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MODELING TUBERCULOSIS IN BARCELONA. A SOLUTION TO SPEED-UP AGENT-BASED SIMULATIONS

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ABSTRACT

Tuberculosis remains one of the world's deadliest infectious diseases. About one-third of the world's population is infected with tuberculosis bacteria. Understanding the dynamics of transmission at different spatial scales is critical to progress in its control. We present an agent-based model for tuberculosis epidemics in Barcelona, which has an observatory on this disease. Our model considers high heterogeneity within the population, including risk factors for developing an active disease, and it tracks the individual behavior once diagnosed. We incorporated the immunodeficiency and smoking/alcoholism, as well as the individual's origin (foreigner or not) for its contagion and infection as risks factors. We implemented the model in Netlogo, a useful tool for interaction with physicians. However, the platform has some computational limitations, and we propose a solution to overcome them.

1 INTRODUCTION

Tuberculosis (TB) is an infectious disease that has co-evolved with humanity. Its particular strategy of remaining almost hidden and acting slowly has brought about its success. The Global Tuberculosis Report 2014 from the World Health Organization estimates that, in 2013, 9.0 million people developed TB, and 1.5 million died from the disease (WHO 2014). Mathematical models have been used for estimating long-term dynamics of tuberculosis epidemics (Zwerling, Shrestha, and Dowdy 2015). Most of these models have been classically built with a structured top-down strategy (Ferrer et al. 2009). They divide the population into different classes (e.g., susceptible, exposed, infected and recovered in the case of an SEIR model) and fix specific fluxes between these groups. This strategy is feasible whenever the size of each class satisfies the continuum hypothesis. Nevertheless, the use of differential equations may be questioned

when the population under study is not big enough. This is often the case since the incidence of sick people among infected is small (on average, only 10% of infected develop an active disease).

Furthermore, tuberculosis infection dynamics inside a host shows a high dependence on the particular characteristics of the host. Although the natural history of tuberculosis is still not fully understood (Cardona 2010), there are several factors that have already been identified as crucial. Among others, we can mention that an immunodeficiency dramatically increases the probability of developing primary active tuberculosis, and that a patient with a cavitation (i.e., showing big lesions with liquefacted necrosis where bacilli can grow extracellularly and exponentially like in a culture medium) has a higher spreading rate than a non-cavitated individual. Such heterogeneities are difficult to take into account in a top-down approach, although they may have long-term consequences. Moreover, when considering a population with a big enough sick fraction to satisfy the continuum hypothesis, the diversity of possible situations of the subpopulations may dramatically increase, thus making proper parameterization of the model difficult. In other words, the calibration of a model is only possible when the conditions are homogeneous enough, which is unlikely to be the case when dealing with significant populations.

As an alternative, TB can be modeled from a bottom-up perspective that allows observing how the dynamics of the global system emerge from the low-level interactions. Agent-Based Modeling (ABM) is an approach for a bottom-up modeling that in recent years has gained popularity as a tool for gaining insights of social complexity. An ABM allows the simulation of the dynamics of a population by controlling the characteristics and behavior of each individual of the system (Ferrer et al. 2009). Moreover, ABM is particularly useful for projecting a population by answering "what if" questions such as the effect of a certain policy on the spread of a disease in a target group. In particular, an ABM of TB spreading would provide the possibility of incorporating contact tracing (Begun et al. 2013).

In this paper, we present an agent-based model for TB epidemics in the city of Barcelona (Spain). Our model simulates the dynamics of the population and the transmission of the disease among a heterogeneous population. Data were obtained from national statistics and the Tuberculosis Investigation Unit in Barcelona. The model was developed in Netlogo, a user-friendly tool that allows carrying out virtual experiments to help in decision-making by non-modelers such as health services workers and tuberculosis control units. The main drawback of this platform is that it is highly time-consuming. In this paper, we propose a computing solution to this problem.

The rest of the paper is organized as follows. Section 2 reviews the recent work done on agent-based simulation of TB epidemics and highlights our contribution to the current state of the art. Section 3 presents our agent-based model for TB transmission in Barcelona. We present the results of our experiments in Section 4 and propose a solution to speed-up the computations. Finally, Section 5 presents our concluding remarks and highlights lines of further work.

