Project Report On

Agent Based Modeling and Simulation Of Drug-Resistant Diseases

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Abstract

The unnecessary use of antibiotics has given rise to antibiotic resistance and for this reason is a cause of growing concern in contemporary health care contexts. Antibiotic resistance means that an antibiotic is losing or has lost the ability to kill a given bacteria and/or to prevent it from reproducing. The result: an increase in the number of patients suffering from and even dying of infections. Resistant bacteria continue to increase in number, as they survive the antibiotic designed and used to kill them. The disease induced by the bacteria lasts longer, therefore, than would have been the case were the bacteria not antibiotic resistant. Thus, prolonged treatment and/or even death results together with an increase in cost associated with these outcomes. This project initiates an environment filled with humans, simulates the spread and development of tuberculosis in particular. Tuberculosis is one of the most prevalent drug-resistant diseases out there with various stages of infection.

Contents

Chapter 1

Introduction

1.1 Goal

In this work , we've built a model to simulate the onset of drug resistance in Mycobacterium tuberculosis and subsequent spread of tuberculosis(TB) in a constrained environment.We've implemented the simulations by an agent-based model where the the individualistic behaviour of humans is considered. The model aims to mimic the realistic development of drug resistance in bacteria by considering disease spread and drug-resistance as the cause for drug resistance. Subsequently, we aim to observe different patterns of how TB spreads.

1.2 Background

Tuberculosis is a disease caused by the bacteria Mycobacterium tuberculosis, which is mainly spread from person to person through air. It usually affects the lungs. TB can be cured using drugs, but improper or inadequate use of drugs might sometimes turn out to be severe and may lead to death. Sometimes drug-resistant TB occurs when bacteria become resistant to the drugs used to treat TB. This means that the drug can no longer kill the TB bacteria. Drug-resistant TB can occur when the drugs used to treat TB are misused or maladministrated. The examples for maladministration are not completing full course of TB treatment, wrong dose or duration of treatment, poor quality drugs, etc. The types of drug resistant TB are Multidrug-Resistant TB (MDR TB) that is resistant to at least isoniazid and rifampin, the two most potent TB drugs, and Extensively drug-resistant TB (XDR TB), a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). Tuberculosis can turn drug resistant either in a host itself or by spread of the bacteria between hosts.

1.2.1 Intra-Host

In the case of maladministration of drugs, the drug kills the weak bacteria but the strong ones survive and turn resistant to the drug. Then they multiply in number, sharing the same genetic material that helps them resist the drugs. This is how bacteria turn drug resistant in a host.

1.2.2 Inter-Host

When a person infected with drug resistant bacteria coughs or sneezes, the bacteria suspends in the air. Their lifetime depends on the environmental factors like humidity, sunlight, etc. So when they survive for a while and a new host inhales the bacteria, they either reproduce or they interact with the bacteria present in the new host and share their genetic material through a process called conjugation. So the bacteria in the new host finally become drug resistant.

1.3 Gap Analysis

The base work that we are considering is "An agent-based computational model of the spread of tuberculosis" by Aquino L de Espındola, Chris T Bauch, Brenno C Troca Cabella and Alexandre Souto Martinez. Here, they propose a model of the spread of tuberculosis (TB) and the emergence of drug resistance due to the treatment with antibiotics. They 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. This model has one class of agents, i.e "Human". This model basically considers agents as humans who are infected with drug susceptible TB, infected with drug resistant TB, unaffected. When a human releases the bacteria, the model takes care of the spreading and conversion of drug susceptible bacteria to drug resistant. The human agents stay in one place and get infected if they are in the vicinity of an infected human.

Our model also has only one type of agent - the Human agent. He has an important attribute that determines the state of his infection. The human agents are simulated to randomly walk to make the model even more realistic. This model will consider three ways how the bacterium turn drug resistant - Intra-Host, Inter-Host, In the Environment. Initially, we'll have a set of human agents who are infected by drug susceptible TB, and another set of unaffected human agents and a few humans with drug-resistant TB. When the infected humans are being treated, maladministration of drugs can happen, causing the bacteria to turn drug resistant(Intra-Host). The Drug resistant infected humans might expel the bacteria into the surroundings. So, the state of the human changes depending on the conditions above and by probabilistic transitions.

