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Tuberculosis Modelling Using Bio-PEPA Approach

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***Abstract*—**Modelling is a widely used tool to facilitate the evaluation of disease management. The interest of epidemiological models lies in their ability to explore hypothetical scenarios and provide decision makers with evidence to anticipate the consequences of disease incursion and impact of intervention strategies.

All models are, by nature, simplification of more complex systems. Models that involve diseases can be classified into different categories depending on how they treat the variability, time, space, and structure of the population. Approaches may be different from simple deterministic mathematical models, to complex stochastic simulations spatially explicit.

Thus, epidemiological modelling is now a necessity for epidemiological investigations, surveillance, testing hypotheses and generating follow-up activities necessary to perform complete and appropriate analysis.

The state of the art presented in the following, allows us to position itself to the most appropriate approaches in the epidemiological study.

***Keywords*—**Bio-PEPA, Cellular automata, Epidemiological modelling, multi agent system, ordinary differential equations, PEPA, Process Algebra, Tuberculosis.

I. Introduction

EPIDEMIOLOGY is "the study of the relationship between disease and various factors that influence their frequency, distribution, evolution".

The main advantage of these models is their use as tools inter-epidemic, to facilitate the retrospective analysis of past epidemics and understand their behaviour. Allowing the combination of large amounts of information in a structured way, we manage to develop scenarios to get an idea of the merits of different strategies in different situations. Thus, decision makers can benefit from guidelines to support their strategies against future outbreaks, these guidelines can be used.

The need for models in epidemiology was understood very early by the scientific community, as the first significant use of modelling has been carried out in the 1920s by Kermarck and MacKendrick [15]. The architecture of these models, based on a classification of individuals in, susceptible (not infected), Infectious (may transmit the disease) and removed (being immunized against pathogenic) close to the clinical status and understandable by the medical is still the most widely used formalism.

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The purpose of this paper was to examine what has occurred in epidemiological modelling over the past 100 years, from 1920 to 2012.

This paper is structured as fellow: In Section II, we present the epidemiological system where we describe in its subsections the compartmental model as well as the principal features to study it. Section III is devoted to the state of the art of the related works with epidemiological system which are represented with different methods and approaches. The implementation of the computational model with Bio-PEPA language, as well as some results obtained for tuberculosis model and comparing it with other work are discussed in Section IV. Concluding remarks and possible extensions of this model are presented in Section V.

II. Epidemiological System

A. Epidemiology

Epidemiology is an exciting field with many applications that are helpful in solving today's health related problems.

For example, epidemiology can demonstrate the risks associated with smoking, as well as those related to exposure to second hand cigarette smoke among no-smokers.

Epidemiology research can identify factors related to such diseases and suggest methods for its prevention [7].

An epidemic term refers to "the occurrence in a community or region of cases of an illness, specific health related behaviour, or other related events clearly in excess of normal expectancy".

The use of the word epidemic is not limited to communicable disease. The term is applied to chronic diseases and other conditions as well.

Other term which is used: pandemic, defined as "an epidemic occurring worldwide, or over a very wide area, crossing international boundaries, and usually affecting a large number of people.

Epidemiology is one of the basic sciences of public health; it is concerned with the distribution and determinants of health and diseases, morbidity, injuries, disability, and mortality in populations. For this, epidemiologic methods could be applied to a variety of public health related fields: health education, health care administration, tropical medicine and environmental health, where, epidemiologists quantify health outcomes by using statistics, formulate hypothesis and they explore causal relationships between exposures and health outcomes.

Epidemiology studies are applied to the control of health problems in populations; they are focused on [34]:

1. Populations where are called population medicine.
2. Distribution: this term implies that the occurrence of diseases and other health outcomes varies in population,

with some subgroups of the populations more frequently affected than others.

3. Determinants: defined as "any factor that brings about change in a health condition or other defined characteristic", like viruses.
4. Outcomes: is all the possible results that may stern from exposure to a causal factor, it may be expressed as types and measures of morbidity, mortality, ...etc
5. Quantification: epidemiology is a quantitative discipline. Quantification means the use of statistical measures to describe the occurrence of health outcomes as well as to measure their association with exposures.

Epidemiology contributes to health policy development by providing quantitative information that can be used by policy makers.

From the public health point of view, there are three modes of prevention, primary prevention which involves the prevention of disease before it occurs, secondary prevention which takes place during the early phases of pathogenesis and includes activities that limit the progression of disease, finally, tertiary prevention which is directed toward the later stages of pathogenesis and includes programs for restoring the patient's optimal functioning.