2 AGENT-BASED MODELS FOR TUBERCULOSIS EPIDEMIOLOGY

In the last decade, ABM has been introduced into the study of tuberculosis epidemiology. An agent-based microsimulation model, which is close to an ABM, was published by Murray (2002). In that paper, the author tackled a heterogeneous population at the individual level whose dynamics were governed by fluxes extrapolated from literature population (compartment) models. This model took into account TB-HIV co-infection as a risk factor, the kind of active tuberculosis developed (either pulmonary or extrapulmonary), the infectious strain, and the social structure of the population (household and neighborhood). It was calibrated with literature data from 7 countries and 2 US prisons. The simulations considered a closed population during a 4-year period and studied the effect of the different factors on the cluster size and distribution of Mycobacterium tuberculosis isolates in a particular community.

Espíndola et al. (2011) introduced an ABM to study drug resistance emergence in relation with different treatment patterns. In fact, their model is close to a cellular automaton, since all the spatial cells were considered to be occupied by a single individual that could acquire different states (susceptible, latent infected or with an active disease) according to a set of probabilistic rules which were not time-

dependent. Two infection routes were considered, neighboring (locally) and non-neighboring (globally) in cause. The authors took into account either drug susceptibility or drug resistance for infected and infectious individuals. Simulations covered a 317 x 317 lattice (100,489 individuals or spatial cells) for a period of up to 300 years, with a time step of 1 day. This model was not fitted to real data but focused on carrying out a mathematical study of the drug resistance emergence patterns and their interaction with the involved model parameters.

Guzzetta et al. (2011) tested three different approaches to study tuberculosis evolution in Arkansas: (i) an Ordinary Differential Equations (ODE) model considering a homogeneous population; (ii) an age-structured ABM with homogeneous mixing and closed community; and (iii) an age-structured ABM coupled with a spatially explicit socio-demographic model that drives the transmission dynamics according to the three levels considered (households, schools and workplaces, and general population) in a closed population. The socio-demographic model had previously been calibrated to Arkansas data. The ABM considered the differing infection status of individuals, taking into account smear-positive or negative disease states and including many age-dependent factors. It was focused on the transmission dynamics but did not explicitly consider the diagnosis and treatment of individuals with an active disease. Thus, heterogeneity of population was related with the age-structure and socio-demographic-structure. The results showed good agreement with Arkansas data.

A more recent study can be found in Kasaie, Dowdy, and Kelton (2013). In this paper, an ABM coupled with a 3-level social network to tackle the role of social contacts on the infection and reinfection dynamics of tuberculosis was presented. The model at the agent level was mostly based on fluxes between different states and considered conditions of a TB high-incidence region with mean disease duration of 11 months. The model was fitted to global WHO data (WHO 2012). A population of about 10,200 individuals (2,000 households, 50 neighborhoods) was simulated for a period of 150 years (with a transitory of 100 years). At this point, no heterogeneity among the population was considered. In a subsequent paper (Kasaie, Dowdy, and Kelton 2014) the authors fitted the model to 2013 WHO data (WHO 2013). The authors introduced the control of particular strains to track the transmission patterns, taking into account the molecular epidemiology.

In general, most of the mentioned models above were conceived from an SEIR (or top-down) perspective. Many of them (Guzzetta et al. 2011; Kasaie et al. 2013; Kasaie et al. 2014; Murray 2002) included sophisticated models for the transmission routes taking into account the socio-demographic structure of the population and the different degrees of contact between social groups. Only Guzzetta et al. (2011) deal with a particular reality (Arkansas), while models by Kasaie et al. (2013, 2014) are fitted to global data. None of them considers high heterogeneity within population, including factors such as the kind of disease, possible immunodeficiency, smoking/drinking habits and immigrant-native origin simultaneously.

Furthermore, the final users of a parameterized and validated ABM of tuberculosis epidemiology would be public health decision-makers. Thus, the implementation of such a model in a user-friendly platform would be of interest for those who are non-modelers. All the reported models were programmed in basic languages far from non-modelers' expertise. This fact is an advantage in terms of computing time and code handling, which makes these models appropriate for research purposes, but it may be a serious hindrance to their use in public health policy. In this paper, we present an ABM that overcomes the limitation of past solutions in the infection and transmission of TB in a heterogeneous context. Moreover, it includes risk factors for developing an active disease such as immunodeficiency and smoking/alcoholism, as well as the individuals' origin (foreigner or not) for its contagion and infection, and it tracks the individual behavior once diagnosed. We can test the confidence of our methodology by focusing on a real scenario (Barcelona, Spain).