Chapter 2

Approach

We came up with three models to simulate the whole process of simulating the drug-resistance of the disease and human environment.

1) Movement Model
2) Infection Model
3) Medication Model

2.1 Movement Model

The movement model of the human agents is designed on the basis of different types of humans. There are 4 types of humans in the simulation.

a) Student
b) Delivery Person
c) Office worker
d) Idle

Each type of human mentioned above have a predefined schedule of when to move out and when to come back to their homes. The movement model also depends on the environment. We have a small urban environment where the agents move around on roads and enter the buildings. For this, we have a GIS model of a sample city with roads and buildings.

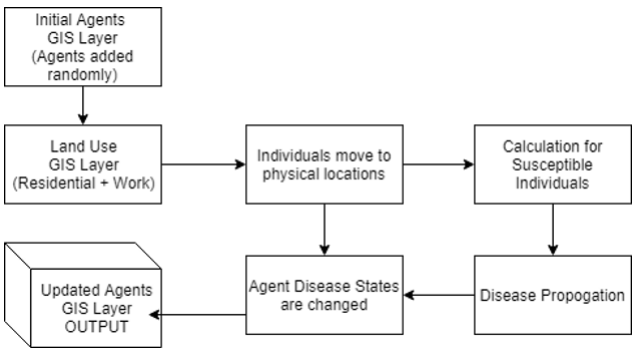

Figure 2.1: GIS life cycle

2.2 Infection Model

Before getting to the actual model, we have some assumptions regarding how the infection spreads. Generally, pathogens of tuberculosis enter the air when an infected person coughs or sneezes. But we make an assumption that the pathogens are always in the defined vicinity of the infected human, and any other human who enters this region has a chance of getting infected. This is decided by a probabilistic transition of the state of the human who enters this region. The mathematical equation for this probability is as follows. The states will be defined later. Constant values taken from publishes papers.

$prob\_LS = 1 - (1 - prob\_BS)^{n\_BS}$
$prob\_LR = 1 - (1 - prob\_BR)^{n\_BR}$
$prob\_L = prob\_LS + prob\_LR - (prob\_LS * prob\_LR)$
$prob\_L\_LS = ((prob\_LS) * (1 - prob\_LR))/prob\_L\ prob\_L\_LR = 1 - prob\_L\_LS$
if $prob\_L\_LS > prob\_L\_LR$ then enter LS state
else enter LR state

where
n_BS = number of agents in AS state in the vicinity,
n_BR = number of agents in AR state in the vicinity,
prob_BS = 0.000137
prob_BR = $0.5 * prob\_BS$

The infection model we've made is inspired from the classic SIRf model. Tuberculosis has a characteristic like many diseases, where it stays in latent state for a while, during which none of the symptoms show up. The disease later develops into an active state where it starts effecting the human. Once a human gets cured, he enters the latent state again instead of the complete cure state as the pathogens become inactive after the treatment. The abstract model is as shown in fig 2.2. This gives us the abstract way of how the disease develops. But when we discuss in