B. Compartmental Model

In order to model the progress of an epidemic in a large population, comprising many different individuals in various fields, the population diversity must be reduced to a few key characteristics which are relevant to the infection under consideration. For example, for most common childhood diseases that confer long-lasting immunity it makes sense to divide the population into those who are susceptible to the disease, those who are infected and those who have recovered and are immune. These subdivisions of the population are called **compartments**.

The compartmental model is dynamic, in that is defined by a variable function of t where the numbers in each compartment may fluctuate over time. The importance of this dynamic aspect is most obvious in an endemic disease with a short infectious period, such as measles in the UK prior to the introduction of a vaccine in 1968. Such diseases tend to occur in cycles of outbreaks due to the variation in number of susceptible (S(t)) over time. During an epidemic, the number of susceptible individuals falls rapidly as more of them are infected (I(t)) and thus enter the infectious and recovered (R(t)) compartments. The disease cannot break out again until the number of susceptible has built back up as a result of babies being born into the susceptible compartment.

Each member of the population typically progresses from susceptible to infectious, to recovered.

For the full specification of the model, the transition between compartments is expressed by rates.

As between S and I, the transition rate is β, where β is the contact rate, which -roughly speaking - takes into the account the probability of getting the disease in a contact between a susceptible and an infectious subject. Between I and R, the transition rate is ν (simply the rate of recovery). If the duration of the infection is denoted D, then $\nu = 1/D$, since an individual experiences one recovery in D units of time, [36].

C. Epidemiology and Modelling Features

Owing to the different properties and behaviour of the epidemiological system, they require different modelling features:

- Outcomes and hierarchy: Despite its great complexity, the epidemiological model is organized as a set of connected modules with specific functions [29], [18]. Taking advantage of this modularity can help to alleviate the complexity burden, facilitating the model analysis. Compositionality is a related concept meaning that two modelling blocks can be aggregated together into one model without changes to any of the submodels.
- Multi-state components, spatial structure and compartmentalization: as mentioned above the epidemiological model could be expressed by different compartment which correspond to the different states of individuals or its place of location.
- Qualitative analysis: Experimental determination of kinetic parameters to build quantitative models is a cumbersome task. Furthermore, they are dependent on the experimental conditions. Therefore, the qualitative characteristics of models allow us to ask qualitative questions about the system and to learn valuable knowledge.

Dynamic simulation and standardization: Dynamic simulation allows the prediction of the transient behaviour of a system under different conditions. For each model, the particular simulation approach depends on the type of components included, which depend on the nature of the involved interactions and also on the available information for their characterization. To do this, epidemiological models need to be represented in a common format for exchange between different tools.

III. Related Work

Since the appearing of epidemiology research, has been a long way between epidemiologists and computer scientists and many formalisms have been used.

The real problem between them is that, the epidemiologist may be more familiar with mathematical modelling and computer scientist also may be familiar with their computational formalism. The following section describes briefly existing formalisms which was used by computer scientist to help epidemiologist.

A. Mathematical Models

The first epidemiological models have emerged in the early twentieth century based on ordinary differential equations (ODEs). [3], [15] It was in 1927 that Kermack and McKendrick, offer the first complete model to model an epidemic. The main idea is that differential equations describe the rate of change of continuous variables. They are typically used for modelling dynamical systems in several areas. Systems of non-linear ordinary differential equations (ODEs)

have been used in epidemiological system to describe the variation of the amount of species in the modelled system as a function of time, the number of new infections is proportional to the product of the number of infected and susceptible [20], [15], [11], [25].

After, the first stochastic model was presented by Frost and Reed in 1928, on a scale of discrete time (typically one generation); it describes the probability of evolution of different classes of the population. In every generation, the population of the state depends only on the previous generation and evolution probabilities are binomial. It was in 1949 that Bartlett [15] offers what will be the standard epidemiological model. At the initial time, the population consists of n infected and m susceptible. Each infected has a period of contagion which follows a law I, independent of the others. And during this period he meets another given individual according the moments of jump of a Poisson process with intensity λ / n. All these processes are independent of one another and periods of contagion. An equivalent construction proposed by Sellke in 1983 [30], is based on the idea to assign to each individual a capacity of resistance to the epidemic and to define, from the number of infected, pressure of the epidemic and criterion of infection on the resistance of the individual. The SIR model extends in a natural way on a graph. In the initial model, the infected individuals contact any type of individuals randomly chosen at an average rate β and are recovering at an average rate γ. The graph allows considering the heterogeneity of contacts in the population, and precise relationships between individuals in a population. Newman showed [27], [28] that the behaviour of the epidemic on the graph can be studied by a percolation on the same graph. In this case, the results of percolation allow having information on the size of the connected components and the epidemic outbreak. These results provide information on the importance degree of the epidemic, but not on its evolution over time [15].

Michael Y. Li in 2010 [22], improved the Kermack and McKendrick model by integrating Heterogeneity of age, using the partial differential equations instead of ODEs, his model could represent realistically the disease transmission process but it was very complex [22].