3 AN AGENT-BASED MODEL FOR TUBERCULOSIS

In 2013, Barcelona registered an incidence of 20.4/100,000 habitants, greater than the 11.8/100,000 inhabitant incidence of Spain overall (Orcau i Palau et al. 2014). This situation is common in big cities that receive a substantial flow of migrants because those fluxes increase the incidence of infection. However, further study of the situation of tuberculosis in Barcelona reveals interesting data. TB incidence presents vast differences depending on the district, from the lowest rate of the Sarrià-Sant Gervasi area of 8.9/100,000 inhabitant to 67/100,000 hab in Ciutat Vella. In particular, the neighborhood of El Raval in Ciutat Vella presents a high rate of 119.9/100,000 inhabitant. The reasons behind the disparity of occurrence are probably due to the difference in immigrant distribution (immigrant population accounts for 43% of Ciutat Vella's inhabitants; over 80% of TB cases diagnosed in this district in 2012 corresponded to immigrants) and population density across the city, as well as the different living conditions for them (e.g. overcrowding, which facilitates spreading, and access to healthcare services, the lack of which may delay the diagnosis).

We present an ABM that reproduces the pulmonary TB spreading dynamics in the Ciutat Vella district of Barcelona. Agents represent individuals whose state variables mainly refer to their status in the TB infection cycle. Other characteristics of agents are age, native/foreign origin, possible risk factors (e.g. smoking and alcoholism) and possible immunosuppression (mainly AIDS). Once a person is infected, the presence (or not) of pulmonary cavitation is also considered. The population is initialized according to demographic data of Ciutat Vella (Orcau i Palau et al. 2011) shown in Figure 1. We simulate a population of 100,000 individuals. The model is partially spatially explicit, i.e., space is considered but it does not mimic the real space of Ciutat Vella. Simulation occurs in a discrete area of 501 x 501 spatial cells. Each spatial cell represents an abstract local space where two individuals can come into contact, and the infection can be spread in a day. Therefore, individuals interact with others locally in a Von Neumann neighborhood. The time step is set to 1 day, and the simulation may cover from 1 to 10 years.

The model is based on general knowledge about the natural history of tuberculosis (Cardona 2010). There are two essential characteristics of TB that must be taken into account in any epidemiological model. On the one hand, an infected individual does not necessarily develop an active disease; on average, only 10% of infected people become ill. Moreover, a person remains infected for a long time and may develop active tuberculosis after several years. Infected people are usually not diagnosed. On the other hand, only an ill individual can disseminate the infection. The infection rate increases if the patient has TB with cavitation. Once an individual is diagnosed with TB, the pharmaceutical treatment lasts six months. Once the treatment is finished, the possibility of getting sick again remains at 1% for two years post-diagnosis.

3.1 The Agent

The basic entities of the model are individuals who can be in one of five possible states according to TB infection dynamics: healthy, infected, ill (i.e., with active TB), under treatment and recovered. The state variables of the individuals refer mainly to their status in the TB infection cycle as well as the time spent in such phases and individual diagnosis time when ill. Other individual parameters are age, native/immigrant origin, possible risk factors (e.g. smoking), and possible immunosuppression (mainly AIDS). Once a person is infected, the presence (or not) of pulmonary cavitation is also considered.

The user can change some initial conditions at the beginning of simulation. Data shown in Table 1 were used to calculate the configuration of the initial population: number of healthy, infected, sick, under treatment and recovered individuals; mean diagnosis delay (MDD); mean treatment abandonment rate; and individuals with risk factors and with AIDS. Some other initial variables were assigned randomly: individual age and time spent in the infection state.

Figure 1 shows the agent dynamics among states of TB. A healthy agent does not have any bacteria in its organism and therefore is not able to infect others as well as not presenting symptoms. However, the

common properties of agents (age, native/immigrant, risk factors, diabetes and immunosuppression) are maintained. In a certain moment, an agent may get infected with TB by one of the agents in a 4-neighbouring spatial cell. The probability depends on the type of TB disease that the sick person has, either cavitated or non-cavitated. A cavitation is considered to double the infection probability. These probabilities are fixed to reproduce the ratios of 10 infections/cavitated TB sick and 5 infections/non cavitated TB sick in 60 days.

