and the chemoprophylaxis efficacy are

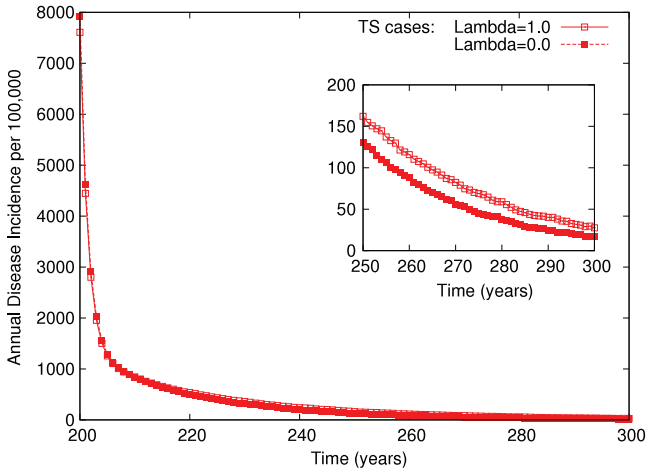


Figure 8. Evolution of tuberculosis during 300 years with treatment and chemoprophylaxis starting at year 200 with only local interactions, $\Lambda = 1.0$, and only global interactions, $\Lambda = 0.0$. Time series from 0th year up to 299th year is omitted. Only T_S cases are shown in this figure. Inset: steady state for T_S individuals from 250th year to 300th year. Parameters are: $\phi = 0.50$, $\sigma = 0.20$ and $r = 0.5$.

high and are combined with a low probability of emergence of drug resistance. Thus, on the one hand, in this first scenario one has the cure for 100% of T_S cases in 60 years after the beginning of the treatment plus a low and stable endemic level for T_R cases.

On the other hand, the second set of parameters with $\phi = 0.50$, $\sigma = 0.20$ and $r = 0.5$ represents a health care system in a developing country, with low efficacy of treatment and chemoprophylaxis in comparison to those of a developed country, combined with 50% probability of treatment failure. In this second scenario, even 100 years after the beginning of treatment, several cases of infective T_S still remain in the population. Besides the high prevalence of T_S cases due to a low effective intervention ($\phi = 0.5$, $\sigma = 0.2$ and $r = 0.5$), the emergence of drug resistance is very high. Therefore, low effective health care strategies do not solve the main problem, in this case TB cases with S type bacteria, and they also create a new and worse problem, a high prevalence of TB cases with R type bacteria.

The parameter Λ controls the intensity between local and global effects. Therefore, to check the influence of this parameter in the system dynamics, we show in figures 8 and 9 the steady state for T_S and T_R, respectively, for two cases: $\Lambda = 1.0$ (only local effects) and $\Lambda = 0.0$ (only global effects).

Figure 8 depicts the evolution of the system during 300 years with treatment and chemoprophylaxis starting at year 200. In this figure, two curves are shown for T_S cases, one for local interactions only (squares) and another for global interactions only (solid squares). The upper part of figure 8 is a zoom from the 250th up to the 300th year and it shows the steady state of T_S cases for $\Lambda = 1.0$ and 0.0. When only local interactions are taken into account ($\Lambda = 1.0$), it is clear that the endemic state is higher than in the case where only global interactions are present ($\Lambda = 0.0$).

J. Stat. Mech. (2011) P05003

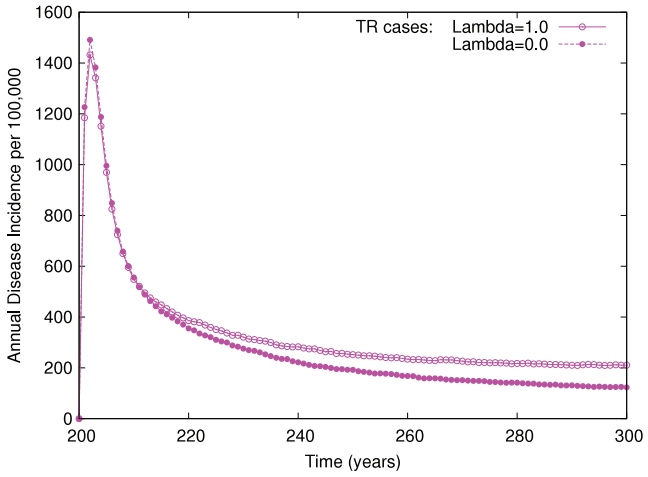


Figure 9. Evolution of tuberculosis during 300 years with treatment and chemoprophylaxis starting at year 200 with only local interactions, $\Lambda = 1.0$, and only global interactions, $\Lambda = 0.0$. Time series from 0th year up to 299th year is omitted. Only T_R cases are show in this figure. Parameters are: $\phi = 0.50$, $\sigma = 0.20$ and $r = 0.5$.