Others mathematical models have been presented. Ronald Ross in his first mathematical model of malaria [25], showed that reduction of mosquito numbers (Transmission threshold) was sufficient to counter malaria - a concept far ahead of his time, Ross could introduce the deterministic differential equation model of malaria by dividing the human population into susceptible (S) and infected (I) compartments, with the infected class returning to susceptible class again leading to the SIS structure. The simple Ross model did not consider the latency period of the parasite in mosquitoes and their survival during a necessary period. After about 40 years, George Macdonald [23], in the 1950s, reasserted the usefulness of mathematical epidemiology based on 20 years of fieldwork. He modified Ross's model by integrating biological information of latency in the mosquito due to malaria parasite development, and implicated the survivorship of adult female mosquito as the weakest element in the malaria cycle. This provided a rationale for a massive World Health Organization (WHO), which focused on using the insecticide dichlorodiphenyltrichloroethane (DDT) that killed mosquitoes, for the elimination of malaria transmission among 500 million people in Africa [23], [25].

One another work which drew our attention because it studied the same case study of us, Blower et al. [8]-[10] who developed a compartmental model for the spread of tuberculosis in a population 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 (Li) latently infected that effectively received chemoprophylaxis (CS), infectious (Ti) and effectively treated individuals (Ei). 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 [8]-[10] for more details).

However, building ODE models requires insight into the reaction mechanisms to select the appropriate rate laws, and experimental data to estimate the kinetic parameters and the spatial characteristics that could potentially play a nontrivial role in the development were not been taking into consideration. Also, as outlined in [17], reported by [16]: "modelling 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 [17], 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".

B. Cellular Automata

Although the differential equation models are perhaps the most common and are typically used to simulate the epidemiological dynamics of particular diseases to try and identify the critical parameters involved [6],

But we have seen that in this previous model, the population is always considered homogeneous — which is obviously untrue in reality. Epidemiologists know that population heterogeneity can greatly influence the propagation of epidemics. To represent this heterogeneity, it is necessary to explicitly represent, in a model, individuals (or groups) instead of the global population: computational models have offered this possibility. Micro-simulation is the first type of model to have addressed these issues: individuals are represented by a vector of parameters and the whole population by a matrix [individuals x parameters] on which global computations are made, which was presented by Artzrouni's work [4]. The drawback of this model that is could not represent relationships between individuals. These relationships can however be crucial to understand the dynamics of epidemics. Of particular interest for epidemiologists is the spatial organization of the individuals particularly the neighbourhood

organization [12]. Obviously, two individuals located at distant locations have a smaller probability of interaction than two neighbours. According to [1], a way to model this hypothesis is to use the cellular automata model, which represents relationships' topology using a grid where individuals can be located. Every cell of the grid contains a parameters vector that represents an individual. Their evolution (which occurs locally) is based on this vector but it is also influenced by the state of its "neighbours". Turner et al. showed in [33] that taking local neighbourhood topology into account can correctly treat cases where the population is not homogeneously distributed over space [31], [21]. However, interactions between individuals hardly follow such fixed contact patterns when there is a necessity to take more realistic populations into account. Other drawback of this model is that the most common way to interrogate the model is simulation, but full exploration of the model requires instantiation over a range of parameter values. Ensuring that all important areas of parameter space have been covered incurs heavy computational expense, and may even be impossible.

C. Agent Based Model (ABM)

Taking relationships among individuals into account is a first step towards a more realistic representation of (human or animal) communities. Nevertheless, the previous models do not offer any help in representing the behavioural heterogeneity of the individuals. Yet, according to specialists, it can play a major role. For instance, vectors able of "long-distance translocations" [32] may transform a successful containment into a wide propagation and it is not possible to model this using previous models. Epidemiologists have then started to use ABMs in order to address this issue. In these models, it is possible to integrate all the information (global factors, heterogeneity of individuals, relationships) represented in the previous models as well as individualized behaviours. Each action of each agent can be designed according to its internal state and perceptions (neighbours and their parameters, global parameters, even environmental data, etc). An example is provided by [18], [1], [2].

De Espindola et al. [16] proposed an agent-based model for the spread of tuberculosis and the emergence of drug resistance due to the use of antibiotics which was based on Blower et al. [8]-[10]. 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 (LS), latent with type R bacteria (LR) and active tuberculosis with type S (TS) and type R (TR) bacteria. This approach has allowed, as mentioned by Espindola, to deal with the problem with more refinement than the existing models based on differential equations.

