Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Lecture with Computer Exercises: Modelling and Simulating Social Systems with MATLAB

Project Report

Impact of Chemoprophylaxis on the Tuberculosis epidemiology

Mihye An & Ayoung Jeong

Zürich
16. Dec. 2011

Agreement for free-download

We hereby agree to make our source code of this project freely available for download from the web pages of the SOMS chair. Furthermore, we assure that all source code is written by ourselves and is not violating any copyright restrictions.

Mihye An Ayoung Jeong

Table of Contents

Individual Contributions

Most of the basic plans for structuring the code were discussed together. Mihye initially made class designs, and Ayoung developed details until the final code. And Ayoung did getting final results from simulations. For writing the report, we divided the work in two parts: Mihye has done the implementation description and Ayoung, for the rest.

I. Introduction and Motivations

1. Epimediology and pathophysiology of tuberculosis

Tuberculosis (TB) is one of the most devastating infectious diseases killing around two million people worldwide every year. Although drugs are available since several decades, TB is still the second leading cause of death in the world and nearly one third of the whole human population is thought to be infected by Mycobacterium tuberculosis. And there isn't an efficient vaccine yet.

When an individual is infected with M. tuberculosis, he/she can develop a primary TB, which means that the infected individual gets TB as an active disease within a year after the infection. However, they more often enter the latent phase: M. tuberculosis is contained in granulomas that limit further spread of the bacteria through the body. As long as the bacteria stay as latency, they don't make any symptom, but they could suddenly develop an active disease by endogenous reactivation especially when the individual's immune system gets weaker, for example in case of HIV/AIDS. The individual co-infected with HIV has a higher chance to develop a primary TB.

2. Treatment regimens and MDR-TB problem

There are well-established standard drug regimens for TB treatment. It is composed of several antibiotics such as isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol. Various combination of these drugs are recommended depending on the previous history of treatment and the appearance of clinical manifestation. Some bacteria strains of M. tuberculosis have resistance against these drugs and they're called MDR-TB(multidrug-resistant tuberculosis) strains if they're resistant to at least isoniazid and rifampicin. The MDR-TB cannot be treated by the standard drug regimens at all, so that they must be treated with reserve drugs such as levofloxacin, moxifloxacin etc. that cost much more than the standard drugs and have much more severe side

effects. M. tuberculosis can have resistance naturally or acquire easily through a treatment failure.

3. Chemoprophylaxis as a new strategy to control tuberculosis

Either the standard drug regimens or reserve ones are to target the active disease with a variety of clinical manifestations. What if the latently infected individuals get treatment? This relatively new strategy is called chemoprophylaxis. Because it isn't clinically manifested yet and thus it isn't easy to identify the latently infected individuals, this strategy usually targets only a limited group of high risk such as prisoners or HIV/AIDS patients. How about implement this strategy to general publics? Would that help eradicating the disease faster? It has been discussed recently. What seems to be worrisome is the fact that the chemoprophylaxis consists of one drug, isoniazid, in most cases. On the one hand, chemoprophylaxis can reduce incidence because the latently infected individuals get treated and less develop into the infectious stage, which might help contribute to control the disease a lot. On the other hand, this monodrug therapy could enhance the development of drug resistance, which might have adverse impact on the epidemiology of the disease.

Now in this work is to investigate the question: whether the chemoprophylaxis would lead to an eradication of the disease or a MDR-TB pandemic?

II. Description of the Model

Our simulation is based on the SEIS model modified from the basic SIR model that consists of S(susceptible), I(infected) and R(recovered). Our SEIS model has S(susceptible), E(latently infected), I(active disease) and additionally Em(latently infected with MDR-TB strains) and Im(active disease by MDR-TB strains). This model doesn't consider R(recovered) as a discrete compartment because the individuals recovered from TB practically don't have an immunity against M. tuberculosis and thus can be infected again with almost the same probability as the susceptible.