Table 1**:** Official data of Ciutat Vella corresponding to 2010 (Institut d'Estadística de Catalunya 2010; Orcau i Palau et al. 2011) used in simulations. All percentages are with respect to the total population of Ciutat Vella, except (*) which is with respect to the total number of TB patients.

District of Ciutat Vella	Number of individuals	Percentage
Total population	104,507	-
Native population	56,611	54.17 %
Foreign population	47,896	45.83 %
Population <= 10 years old	7,688	7.36 %
Population 10 - 65 years old	80,373	76.91 %
Population > 65 years old	16,446	15.89 %
Detected cases of TB	104	-
Estimation of infected individuals	1,486	1.42 %
Cavitation forms*	11	10.57 %
Detected cases of HIV	1,304	1.25 %
Risk factors*	-	65.4 %
Total annual mortality	936	0.89 %
Treatment abandonment rate*	-	2.2 %
Diagnosis delay (days)	48	-

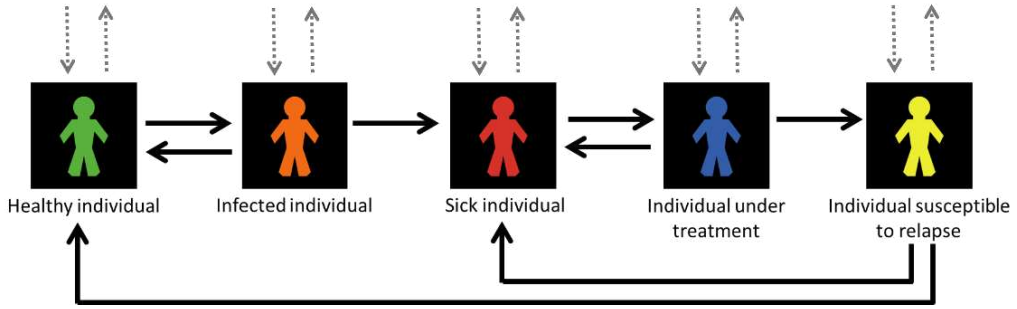

Figure 1**:** State diagram of the TB infection**.**

Once infected, the individual may develop active TB according to a certain annual probability that decreases with infection time following a quadratic during the 7 years' post-infection. It is neglected for the subsequent years (t > 7 years). Since simulation time does not cover periods longer than 10 years, the approximation is good enough. This probability has a 10-fold increase for immunosuppressed people, and it is multiplied by a factor of 1.5 if there are other risk factors. The chance of becoming ill is evaluated at each time step for all infected persons. Globally, the average of 10% of the infected developing an active disease is satisfied. The possibility of relapse (getting sick again) for recovered patients is also evaluated daily according to the individual relapse probability (see below). Once an individual gets sick, the disease time counter starts running until the assigned individual diagnosis time is reached.

If the disease is developed, then the agent enters the sick state. When sick, the agent not only presents symptoms but also becomes infectious (that is, can spread the tuberculosis among healthy or treated people). This state considers the time since the disease became active, whether the lesions include cavitated tissue, and the number of days that will pass until the individual is diagnosed (diagnosis time delay). Each individual has a particular diagnosis time that is randomly assigned when becoming ill, following a truncated exponential with mean diagnosis delay of 45 days.
Once diagnosed, the agent enters the medical treatment state and stops spreading TB. The treatment finishes in 180 days. There is a certain probability that an individual may abandon the treatment before finishing it. This possibility is evaluated at every time step for each patient under treatment, according to the input abandonment probability. If an individual abandons the treatment during the initial 15 days post-diagnosis, the patient becomes sick again. If the patient abandons the treatment after 15 to 180 days post-diagnosis, then he or she is considered to be recovered but with a certain probability of relapse the following 2 years. This probability is considered to linearly decrease from 100% at 15-day abandonment to 1% at the 180-day treatment period. Finally, when a sick individual is treated for 180 days, it recovers and a relapse probability of 1% is assigned. After 2 years, the individual is considered to be healthy.