More generally, ABMs allow epidemiologists to test hypotheses related to the behaviours of the individuals that may be impossible to test on the field. These models are able to represent global parameters, individuals, their behaviours and their effect on the environment, their relationships, in combination with any of the environmental representation above. However, considering more detailed descriptions of the environment is currently beyond their scope and they may have difficulties in dealing with unstructured or dynamic ones, also, in order to achieve a good ABMs model, the computer scientist should be an excellent developer, something that is not always possible.

D. Process Algebras

Process algebras are abstract languages used for the specification and design of concurrent systems. The most widely known process algebras are Milner's The Calculus of Communicating Systems (CCS) and Hoare's Communicating Sequential Processes (CSP) [24]. The process algebras take inspiration from both these formalisms.

In the process algebra approach systems are modelled as collections of entities, called agents, which execute atomic actions. These actions are the building blocks of the language and they are used to describe sequential behaviours which may run concurrently, and synchronizations or communications between them. The first works which started using process algebra in epidemiology is PEPA (the Performance Evaluation process Algebra) and WSCCS *(Weighted Synchronous Calculus of Communicating Systems*). PEPA was started in Edinburgh in 1991 [19], it was motivated by problems encountered when carrying out performance analysis of large computer and communication systems, based on numerical analysis of Markov processes. Performance analysis seeks to predict the behaviour of a system with respect to dynamic properties such as the number of requests that can be satisfied per unit time and response time. McCaig et al. [26] used "Weighted Synchronous Calculus of Communicating Systems" (WSCCS). The semantics of WSCCS can be viewed as a Discrete Time Markov Chain (DTMC). Simulation can be used to explore the model, steady state analysis can be carried out, and properties of the Markov Chain computed. Benkirane in 2009 [5], tried to reproduce with PEPA the propagation of bubonic plague in a prairie dog burrow studied by Webb et al. [35], by doing this, he could reproduce the same results as ODEs, but he could not expressed explicitly the space and the transmission from fleas to prairie dogs, and the reproduction of fleas which is driven by density dependent terms, cannot be precisely described in PEPA, he also, published the similar work [5], where he deduced that : "process algebras provide different forms of analysis not previously available to biologists and in the case of epidemiology, the study of disease spread, process algebra gives us a way to describe individual based models (drawn from observations of individual behaviour) and to then automatically derive population level models". In parallel, Ciochetta developed Bio-PEPA, to specifically deal with biochemical networks [13]. She also defined a variant of it suitable for representing epidemiological models. She specified that some features of Bio-PEPA are useful in the context of epidemiology as well: location can abstract spatial structure and event can describe the introduction of prophylaxis in a population infected by a

disease at a given day and concerning the analysis, from Bio-PEPA, we can take advantage of the various kinds of analysis supported by Bio-PEPA, such as, stochastic simulation, model checking and ODE-based analyses. In particular, the modeller can select the most appropriate approach for the study of the model and analysis techniques can be used together for a better understanding of the behaviour of the system [13].

IV. Modelling Tuberculosis in Bio-PEPA

The previous section helped us to detect that the best methods to study epidemiological system are ABMs and Bio-PEPA approaches, for the reasons mentioned above.

For this in this section we tried to compare between them, and conclude which one is better than the other for epidemiological modelling.

By coming back to the related work we chose Espindola's model [16].

Taking this ABMs-based model as a reference, we propose an alternative computational Bio-PEPA model, to study TB dynamics and the emergence of drug resistance.

A. The ABM Model

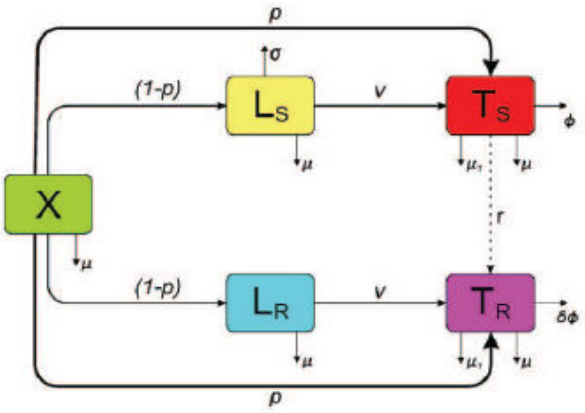

Fig. 1 Schematic representation of the interaction between the five states of tuberculosis (taken from [16])

According to [16], in ABM model, the individual is described by I_{ij}, with (i, j) = {1, 2, . . . ,L}, and placed on one site of a square lattice of side L. The quantity I_{ij} belongs to a population of size N = L ×L and it can have one of five possible states: $I_{ij} \in \{X,LS,LR,TS,TR\}$. If Iij = 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) 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 I, which are reported in [16]. Transitions are allowed between states and their respective probability can be seen in the scheme shown in Fig. 1.