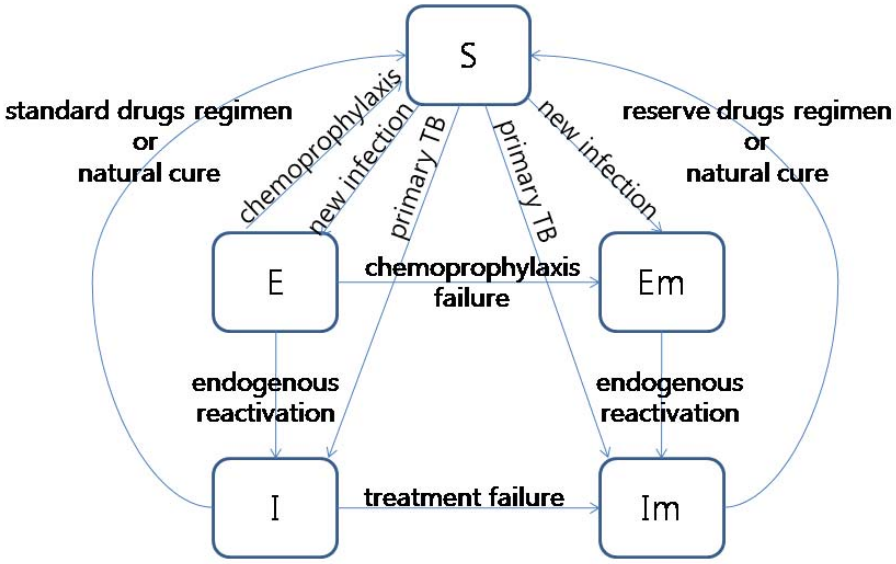

Figure 1. Structure of model. Population change due to birth and death from each compartments are not shown here.

SIR model is usually formulated using differential equations, but our simulation in implemented with agent-based cellular automata so that our model isn't described as a set of differential equations. Instead, all the transition rates between the compartments are listed in a table below. All the parameters are reasonably adopted or calculated based on the empirical data provided by WHO except the chemophylaxis success rate,

which is not known and thus estimated as 0.5 which is a little lower than the standard drug regimen's success rate.

Table 1. Transition rates between compartments. (*:estimated value)

transition	explanation	HIV	MDR	transition rate			
				South Africa	China	South Korea	Switzerland
S to E	new infection (and enter latent phase)	+	-	0.4*(1-0.67) = 0.132			
		-		0.35*(1-0.14) = 0.301			
S to Em	new infection (and enter latent phase)	+	+	0.4*(1-0.88) = 0.048			
		-		0.35*(1-0.88) = 0.042			
S to I	new infection and primary TB development	+	-	0.4*0.67 = 0.268			
		-		0.35*0.14 = 0.049			
S to Im	new infection and primary TB development	+	+	0.4*0.88 = 0.352			
		-		0.35*0.88 = 308			
E to S	chemoprophylaxis success	+/-	+	0			
			-	0.5*			
E to Em	chemoprophylaxis failure	+/-	+	1			
			-	1-0.5* = 0.5*			
E to I	endogenous reactivation	+	+/-	0.003			
Em to Im		-		0.000113			
I to S	standard drugs regimen success	+/-	+	0.72*0.76 = 0.05472	0.75*0.94 = 0.705	0.89*0.84 = 0.7476	0.89*0.85 = 0.7565
			-	0.06*0.6 = 0.036			
	natural cure	+/-	-	0.2			
I to Im	standard drugs regimen failure	+/-	-	0.06*(1-0.6) = 0.024			
	inappropriate chemoprophylaxis	+/-	-	1-0.72 = 0.28	1-0.75 = 0.25	1-0.89 = 0.11	1-0.89 = 0.11
Im to S	reserve drugs regimen success	+/-	+	0.72*(1-0.76) = 0.1728	0.75*(1-0.94) = 0.045	0.89*(1-0.84) = 0.1424	0.89*(1-0.85) = 0.1335
	natural cure	+/-	+	0.2			

III. Implementation

1. General Structure

In this model an object defined by the class Agent is conceptually equal to an individual of each given country environment. Each agent freely moves around in the space and its neighbours are decided depending on the distance to each other: therefore, it is a continuous space.