Common actions among all individuals include their daily growth (i.e., they increase their age by 1 day each time step), movement (which is random to a neighboring cell) and death (according to a certain specific probability). Probabilities for dying are fixed using demographic data (Institut d'Estadística de Catalunya 2010). However, those ill with TB have a specific probability of dying from TB. This probability is evaluated daily for each sick individual, taking into account that 40% of non-treated TB sick may die within 5 years. Each time an individual dies, a new random arrival is generated according to the distribution of the initial population.

3.2 The Simulation Scheduler

The simulation starts with the setup of the initial configuration. A population of 100,000 people is placed in a 501 x 501 grid. The model assumes discrete time steps of 1 day. Each day, all individuals execute a series of actions, and their variables are updated immediately. The user can change some initial conditions at the beginning of the simulation. For this specific study, most of the input parameters were taken from Orcau i Palau et al. (2011). All percentages shown in Table 1 were used for calculating the configuration of initial population: number of healthy, infected, sick, under treatment and recovered individuals; mean diagnosis delay (MDD); mean treatment abandonment rate; and individuals with risk factors and with AIDS. Some other initial variables are assigned randomly: individual's age (following the percentages shown in Table 1) and time spent in the initial infection state.

Once the simulation is initialized, the following processes are executed: grow, move, get infected, get sick, be diagnosed and start a treatment, abandon or finish the treatment, recover and die. A flow chart of these processes can be seen in Figure 2A.

4 SIMULATION EXPERIMENTS

Our model was built in Netlogo, a popular simulation and modeling tool among social simulation practitioners (Tisue and Wilensky 2004). Netlogo is well suited for modeling a wide variety of agent-based systems. It has a user-friendly interface that allows non-experts to run simulations and perform virtual experiments (see Figure 2B for a screenshot of the implemented program user interface). A closed population of 100,000 individuals was simulated, very close to the population of the Ciutat Vella district.

The simulator was initially calibrated with available epidemiological data (Orcau i Palau et al. 2011), and then validated with data from subsequent reports (Prats et al. 2015). Our results proved to match the trends of TB in Ciutat Vella for a year. As an example, Figure 3A shows the daily number of infected individuals and the weekly number of sick individuals during one simulated year. As can be seen, the ABM simulation is capable of working with both small numbers far from the continuum hypothesis (order of magnitude 10^1) and larger numbers arising from the infected subpopulation (order of magnitude

10^3) in a global population of 10^5 individuals. Figure 3B shows an example of using this model for epidemiological predictive purposes. We designed a virtual experiment to test the effect of a delay in immigrant diagnosis due to a hypothetical exclusion of this collective from the public healthcare system.