TABLE I
Model Parameters (taken from [16])

Parameter	Description
μ	Probability of natural death
μ_T	Probability of death due to tuberculosis
P	Probability of developing active tuberculosis from X state
υ	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
η_L	Proportion of latent individuals that receive chemoprophylaxis
η_T	Proportion of infective individuals that receive treatment

Refer to [16] for further description of each state of the model and the dynamics of interaction between them.

B. Translating the Model to Bio-PEPA

To describe the various components of tuberculosis model in Bio-PEPA, we must first present the most important elements of Bio-PEPA, [14].

Bio-PEPA Language

In this subsection, we present a brief description of Bio-PEPA. Its main components are the component "species", describing the behavior of each species, and component "model", describing the interaction between different species.

The syntax of Bio-PEPA is defined as follows:

S:= (α,k) op S:=S ; S:=S+S; S:=C
with
op = ↓I ↑I⊕I⊖I⊙
And

$$s ::= s \underset{L}{\bowtie} s \mid s(x)$$

where,

S: the species component (different types of individual);

P: the model component describing the system and interactions between components.

The prefix term (α, k) op S, k: the stoichiometry coefficient of species S in reaction α, where, prefix combinatory "op" represents the role of S in the reaction.

Op={ ↓: a reactant, ↑: a product, ⊕ : an activator, ⊖ : an inhibitor, ⊙ : a generic modifier}.

The operator "+": expresses the choice between possible actions.

The constant C: defined by an equation $C \stackrel{def}{=} S$.

The process $P \underset{L}{\bowtie} Q$: denotes synchronization and cooperation between components P and Q, where L, determines those activities on which the operands are forced to synchronize, with $\underset{L}{\bowtie}$, denoting synchronization on all common action types.

S (x): The model component, where the parameter $x \in R$ represents the initial amount of the species [13], [14].

Among the most important properties of Bio-PEPA, that it could support the events and the environment which are

expressed directly by Bio-PEPA's syntax [13], [14]. According to the syntax of Bio-PEPA we define:

1. Location: As defined in [16], besides the probability that the individual to be infected by the neighbourhood, there is also the probability of contagion due to other individuals with TB in the lattice. Thus, in Bio-PEPA we use tow compartmental components, the first one for the local contagion and second one for global contagion. Which are expressed by:

Location "Local in world": size = sizeLocal, type = compartment;

Location "Global in world": size = sizeGlobal, type = compartment;

2. The Functional Rates : As mentioned above the individual could be in different states expressed in Bio-PEPA by: (for more clarity of this paper, we decided to present in following only functions corresponding to a spread without treatment)

- susceptible_infected: p * X@Local * T@Local, describes the contact between susceptible X and local infected T with rate p.
- susceptible_infected_Global: p*X@Local* T@Global, describes the contact between susceptible X and infected T in other place in the lattice with rate p. for these two functions, X goes directly to the infected state T.
- susceptible_exposed : Beta * X@Local * T@Local (susceptible_exposed_global : Beta * X@Local * T@Global), the same descriptions as the two firsts, but here X goes to the latent state L.
- exposed_infected: v * L@Local, Describes the latent's L transition to T by a parameter v.
- infected_died: MuT * T@Local (infected_died_G : MuT * T@Global), Describes the local T (global T) which died by a parameter MuT.
- died_X : Mu * X@Local(died_L : Mu * L@Local, died_T : Mu * T@Local, died_T_G : Mu * T@Global), describes the natural died of X (L, T(local/global))by parameter Mu.

3. The Species Components:

- **X** =(susceptible_infectedTr,1) ↓ X+(succ_Tr,1) ↑ X+ (died_inf_Tr,1) ↑ X+ (died_inf_Tst,1) ↑ X+(succ_Tst,1) ↑ X+(susceptible_exposedTr,1) ↓ X + (succ_Lst,1) ↑ X+(infected_diedTs,1) ↑ X +(died_Ls,1) ↑ X +(died_Ts,1)↑ X+ (died_X,1)□ X+(susceptible_exposedTs,1)↓X +(susceptible_infectedTs,1)↓ X.
- **Ls**=(trait_Ls,1)↓Ls+(inf_Ls,1)↓Ls+(susceptible_exposed Ts,1)↑Ls +(died_Ls,1)↓Ls + (exposed_infected,1)↓Ls.
- **Lst**=(trait_Ls,1)↑Lst+(succ_Lst,1)↓Lst+(resi_Lst,1)↓Lst+ (infl_Lst,1) ↓ Lst+ (inf2_Lst,1) ↓ Lst.
- **Lr**=(resi_Lst,1)↑Lr+(susceptible_exposedTr,1)↑Lr+(inf_ Lr,1)↓Lr.
- **Tr**=(susceptible_infectedTr,1)↑Tr+(inf_Ls,1)↑Tr+(inf2_L st,1)↑Tr+ (inf_Lr,1)↑Tr+(resi_Tst,1)↑Tr+(died_inf_Tr,1)↓Tr + (succ_Tr,1) ↓ Tr.
- **Ts**=(trait_Ts,1)↓Ts+(infl_Lst,1)↑Ts+(susceptible_infecte dTs,1)↑Ts +(infected_diedTs,1)↓Ts+(died_Ts,1) ↓ Ts+ (exposed_infected,1) ↑ Ts.
- **Tst** =(trait_Ts,1) ↑ Tst+ (succ_Tst,1) ↓ Tst+ (resi_Tst,1) ↓ Tst + (died_inf_Tst,1) ↓ Tst.