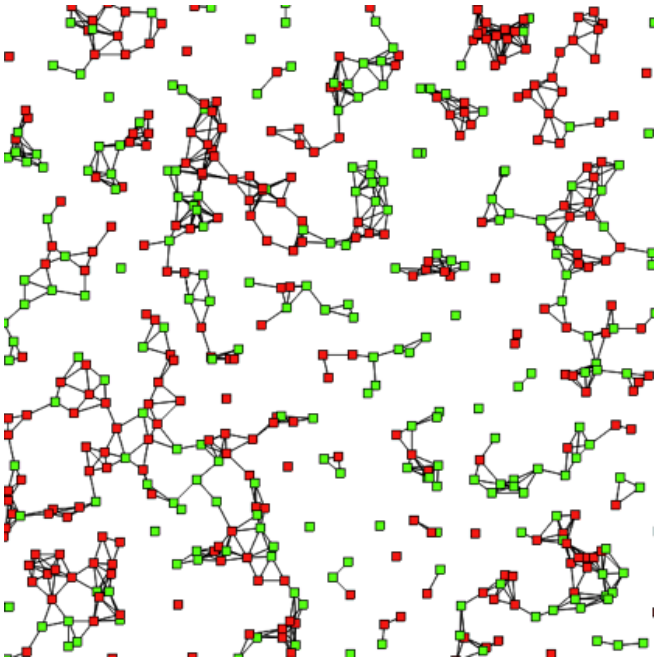

Figure 2. Initial graphical sketch of Agent Based Modelling in Continuous Space

The reason why we chose to have continuous based simulation was to provide flexible movements to agents. Firstly, they have each time different numbers of neighbours, whereas it is fixed in the case of grid based modelling (Figure 3.), although we could also have multiple levels of neighbours in the grids. Secondly, it looks very much intuitive when the possibility of infection is raised through the connected lines between neighbour agents.

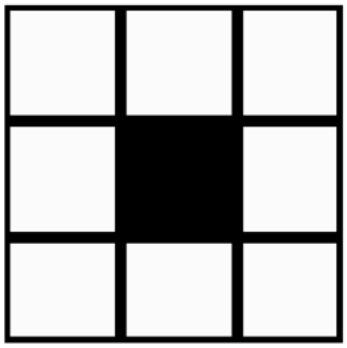

Figure 3. Grid based modelling and neighbours.

The second important point that we paid attention is here: this simulation is meant to mimic the realistic conditions, but it's not really possible to simulate it with actual number of agents (individual) that equals to the population of a country. The biggest issue is the transmission of the disease, which is usually determined by the contact rate per capita (number of people in average that one person get contacted) and the probability of contagion in the original SIR model. In our model, the contact rate could be implemented through adjusting the speed of agents or the maximum distance enabling contagions. However, this approach would strongly influence the visualization that might feel awkward. Therefore, we rather decided to adjust the number of agents instead, through a preliminary simulation. Preliminary simulations (preSearch.m) were done to find out a kind of appropriate number of agents and final simulations (main.m) are based on this figure.

2. Description of the Files

main.m Loading country setup, Initialization of the agents, updating agents status and other functions for saving data.

Agent.m "Agent" class is defined with set of properties that an individual have and methods to move, infect, be cured and die and so on.

parameterSetup.m Main parameters about probabilities with regard to SEI model.

Country.m "Country" class is defined by several parameters that are taken into account in evaluation of TB epidemiology

countrySetup.m Actual country profiles from WHO (SouthAfrica, China, Republic of Korea, Switzerland).

preSearch.m Test file to find out realistic agent number (as mentioned earlier).

realPrevalence.m Calculation of realized prevalence of HIV, TB and MDR-TB

drawAgents.m Function about visualizing agents on the Figure window.

3. Visualization of the Results

The agents were scattered and moved freely as circles. In the beginning, there are no TB disease in general (Figure 4) and a very small amount of agents displays it later (in red, Figure 5). TB does not drastically spread itself but we can observe its connections and transmission through the visualization.