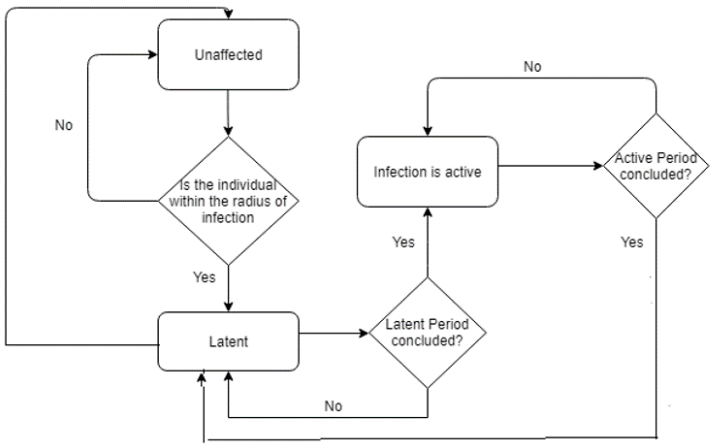

Figure 2.2: Infection Model

depth about how the transitions actually happen, we run into many cases as a drug-susceptible infection might turn into a drug-resistant infection and this adds many other cases that the simple SIRf model doesn't mention. Tuberculosis state transitions happen between almost every adjacent states according to our assumptions.

The transitions are shown in fig 2.3. The states showed in the diagram are as follows.

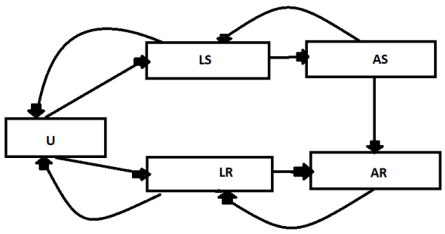

Figure 2.3: Disease State Transitions

a) U - Unaffected
b) LS - Latent Susceptible
c) LR - Latent Resistant
d) AS - Active Susceptible
e) AR - Active Resistant

2.3 Medication Model

The medication model can be implemented by simply putting each agent in a particular state for a certain amount of time. Here, we make an assumption that a person who initially enters the latent state will no realise that he/she is infected by the disease.

Treatment for Latent TB (Takes upto 5 months on an average)
Three drugs
a) Isoniazid
b) Rifampin
c) Isoniazid and Rifapentine

Treatment for Active Drug Susceptible TB (Takes upto 10 months on an average)
a) Ethambunol
b) Isoniazid
c) Pyrazinamide
d) Rifampin

Treatment for Active Drug Resistant TB
The first level of medication takes upto 6 months and the patient has a probability to be cured in that time. If not, he/she needs to go through a second level of medication which takes upto 25 months on an average. The drugs are as follows.
a) Fluoroquinones
b) Amikacin, Kanamycin, Capreomycin
c) Linezoid, Bedaquiline (Level 2 Medication)

Initial Latent State

The disease cannot be identified by the patient when he is in Latent states when he gets affected by the bacteria from another person. Thus, a patient who turns into LS or LR from U will not go through any medication. Hence, there is no chance for the bacteria to turn drug resistant in this case. So this assumption restricts the transition from LS to AS only and LR to AR only.

Final Latent State
When a patient is treated with drugs for Active Susceptible TB or Active Resistant TB, and if the treatment is successful, then the patient goes into the respective latent state. This is because the bacteria's activity is killed but not the bacteria itself. To kill this inactive latent bacteria, the patient needs to go through another set of medication for around 9-12 months.
All this matches with the reality and have been implemented in our model, but the later part is where we made an approximation. Once the patient reaches a latent state after getting treated, the patient takes the medication and gets to cured for with 100% probability right after the medication duration end.

Chapter 3

Project Installation, Structure And Execution

3.1 Prerequisite software

The project runs on the Eclipse IDE using the Repast City framework. There is an alternative where we can directly install Repast Simphony to run the same project. Use the below links to download and install the software.
https://www.eclipse.org/downloads/
https://code.google.com/archive/p/repastcity/

To visualize the final output, we wrote a python script which runs on Jupyter notebook and needs matplotlib to be installed.

3.2 Execution

3.2.1 Opening Project

Open eclipse and open the "repast3" directory in the project directory. Make sure that repast city framework is already installed before opening the project.