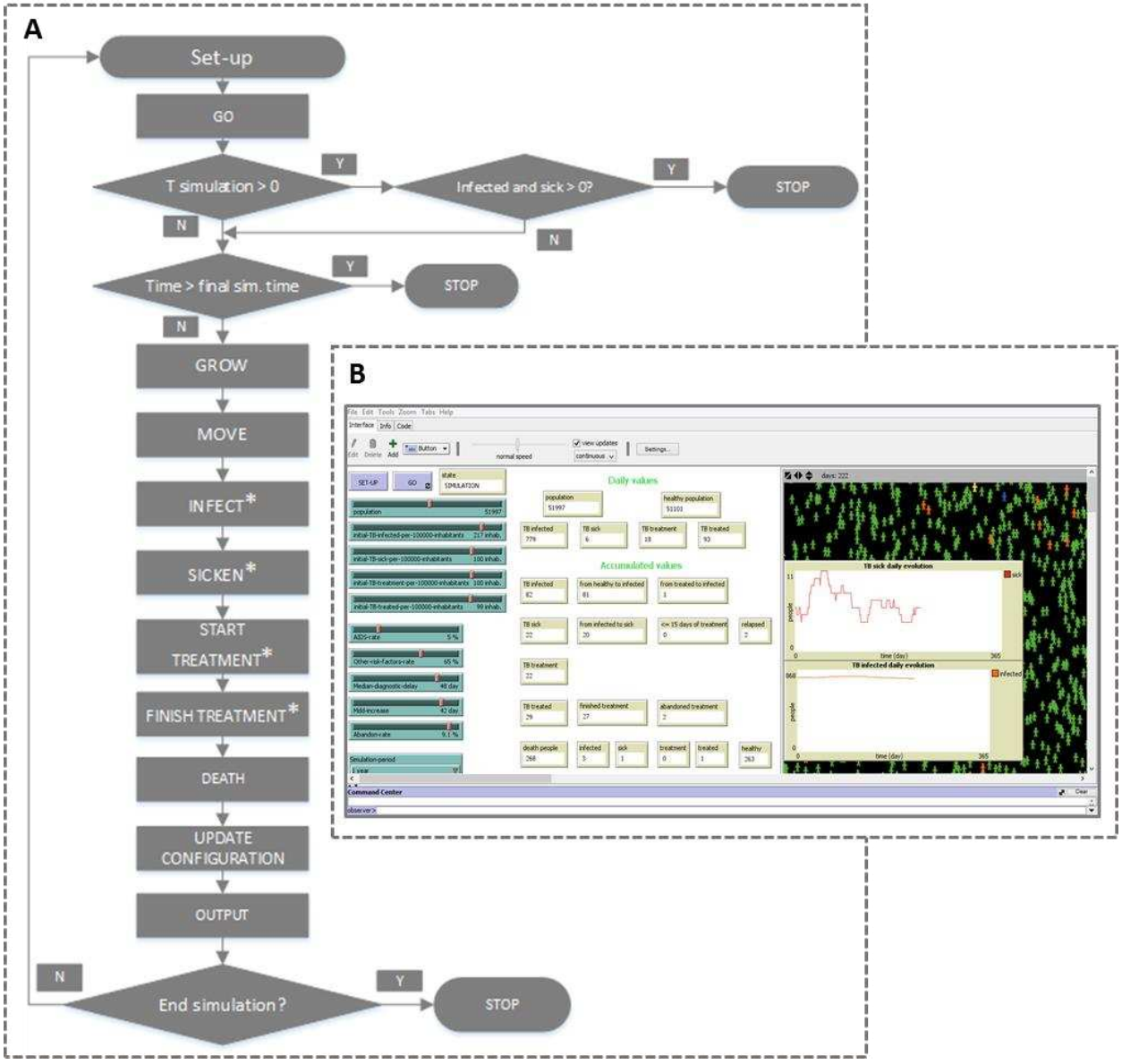

Figure 2**:** A. Simulation scheduler. The processes marked with an asterisk only affect certain states, e. g., only healthy and treated people can be infected. B. Screenshot of the simulator. Green slides (left) are initial values that can be changed. Numerical outputs, as well as the world representation and the graphical evolution of TB-sick and TB-infected, are also seen.

Further predictions of the ABM have limited validity because of the lack of a socio-demographic model that accounts for fluxes. In fact, the simulation is capable of maintaining epidemiological conditions constant only at short-term (3 years), but they are lost at long-term, when the tuberculosis incidence starts varying.

4.1 Proposed Optimization of the Model

Although the proposed implementation in Netlogo shows good results, with 100,000 agents the simulation is too slow. Therefore, we proposed a solution to reduce the execution time. It seems that most of the simulation time is spent updating the worldview, since the simulation is moving and updating 100,000 agents constantly. During a simulation, most of the agents are in the healthy state (> 95 %). The agents in this state do not have any particular information apart from the few attributes that are shared by all agents and that are assigned to them initially. They can move, grow in age and die according to probability, but there are no relevant changes in their variables until they get infected. Furthermore, the order of magnitude of this subpopulation (10^5) is far from the order of magnitude of infected (10^3) and sick (10^1) subpopulations. Therefore, we proposed to model them with global (or local) continuous variables.