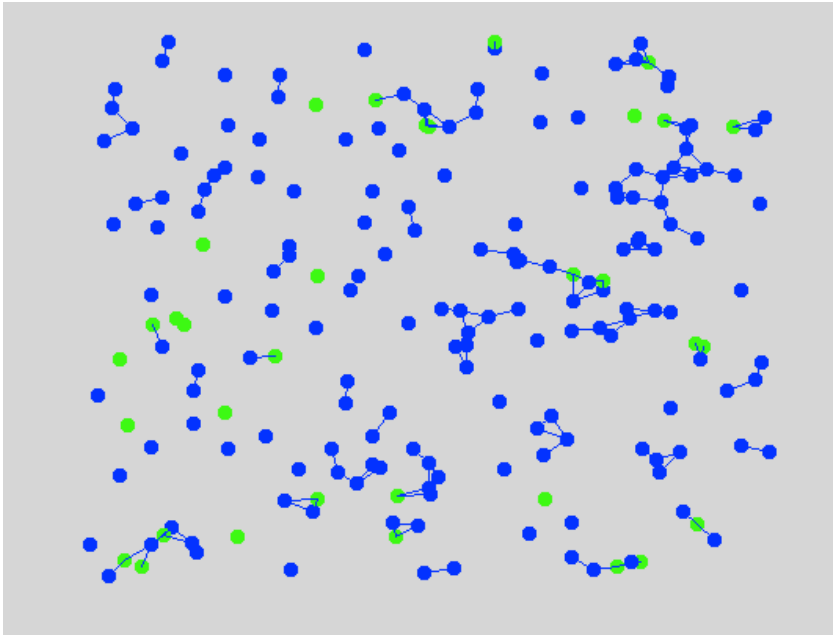

Figure 4. When the simulation has just begun

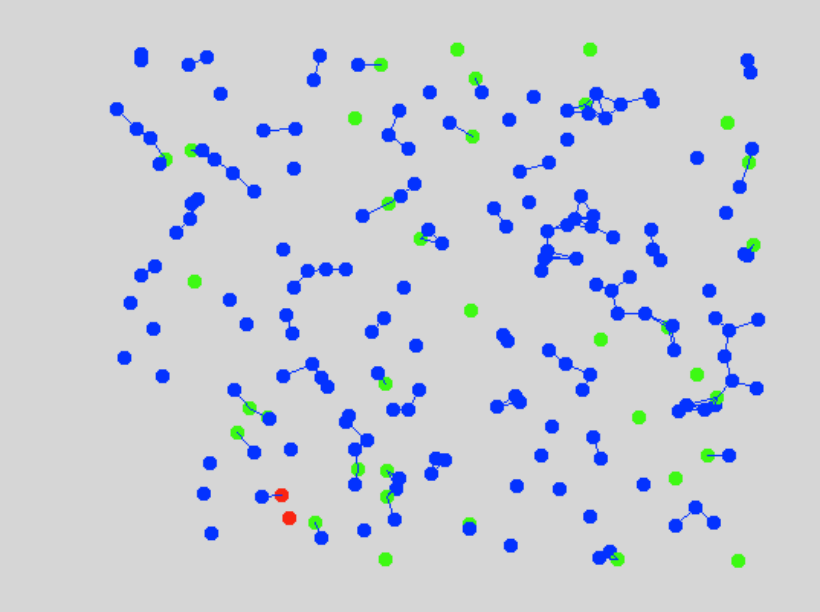

Figure 5. When MDR-TB has appeared (red agents)

4. Iteration Loop and Speed problem

```
function newcase=infection(agent,agents,probInf,probInfHIV,probPrm,probPrmHIV,probPrmMDR)
    % determine whether the susceptible individual will be infected
    % by contact with the neighbors who have TB disease
    % newly infected individuals could develop primary TB disease,
    % instead of entering latency
    % the probabilities depend on the HIV status and drug
    % susceptibility of the TB strain infected
    newcase=0;
    if agent.TBstatus==0
    for i=1:length(agents)
        dx=agent.x-agents(i).x;
        dy=agent.y-agents(i).y;
        if (dx<agent.maxD)&&(dy<agent.maxD)
        d=(dx*dx+dy*dy);
        if d<agent.maxD
            patch([agent.x agents(i).x],[agent.y agents(i).y],'k','EdgeColor','b')
            if agent.HIVstatus==0
                if (agents(i).TBstatus==2)&&(rand<probInf)
                    agent.TBstatus=1;
                    agent.MDRstatus=agents(i).MDRstatus;
                    if (agent.MDRstatus==0)&&(rand<probPrm)
                        agent.TBstatus=2;newcase=newcase+1;
                    elseif (agent.MDRstatus==1)&&(rand<probPrmMDR)
                        agent.TBstatus=2;newcase=newcase+1;
                    end
                end
            elseif agent.HIVstatus==1
                if (agents(i).TBstatus==2)&&(rand<probInfHIV)
                    agent.TBstatus=1;
                    agent.MDRstatus=agents(i).MDRstatus;
                    if (agent.MDRstatus==0)&&(rand<probPrmHIV)
                        agent.TBstatus=2;newcase=newcase+1;
                    elseif (agent.MDRstatus==1)&&(rand<probPrmMDR)
                        agent.TBstatus=2;newcase=newcase+1;
                    end
                end
            end
        end
         end

    end
    end
```

Figure 6. “Infection” method and checking neighbours

It has turned out, almost at the final stage of our implementation, that Continuous space based simulation with large number of agents can cause a considerable problem, in terms of the speed. The reason is here: in the most important method of class Agent, “infection” (Figure 6), we check neighbours each time through all existing agents. When the total number of agents is less than one hundred, the simulation goes quite smooth (Figure 7). However, the actual number we searched out for the ideal simulation was, for example, more than five hundred for South Korea. In this case, the figure window freezes after small amount of iteration (Figure 8) and it was not possible to continue any longer (although it depends on the capacity of the computer, it seems that it requires very high spec.)