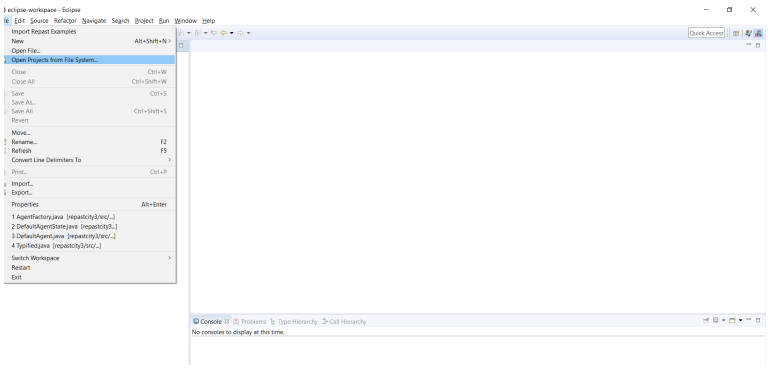

Figure 3.1: Opening project on eclipse

3.2.2 Project Structure

Before going into execution of the code, here is a brief explanation of the project structure. The "src" directory has all of the code in it.

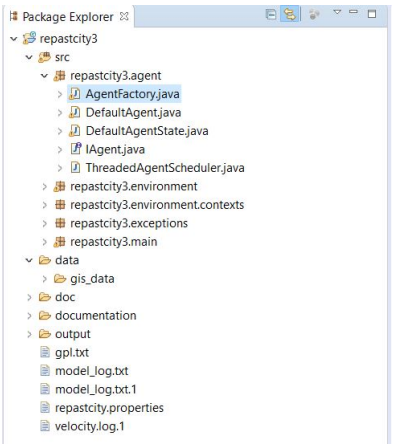

Figure 3.2: Project structure

The "repastcity3.agent" directory consists of all the java files related to the agents. "AgentFactory.java" has the code that creates and initiates all the agents. "DefaultAgent.java" contains the code that defines the type of agent and its attributes and fucntions. "DefaultAgentState.java" defines the state of the human agent and has the probabilistic transition model of the disease in it.

The "repastcity3.environment" directory contains various java files about how the GIS environment should be read from the shape files, spatial coordinates of buildings and roads, etc.

The data folder has the GIS data in it, where the city environment is defined in the roads and buildings shape files. If one wants to edit these files, then please look up the tool called "Q-GIS" that helps us edit vector and shape files. The file "repastcity.properties" contains general configuration information for the model and this is the file where the shape files and other GIS related data is given as input. If one wants to change the environment, this file can be changed accordingly to take other files as input.

3.2.3 Execution

To run the project, click on the play button on the task bar. The play button gives us some options to choose. Choose "Run RepastCity3 Model" to execute the code (As shown in fig 3.3). The output would come in a new screen that has many options in it. The play button on the top will start the simulation as shown in fig 3.4. The stars are the human agents and the blocks are the buildings. The right top corner shows us the tick count, where tick is the fundamental unit of time of this tool. So, this helps us check the elapsed time. Each tick is equal to 60 seconds of real life in our simulation. This value can be changed in "DefaultAgent.java", "DefaultAgentState.java" files. The bottom left corner has some tabs, where one