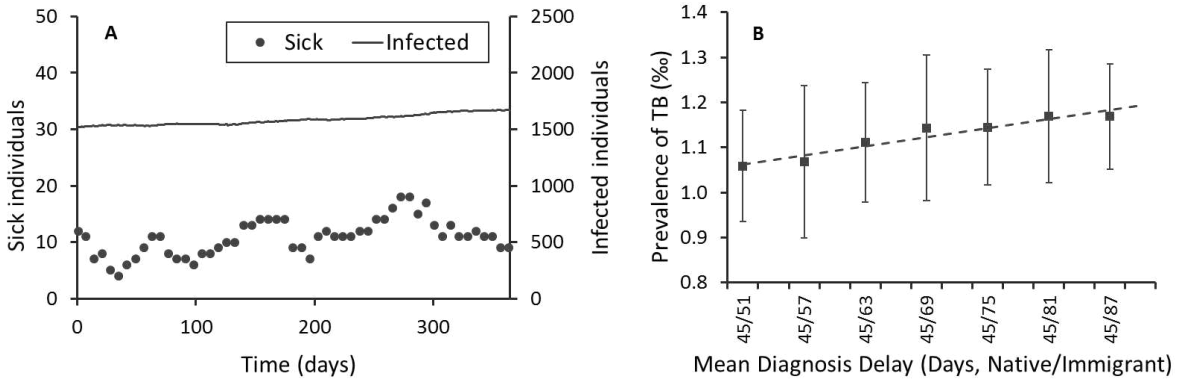

Figure 3**:** A. Annual simulation of the evolution of tuberculosis in Ciutat Vella with the original ABM. B. Effect of a diagnosis delay in immigrant subpopulation due to a lack of access to healthcare systems after one year.

As a result, we included healthy agents as a property of the environment. Other approaches have been made to reduce the computational time in the simulation of social entities, such as working with aggregates (Parry and Evans 2008), or ghost agents (Parunak and Brueckner 2007). In NetLogo, the spatial cells of the grid are called patches and are described by local variables that may change according to specific rules. Therefore, we defined the local number of healthy individuals as a new property of the patches. With this modification, all agents in a healthy state are removed (> 95 % of the agents), but we still consider them from a collective perspective. The infection process occurs in a similar way taking into account the number of healthy individuals in the Von Neumann neighborhood of a sick individual. The particular properties of the resulting infected individuals are assigned according to the percentages shown in Table 1. In the following section, we show how we obtain similar results with respect to the original (non-optimized) version.

4.2 Comparison of Results

After changing the implementation, we verified that the results obtained with the new version were equivalent. To do so, we slightly modified the initial conditions of the original simulator to get observable (reproducible) tendencies in all subpopulations. Then, we compared the evolutions of the population of each state during one year of simulation. In Figure 4, Figure 5, and Figure 6 we see the comparison of those evolutions for both models. The results show the mean of 50 runs for each case. We also performed a Wilcoxon statistical test to check whether both data series are similar with 95% confidence. Therefore, we consider that both models behave equivalently.

Once we established that the comparison of the results was satisfactory, we recalculated the execution time to see how important the reduction obtained with this new implementation was. Table 2 shows the execution time for both models on a Quad 3.20 GHz Intel Core i5 personal computer. The new version reduced the time spent by 88%.

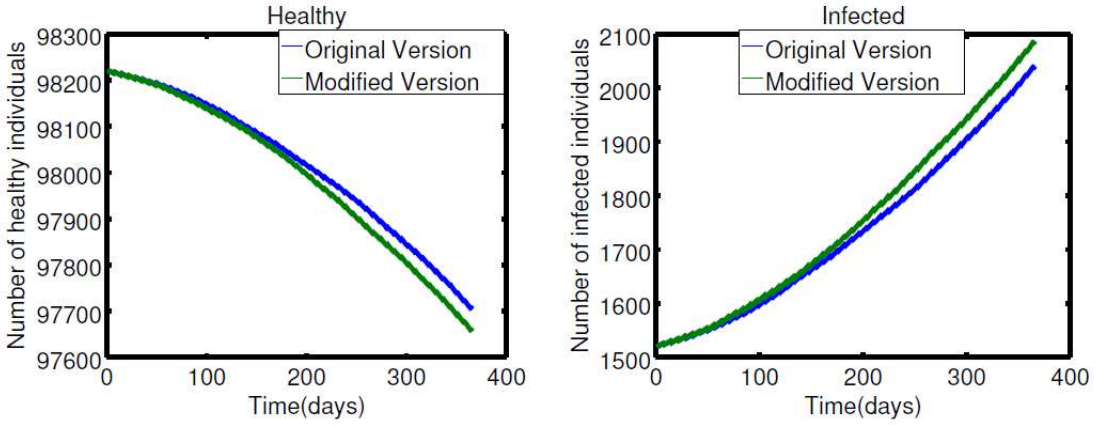

Figure 4**:** Evolution of the number of healthy agents in both implementations (left) and the number of infected individuals (right).