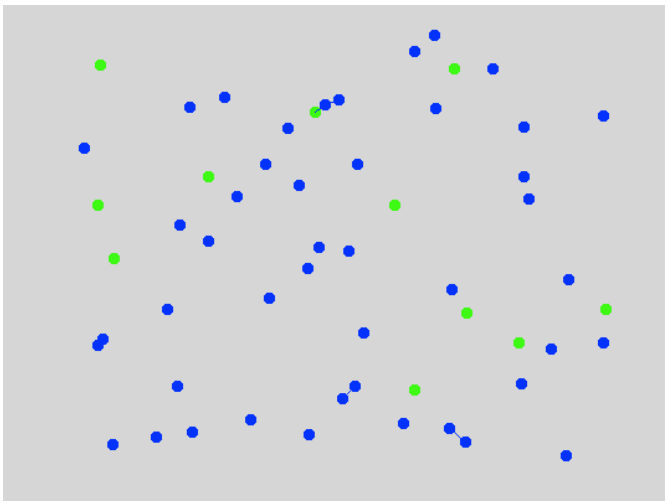

Figure 7. Number of agents less than 100

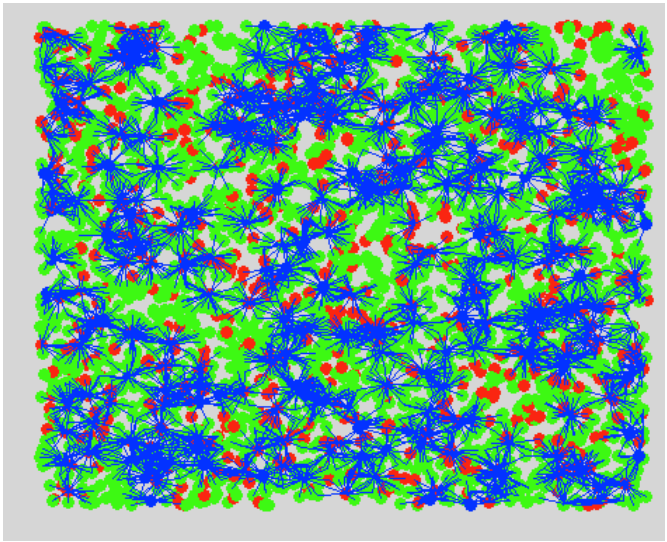

Figure 8. Number of agents more than 500

Removing neighbour lines did not help so much, and unfortunately, we could not improve this issue further due to the lack of time.

IV. Simulation Results and Discussion

1. Preliminary simulation

In South Africa(countryID=1), the preliminary simulations with a varying number of agents from 200 to 500 are done to find out which number of agents will give a realistic incidence in South Africa, 0.00971. For each simulation run the incidence was followed up for 30 years of time and their average was calculated and plotted. The simulation was 10 times repeated for each number of agents. As shown in Figure 9, agents < 450 result in no incidence and about 475 agents is thought to give a reasonable incidence. A very wide error bar means that this simulation could lead to a vast variety of different results. Considering this result, 475 is set as the number of agent in South Africa for further simulations.

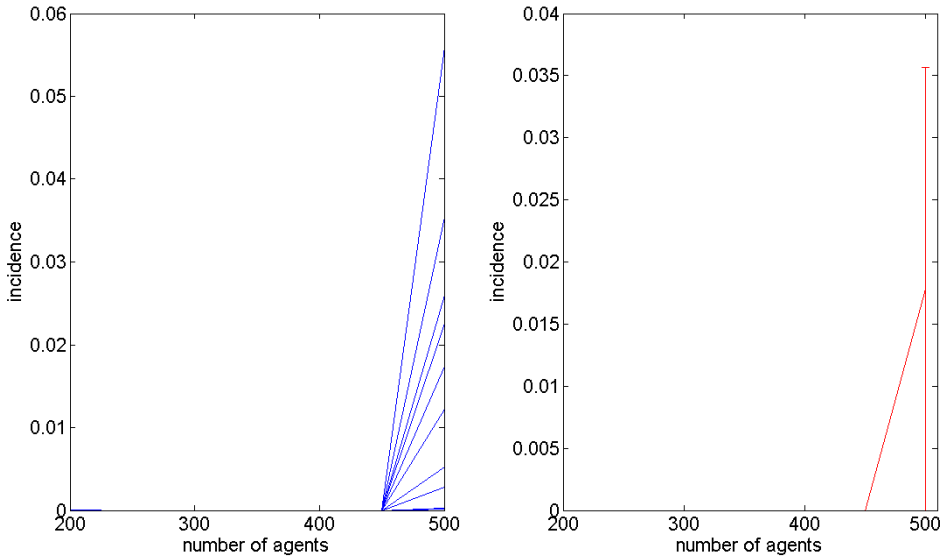

Figure 9. Preliminary simulation in South Africa: incidence in average of 30 years as a function of the number of agents for 10 different simulation runs. Left: each curve for one run. Right: average of every runs with error bars.