where: X (susceptible), Ls (sensitive Latent), Lst (Latent sensitive with treatment), Lr (resistant Latent), Tr (resistant infected), Ts (sensitive infected), Tst (sensitive infected with treatment).

4. Model Component:

X[x] ⋈ L Ls[ls] ⋈ L Ts[ts] ⋈ L Lst[lst] ⋈ L Lr[lr] ⋈ L Tr[tr] ⋈ L Tst[tst].

where x, ls, lst, lr, tr, tst are the initial number of species (individual), and **L:** all the functional rates.

C. Simulation Results and Comparisons

In this section, we reproduced all the parameters used in [16], and also we took the same remarks for the best comparisons and prove that Bio-PEPA could reproduce the same results.

1. No Treatment For Tuberculosis

The simulation started at t = 0 where only X and Ts individuals are present. The amount of TS individuals is 20% of the total population. The system evolves with no public health intervention (no treatment for TB) until the 200th year. In this stage, three states can be seen in the lattice: X, Ls and Ts. At this step, we could reproduce the same result as in [16], i.e., the reduction in the amount of TS 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, Fig. 2. This figure is the reproduction of local contagion.

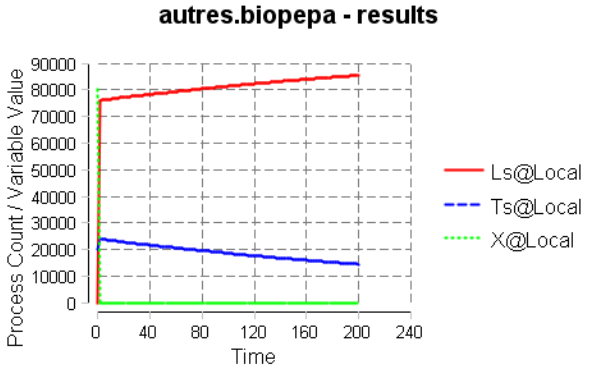

Fig. 2 No treatment for tuberculosis for local interaction during 200 years

The global contagion is illustrated in Fig. 3. The comparison between this figure and Fig. 2 shows that the time

to reach a steady state is longer when we assume only local interactions. When only local interactions are taken into account the spread of the disease is limited to the neighbourhood of the susceptible individuals. On the other hand, when only global interactions are present, the pool of susceptible individuals subjected to be infected is bigger, speeding up the spread of TB.

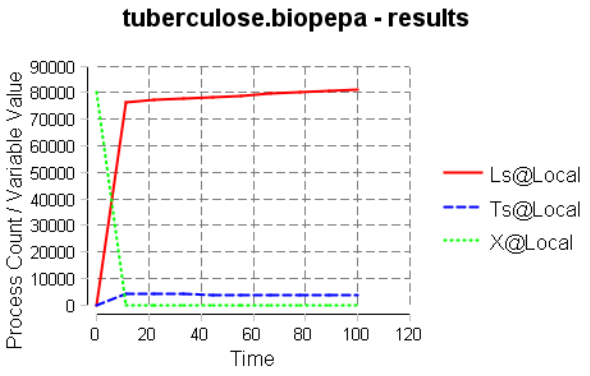

Fig. 3 No treatment for tuberculosis for global interaction during 200 years

2. Simulation with Treatment

Then, in order to visualize the effect of this public health intervention, the introduction of treatment with antibiotics and chemoprophylaxis started on the first day of the 200th year, we can see in Fig. 4, as expected, the amount of TS (yellow) individuals has decreased dramatically (from the 200th year) due to treatment with 50% probability of effective cure (φ = 0.5). There is also a decrease in the amount of LS (blue) individuals because of the lower quantity of TS people (source of infection) and the response to chemoprophylaxis.