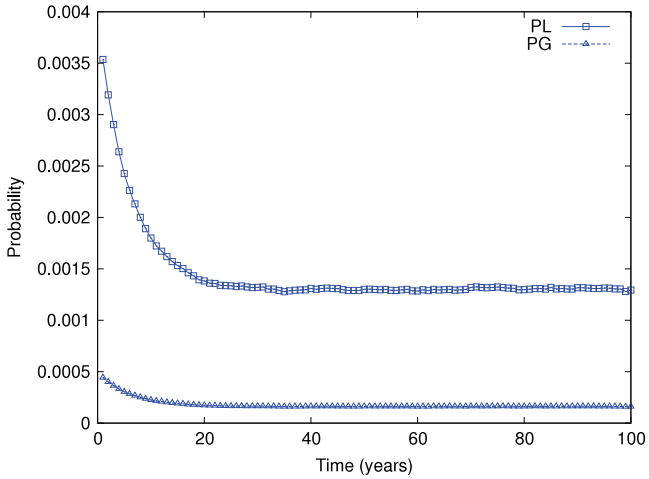


Figure 10. Time evolution of the average probability for local, $\langle P_{\mathcal{L}} \rangle$, and global, $\langle P_{\mathcal{G}} \rangle$, interactions. Squares: average $\langle P_{\mathcal{L}} \rangle$; triangles: average $\langle P_{\mathcal{G}} \rangle$. Parameters are: $\phi = 0.50$, $\sigma = 0.20$, $r = 0.5$ and $\Lambda = 1.0$.

Figure 9 presents T_R cases for local-only and global-only interactions from the 200th to the 300th year in both curves. The amount of T_R cases depends upon the pool of available T_S individuals who might have treatment failure. Then, as T_S cases are higher for local interactions only ($\Lambda = 1.0$), the amount of T_R cases will be higher as well.

The reason why local interactions only ($\Lambda = 1.0$) favor a higher prevalence of T_S and T_R cases can be understood by looking at figure 10. This figure depicts the time evolution of the average local probability, $\langle P_{\mathcal{L}} \rangle$, and the average global probability, $\langle P_{\mathcal{G}} \rangle$, evaluated by equations (3)–(6), respectively. At time t, the local probability, $P_{\mathcal{L}}(i, j)$ is calculated for all X individuals placed in the coordinates (i, j) of the lattice. Then, all

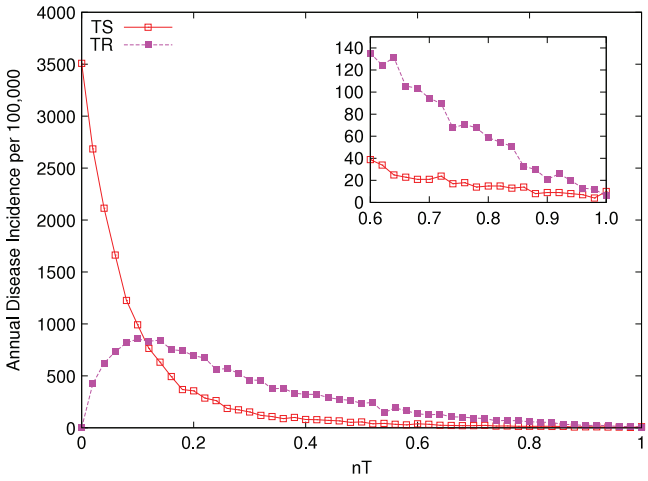


Figure 11. T_S and T_R cases as a function of the proportion of infective individuals that receive treatment, n_T. The values presented in the figure are from the 220th year. Treatment and chemoprophylaxis start at year 200. Parameters are: $n_L = 0.2$, $\phi = 0.50$, $\sigma = 0.20$, $r = 0.5$ and $\Lambda = 1.0$.

probabilities are summed, $\sum_{(i,j)} P_{\mathcal{L}}(i,j)$, and divided by the total of X individuals. The same procedure is performed for the calculation of the global probability $P_{\mathcal{G}}(i,j)$.

Figure 10 clearly shows that the average local probability is higher than the average global probability during the evolution of the system. The values $\langle P_{\mathcal{L}} \rangle \gg \langle P_{\mathcal{G}} \rangle$ explain why in figures 8 and 9 the endemic states for both T_S and T_R cases are higher for the scenario with local interactions only ($\Lambda = 1.0$).

As already defined in section 3, parameters σ and ϕ are the probability that chemoprophylaxis therapy is effective and the probability of effective treatment for infectious individuals, respectively. In our model, these parameters are adjusted in order to simulate different scenarios regarding the efficacy of the chemoprophylaxis therapy and antibiotics treatment. In other words, this means that σ and ϕ are predetermined instead of being a consequence of the system dynamics. Thus, n_T, the proportion of infective individuals that receive treatment, and n_L, the proportion of latent individuals that receive chemoprophylaxis, are key control parameters from the point of view of health care system intervention.

In figure 11 one can see the endemic state of TB as a function of the proportion of infective individuals that receive treatment, n_T. The values presented in the figure are from the 220th year, i.e. 20 years after the beginning of treatment and chemoprophylaxis. For all values of n_T, the proportion of latent individuals that receive chemoprophylaxis is kept constant, $n_L = 0.2$.