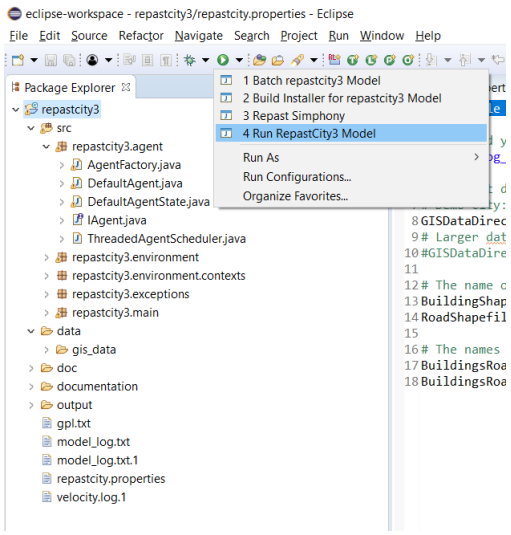

Figure 3.3: Code execution

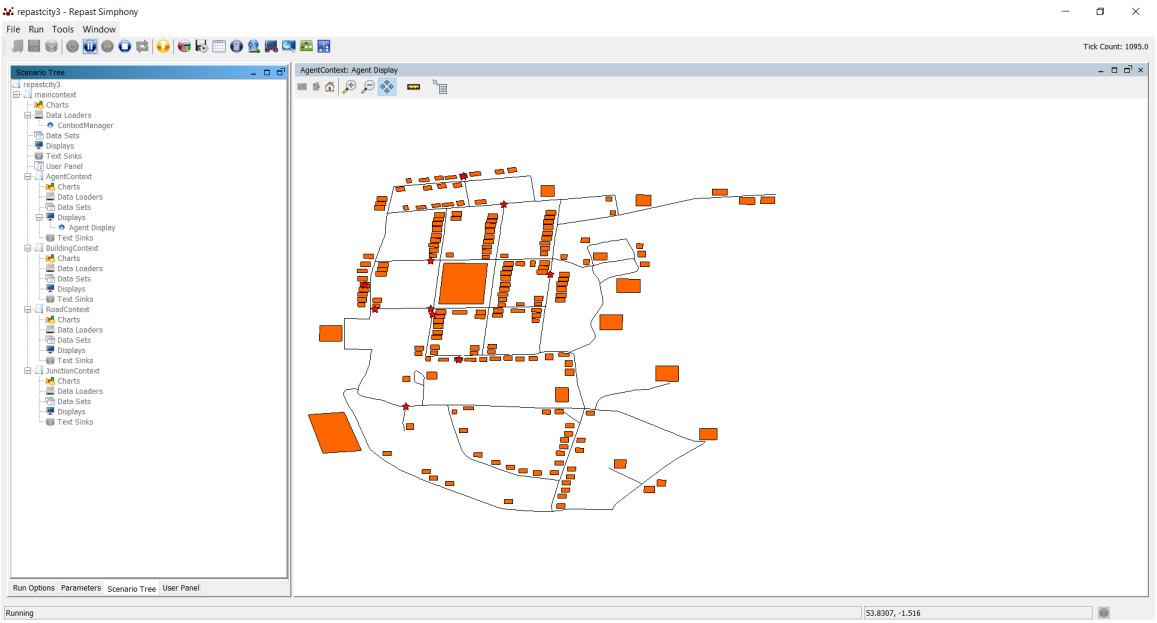

Figure 3.4: Simple Output With 10 Agents

of them is the parameters tab that lets us change the duration of the simulation, number of agents, etc.

When we do a batch simulation, by the end of the simulation, we can find some log text files in the "output" directory of the project, which have the details of the state of each agent for every tick. We used these files to visualize how the number of agents in each state are varying. We used a python code to visualize this data, which can be opened and executed using Jupyter notebook or Google Collab. This python code can be found in the directory "visualization_python_code" along with the repast project directory.

Chapter 4

Results

The results are graphs of number of agents in each state vs the time elapsed. We considered two simulations for 1000 years and 2000 years duration with 100 human agents after fine-tuning the probability parameters. The results are as shown.