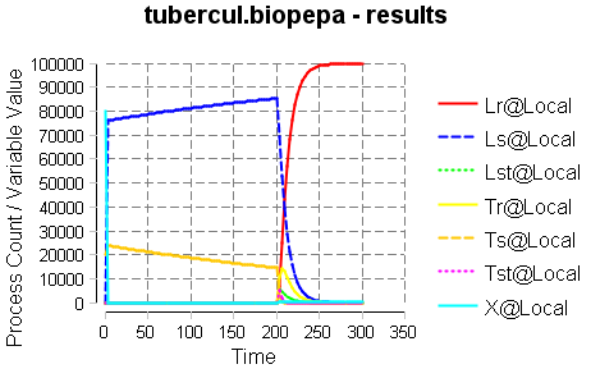

Fig. 4 Model with treatment injected after 200 years

In the period running from the 200th to 300th year, we can see in Fig. 5 that cases of tuberculosis sensitive to antibiotics (TS) have vanished around 20 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 TR cases between the 200th and 210th years. The emergence of TR cases depends upon the treatment failure of TS cases. Thus, initially, the amount of TS individuals is higher, which creates a pool of TS individuals to be converted to TR cases. After a few years, as soon as TS has decreased, the amount of TR cases also decrease, and the peak shown in the figure converges to a stable endemic state. This convergence is due to the TR cases which are cured with an efficacy relative to TS cases defined by the parameter δ. It is then expected that infective individuals TR remain in the population, even though in the case of high efficacy treatments.

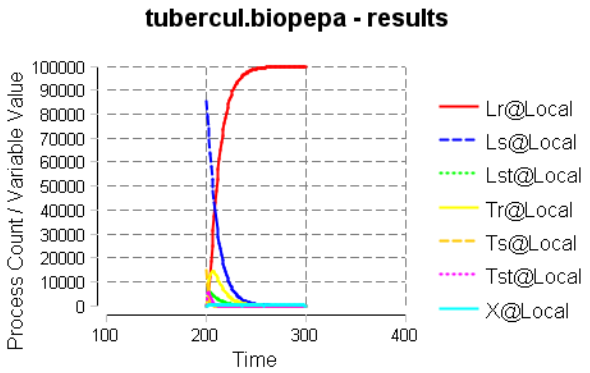

Fig. 5 Impact of treatment

V. Conclusion

Here we proposed a Bio-PEPA 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 same or different place. Different from agent-based model, we taken into account all the parameters and features of this model with a simple syntax and without doing a computing probabilities. These individuals can be in one of five states of the disease: susceptible (X), latent with type S bacteria (LS), latent with type R bacteria (LR) and active tuberculosis with type S (TS) and type R (TR) bacteria. This approach has allowed us to deal with the problem with more refinement than the existing agent-based model with which was inspired.

We remembered here, that our aim is not to improve the ABMs model, but to prove that it is simpler to use Bio-PEPA in modelling than other, and also the drawback which was observed for ABMs model is dealing here.

References

[1] E. Amouroux, S. Desvaux, A. Drogoul, “Towards virtual epidemiology: an agent-based approach to the modeling of H5N1 propagation and persistence in North-Vietnam”, journal of Intelligent Agents and Multi-Agent Systems, Springer, p.26-33, (2008).

[2] E. Amouroux, P. Taillandier, A. Drogoul, & Nord, I. R. D. F, « Complex environment representation in epidemiology ABM: application on H5N1 propagation », 1–12, (2010).

[3] H. Andersson and T. Britton, “Stochastic Epidemic Models and their Statistical Analysis”. Lecture Notes in Statistics, Springer Verlag, (2000).

[4] M. Artzrouni, et J.P. Gouteux, “Population dynamics of sleeping sickness : A micro simulation”, Simulation & Gaming, Vol. 32, No. 2, 215-227 (2001)