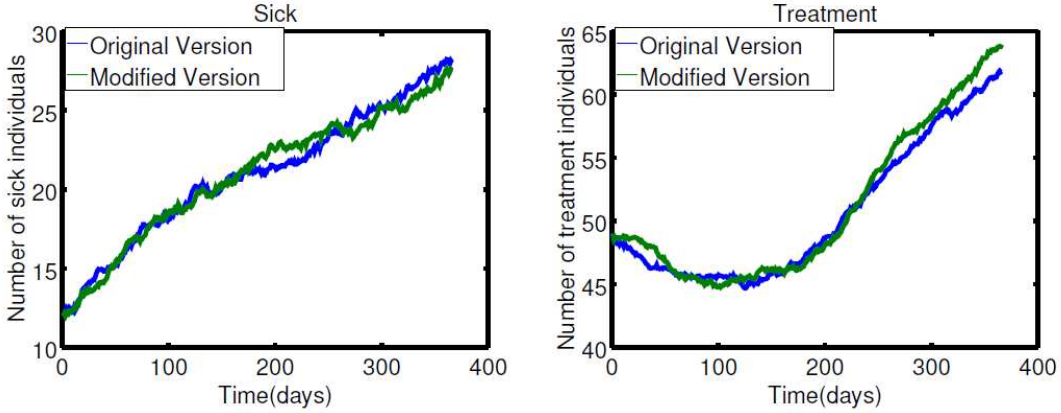

Figure 5**:** Evolution of the number of sick agents in both implementations (left) and the number of individuals already treated but with a certain probability of relapse, i.e., within the post-diagnosis period of 2 years (right).

5 CONCLUSIONS

The presented ABM is a first step towards a user-friendly integrated platform for the simulation of the spread of tuberculosis in a distinct community. The ABM was built from a mechanistic perspective that accounts for the existing knowledge of the natural history of the disease and the infected individuals' behavior. Current proposed ABM works address TB modeling from an SEIR (top-down) perspective. In contrast, our approach allows the study of a heterogeneous population, taking into account factors like the native/immigrant origin of individuals, their immunologic capacities and several important risk factors, as well as their age. All the parameters were calibrated to fit the tuberculosis situation in the Barcelona district of Ciutat Vella, but the model is robust enough to be calibrated to any other region.

Its implementation on NetLogo has made evident the computing limitations of this platform, although it has proven to be useful for its use by non-experts. Therefore, we have proposed and proved the success

of a solution that overcomes these limitations. We combined the ABM approach of those individuals which are relevant for the course of the disease spread with collective treatment of those individuals that do not require such explicit control (healthy subpopulation). We have shown the capability of the new model in providing equivalent results to those obtained with the original model with a considerable reduction in the computing time. This strategy is an important innovation that may be used in epidemiological studies of other diseases.

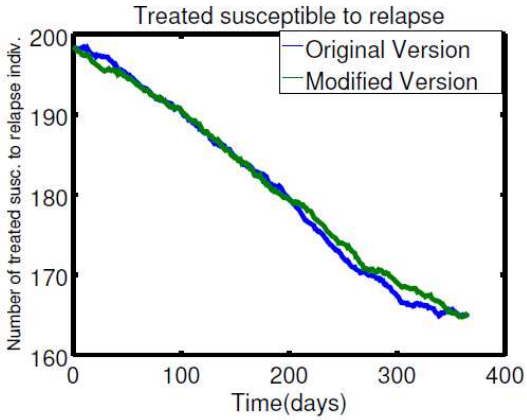

Figure 6**:** Evolution of the number of agents under medical treatment in both implementations**.**

Table 2**:** Comparison of the original Netlogo implementation and after the optimization, considering healthy individual as a property of the spatial cell.

Model	Original (all states have agents)	New version (healthy individuals as property of the medium)
Execution time (min)	126.03	15.03

The most important limitation of the current model is the absence of a socio-demographic structure of the population to account for the social network of individuals, and therefore allow long-term simulations. In this sense, the existing solutions described in Section 2 should be useful for building such a model. In the case of Barcelona, the migratory fluxes will be of particular interest since there is a significant arrival of immigrants from high TB-incidence regions. This improvement does not seem feasible in a platform like NetLogo; it should be implemented in a High-Computing platform, probably with a parallel simulation design that reduces computing time. This platform should be conceived with the end purpose of being used by non-experts and should therefore be designed with a user-friendly interface.

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