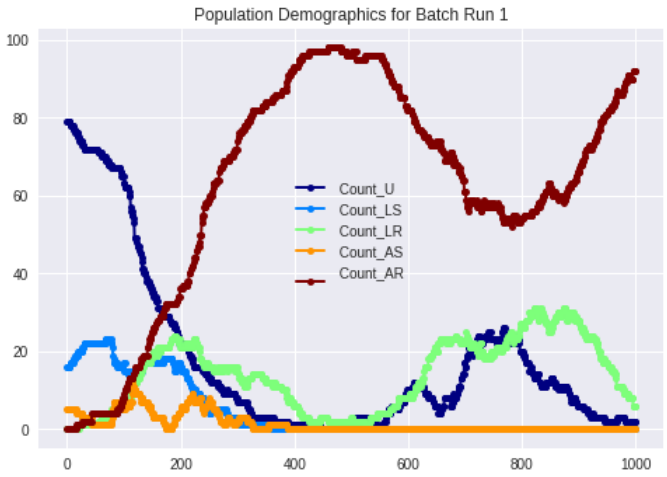

Figure 4.1: Result of Simulation of 1000 years with 100 human agents

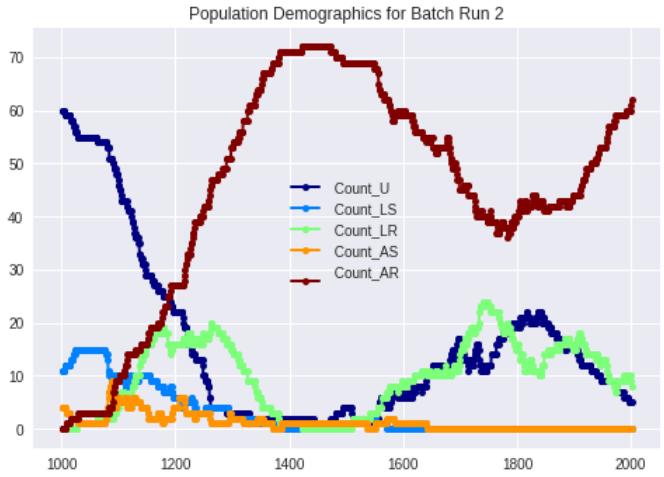

Figure 4.2: Result of Simulation of 2000 years with 100 human agents

In both the simulations, we can observe that over a long period of time, the Active

Susceptible bacteria cease to exist and the number of Active Resistant infections reaches a peak, goes down and again increases. This observation can be termed as what is called a "Superbug". "Superbugs" is a term used to describe strains of bacteria that are resistant to the majority of antibiotics commonly used today. So, we probably had a set of probabilistic parameters where the best level of medication isn't being administered and hence drug-resistance is easily being developed.

Chapter 5

Conclusion And Future Work

5.1 Conclusion

The GIS-agent based model designed for this study can be easily customized to study the disease spread dynamics of any other communicable disease by simply adjusting the modeled disease timeline and/or the infection model and modifying the transmission process. This type of simulations can help to improve comprehension of disease spread dynamics and to take better steps towards the prevention and control of an epidemic outbreak.

5.2 Future Work

As mentioned previously in the approach of our models, there were a few assumptions we made regarding the behaviour of humans, disease development and the medication process. And many of these assumptions are not the same when it comes to reality.

The tool we are using simulates the environment in a 2D space. This definitely creates a huge problem of accommodating human agents in each building. In fact, this is exactly why there are only 3 or 4 agents per building in our model as we can't model the 3D aspect of having multiple floors in each building, which is the exact opposite of how it would be in an urban region. This made us restrict the number of agents in each simulation at maximum to 100. So this can be something one can work on as future work where there can be different compartments for each building. These compartments can be considered as different floors.

There were some assumptions we made about the disease development. We assumed that a person who get affected by the infection and enters the initial Latent Susceptible state can only go to Active Susceptible state since there won't be any signs of the infection. But it is not true in reality. People who go for regular check ups can still get to know that they have a latent infection of the disease and start taking medication. So, in this case, the agent can either get cured or go to a Latent Resistant state due to maladministration of the drugs. Our model doesn't consider these scenarios as a latent infected patient is treated only after he came to that state by getting treated in an Active state of the disease. We also made another assumption that a person who enters the latent state after getting treated in the Active state would definitely get cured and turn unaffected after the medication time. All these assumptions are not that close to the reality, and can be changed in

order to make the model more realistic.

The model can still be improved to get better results. The spread of the disease can be considered in a network with more realistic environment, such as small-world and real infectious networks, where climate also plays role as the bacteria's life cycle in air depends on the climate. These were not included in our model to keep it as simple as possible.

The probabilistic parameter values are decided by trail and error method to get a better result. But the simulation takes a lot of time, so we are not sure how good are the parameter values that we chose. This can be something one can work on for a better result.

Chapter 6

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