The appropriate number of agents is searched for China(countryID=2) in similar way. 200 to 500 agents have been shown not to be enough to reach the realistic value of incidence(Figure 10), so it was simulated once more with a higher range of

numbers(Figure 11). Based on the latter result, the number was decided to be 675 which is believed to probably give incidence in the range around the realistic value, 0.00096. Due to the vast variety of the result, however, it was not expected to result in a sustainable value.

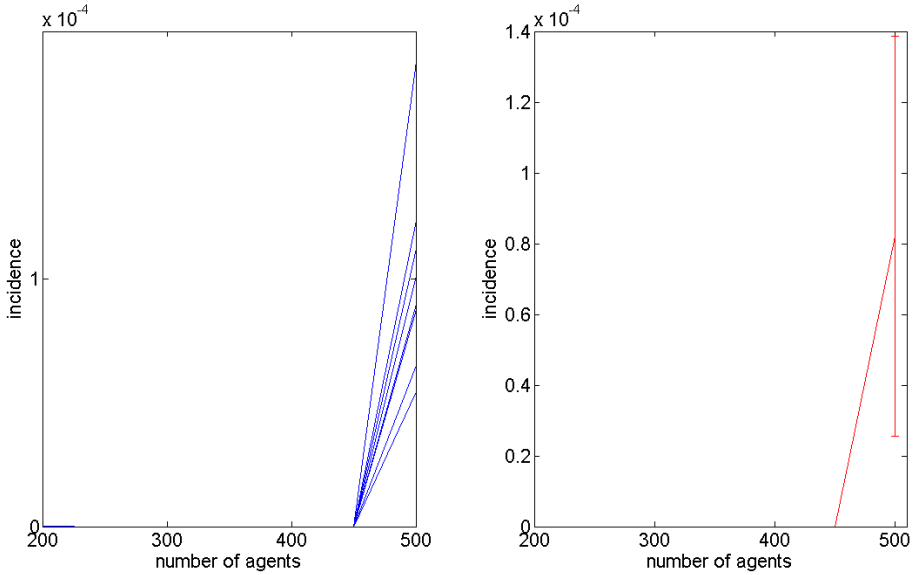

Figure 10. Preliminary simulation in China: incidence in average of 30 years as a function of the number of agents for 10 different simulation runs. Left: each curve for one run. Right: average of every runs with error bars.

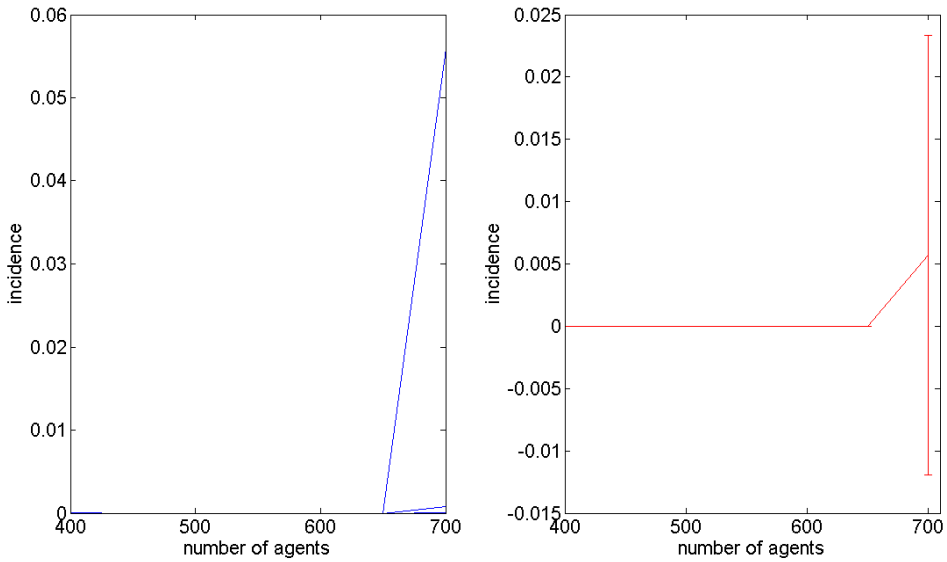

Figure 11. Second preliminary simulation in China: incidence in average of 30 years as a function of the number of agents for 10 different simulation runs. Left: each curve for one run. Right: average of every runs with error bars.