When there is no individual under treatment in the system, $n_T = 0$, the prevalence of TB cases with type S bacteria is very high. But there are no cases involving type R bacteria, because the emergence of resistant strains is due to treatment failure. As the proportion of individuals under treatment increases, T_R cases emerge and there is a peak around $n_T \approx 0.15$. On the other hand, for $n_T > 0.15$ the amount of T_S individuals that are cured increases, consequently, the cases of T_R have to diminish. Nevertheless, even for $n_T = 1.0$, i.e. all sick individuals are under treatment, there are still a few remaining T_S

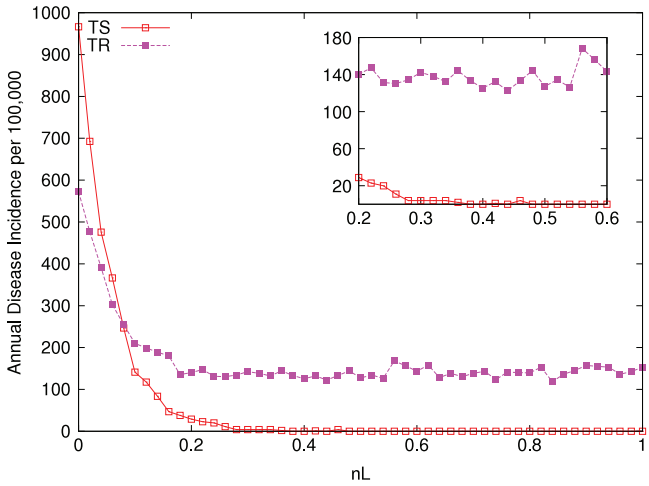


Figure 12. T_S and T_R cases as a function of the proportion of latent individuals that receive chemoprophylaxis, n_L. The values presented in the figure are from the 220th year. Treatment and chemoprophylaxis start at year 200. Parameters are: $n_T = 0.6$, $\phi = 0.50$, $\sigma = 0.20$, $r = 0.5$ and $\Lambda = 1.0$.

and T_R cases. This behavior is a consequence of the probability of effective treatment for infectious individuals $\phi < 1.0$.

The plotting of the endemic state of TB as a function of the proportion of latent individuals that receive chemoprophylaxis, n_L, can be seen in figure 12. The values presented in the figure are from the 220th year, i.e. 20 years after the beginning of treatment and chemoprophylaxis. For all values of n_L, the proportion of infective individuals that receive treatment, n_T, is kept constant, $n_T = 0.6$.

In figure 12 one can see that the total of T_S and T_R cases are diminishing as n_L increases. There are two interesting results that can be seen in this figure. The first and more important result is that for $n_L \approx 0.38$ the population is free of T_S cases! In other words, when only 38% ($n_L = 0.38$) of the latent individuals in the population receive chemoprophylaxis, the type S bacteria vanish! This suggests that the public health policies should pay more attention to the prevention of TB as soon as the *M. tuberculosis* has been detected in a person. The second interesting result is the steady prevalence of T_R cases for $n_L > 0.18$. This behavior is explained because in our model chemoprophylaxis therapy has no effect in latent individuals with R bacteria, L_R.

5. Conclusion

Here we proposed an agent-based model for the spread of tuberculosis and the emergence of drug resistance due to the use of antibiotics. The model is based on the interactions among individuals placed on the sites of a square lattice. Different from models based on differential equations, the spatial structure is taken into account in this model. These individuals can be in one of five states of the disease: susceptible (X), latent with type S bacteria (L_S), latent with type R bacteria (L_R) and active tuberculosis with type S (T_S) and type R (T_R) bacteria. This approach has allowed us to deal with the problem with more refinement than the existing models based on differential equations.

J. Stat. Mech. (2011) P05003

Our approach was validated by reproducing results already known from the literature. In the simulations different regimes of treatment have been tested. These different regimes showed how inefficient treatments can create conditions for the emergence of drug resistance. We also showed how locality and non-locality (local or global interactions) affects the model, resulting in different prevalences of the disease. Once the model has a spatial structure, the different patterns of TB spread can be visualized at any time of the system evolution.

There are several possibilities to extend the model presented here. A straightforward modification would include a state of coinfection of tuberculosis. In this extension, individuals could be infected with type S and R bacteria simultaneously, which creates a new state T_{SR}. A second possible modification of the model would consider changes in the topology of the lattices in which individuals are located. We could study the spread of tuberculosis when the contacts between individuals would be, for example, in lattices of the type small world or scale free [20].

A more sophisticated variation of this work would focus on the emergence of drug resistance through the development of within-host pathogens. In other words, the status of each individual would not be defined by transitions related to certain probabilities, but the number and type of pathogens that they have within themselves. In the case of tuberculosis, latent and infectious states were determined by the amount of pathogens in each of the individuals.

Acknowledgments

ALE thanks FAPESP for the financial support that made this work possible. BCTC wants to thank CAPES for the fellowship. We thank the anonymous referees for comments and suggestions for the improvement of this paper.

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J. Stat. Mech. (2011) P05003

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