[5] S. Benkirane, J. Hillston, C. McCaig, R. Norman and C. Shankland, "Improved Continuous Approximation of PEPA Models through Epidemiological Examples", ENTCS 229 (1), pp. 59–74, (2009).
[6] G. A. Bocharov, A. A. Romanyukha, "Mathematical model of antiviral immune response III. Influenza A virus infection", J. Theor. Biol. 167 (4), 323–360, (1994).
[7] J. Bouyer, S. Cordier, P. Levallois, « Épidémiologie », In: Environnement et santé publique - Fondements et pratiques, pp.89–118. (2003).
[8] S. M. Blower, J. L. Gerberding, "Understanding, predicting and controlling the emergence of drug-resistant tuberculosis: a theoretical framework", J. Mol. Med. 76 624, (1998).
[9] S. M. Blower and al, "The intrinsic transmission dynamics of tuberculosis epidemics", Nat. Med. 8 815, (1995).
[10] S. M. Blower, T. C. Porco, T. M. Lietman, "Tuberculosis: the evolution of antibiotic resistance and the design of epidemic control strategies", Mathematical Models in Medical and Health Sciences, (1998)
[11] F. Brauer, "Compartmental Models in Epidemiology", Mathematical epidemiology, p19-79, springer, (2008).
[12] L. Brouwers, "MicroPox: a Large-scale and Spatially Explicit Microsimulation Model for Smallpox Transmission", Proc. of the Intl. Conf. of Health Sciences Simulation, (2005).
[13] F. Ciocchetta, J. Hillston, "Bio-PEPA for epidemiological models", 1–20. Electronic Notes in Theoretical Computer Science, *Volume 261*, *22 February 2010*, *Pages 43-69,* (2009).
[14] F. Ciocchetta, J. Hillston, "Bio-PEPA: a Framework for the Modelling and Analysis of Biochemical Networks", Theoretical Computer Science 410, pp. 45–68, (2009).
[15] M. Costa, « Modélisation stochastique d'une épidémie SIR Un bref historique », 1–11, (2011).
[16] A. L. De Espíndola, C. T. Bauch, B. C. Troca Cabella & A. S. Martinez, "An agent-based computational model of the spread of tuberculosis". *Journal of Statistical Mechanics: Theory and Experiment*, P05003. doi:10.1088/1742-5468/2011/05/P05003, (2011).
[17] S. C. Fu, "Modelling epidemic spread using cellular automata", Master's Thesis The University of Western Australia, Department of Computer Science and Software Engineering, (2002).
[18] L. Hartwell, J. Hopfield, S. Leibler, A. Murray, "From molecular to modular cell biology". Nature 402:C47–C52, (1999).
[19] J. Hillston, "Tuning Systems: From Composition to Performance", BCS Roger Needham Award Lecture, The Royal Society, London, (2004).
[20] W. O. Kermack, A. G. McKendrick, "A contribution to the mathematical theory of epidemics". Proc. R. Soc. Of London Series A 115 (772), pp. 700—721, (1927).
[21] E. L. Landguth," A Cellular Automata SIR Model for Landscape Epidemiology", 1–10, (2007).
[22] M. Y. Li, "Mathematical Epidemiology: Models and Analysis", University of Alberta Lecture Notes, (2010).
[23] G. Macdonald, "The epidemiology and control of malaria London", Oxford University Press, (1957).
[24] D. Machado, R. S. Costa, M. Rocha, E. C. Ferreira, B. Tidor & I. Rocha, "Modeling formalisms in Systems Biology". *AMB Express*, *1*(1), 45. doi:10.1186/2191-0855-1-45, (2011).
[25] S. Mandal, R. R. Sarkar & S. Sinha, "Mathematical models of malaria", a review. *Malaria journal*, *10*(1), 202. doi:10.1186/1475-2875-10-202, (2011).
[26] C. McCaig, R. Norman and C. Shankland, "Process Algebra Models of Population Dynamics", in: Proc. of Algebraic Biology, 3rd International Conference, AB 2008, LNCS 5147, pp. 139–155, (2008).
[27] M. E. J Newman, "Spread of epidemic disease on networks". Physical Review E66, (2002).
[28] A. S. Perelson, "Modelling viral and immune system dynamics". Nat. Rev. Immunol. 2 (1), 28–36, (2002).
[29] E. Ravasz, A. Somera, D. Mongru, Z. Oltvai, A. Barabási, "Hierarchical organization of modularity in metabolic networks". Science 297(5586):1551–1555, (2002).
[30] T. Sellke, "On the Asymptotic Distribution of the Size of a Stochastic Epidemic", *Journal of Applied Probability,* Vol. 20, No. 2, pp. 390-394,(1983).
[31] H. Situngkir, "Epidemiology through cellular automata: case of study avian influenza in Indonesia", Bandung Fe Institute, (2004).
[32] D. L. Smith, L. A. Waller, C. A. Russell, J. E. Childs, L. A. Real, "Assessing the role of long-distance translocation and spatial heterogeneity in the raccoon rabies epidemic in Connecticut", Prev. Vet. Med., 71, 3-4, 225-240, (2005).
[33] J. Turner, M. Begon, R. Bowers, "Modelling pathogen transmission: the interrelationship between local and global approaches". Proc Biol Sci.,270(1510): 105–112, (2003).
[34] A. J. Valleron, « L'épidémiologie humaine: Conditions de son développement en France, et rôle des mathématiques », Volume 23 de Rapport sur la science et la technologie : RST / Académie des sciences , EDP Sciences, 2868837964, 9782868837967, 424 pages, (2006).
[35] C. T. Webb, C.P. Brooks, K.L. Gage, and M. F. Antolin. "Classic flea-borne transmissoin does not drive plague epizootics in prairie dogs". PNAS, 103(16):6236–6241, (2006).
[36] http://en.wikipedia.org/wiki/Compartmental_models_in_epidemiology.