The results of preliminary simulations above imply that this agent-based modelling might be inadequate to simulate an epidemiology over a huge population. Even in a country of middle burden, the incidence remain in a range of 10^{-3} to 10^{-4}, for example 0.00090 in South Korea, which means that it may need to have more than 1000 agents to see at least one case each time step, a year, but it would be difficult to render a simulation with such high number of agents because of limited computing power. The number of agents needed would be much higher in case of middle or low burden country like Switzerland where the incidence remains around 10^{-5}. Considering that, we decided not to investigate further on middle or low burden country with a very low incidence and only focus on the high burden countries, South Africa and.

2. Evaluation of the impact chemoprophylaxis on MDR-TB prevalence

With the number of agents determined by the preliminary simulation above, the impact of the chemoprophylaxis in South Africa and China was examined. We repeated the simulation 20 times for each country with or without chemoprophylaxis to compensate the vast variety of possible results due to the relatively small number of agents.

South Africa

As shown in Figure 12, TB epidemiology has been shown to be getting worse for next couple of decades. After that time period the situation would be stabilized with a very high prevalence and incidence. Unlike some typical epidemiology describing infectious diseases, our model showed a plateau instead of a decrease after a peak. It is thought to be explained by the fact that the infected individuals usually don't get immunity, which makes TB even more special infectious disease.

The situation wouldn't be much different, if chemoprophylaxis is on act, except MDR-TB ratio. Prevalence of TB(blue curves in Figure 13 top) and MDR-TB(black curves in Figure 13 top) overlap nearly perfectly, which means almost all case of TB infection would consist of MDR-TB strains if chemoprophylaxis is chosen as a strategy to control TB over a whole population.

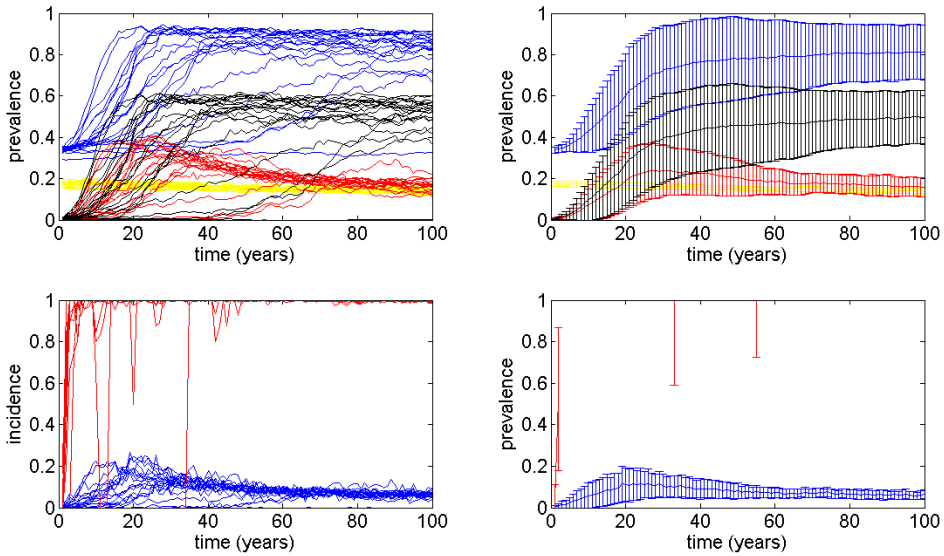

Figure 12. South Africa without chemoprophylaxis: Top: prevalence of HIV(yellow), TB in all forms(blue), TB disease(red) and MDR-TB(black) follow up for 100 years, Bottom: incidence(blue) and ratio of MDR-TB to total TB(red). Left: each curve for one run. Right: average of every runs with error bars.

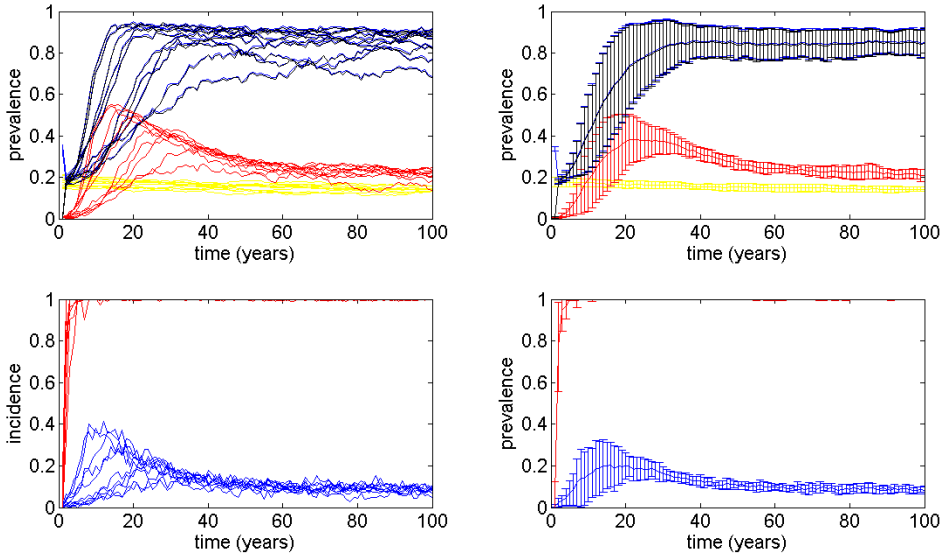

Figure 13. South Africa with chemoprophylaxis: Top: prevalence of HIV(yellow), TB in all forms(blue), TB disease(red) and MDR-TB(black) follow up for 100 years, Bottom: incidence(blue) and ratio of MDR-TB to total TB(red). Left: each curve for one run. Right: average of every runs with error bars.

China

In the simulation results of China(Figure 14 top), you can read approximately three different scenarios: (1) TB reaches a plateau after a burst period, similar to South Africa, (2) TB stays stable for a very long time and suddenly increases, (3) TB stays stable for the whole time period simulated. This higher inconsistency compared to South Africa would be explained by the fact that China has much lower incidence of TB than South Africa. Although China and South Africa are classified into high burden country in regard to TB, the incidence is much lower in China than South Africa, which is thought to be mainly due to the lower HIV prevalence. HIV positive individuals have weaker immune system and thus higher probability of getting infected and of developing disease by endogenous reactivation.

The impact of chemoprophylaxis in China seems to be the same as in South Africa: almost all TB cases come from MDR-TB strains (Figure 15).

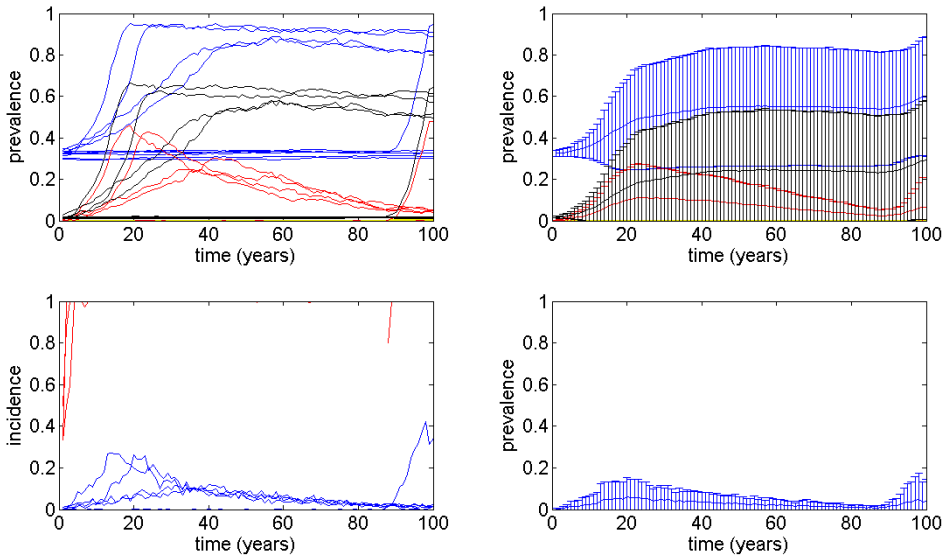

Figure 14. China without chemoprophylaxis: Top: prevalence of HIV(yellow), TB in all forms(blue), TB disease(red) and MDR-TB(black) follow up for 100 years, Bottom: incidence(blue) and ratio of MDR-TB to total TB(red). Left: each curve for one run. Right: average of every runs with error bars.

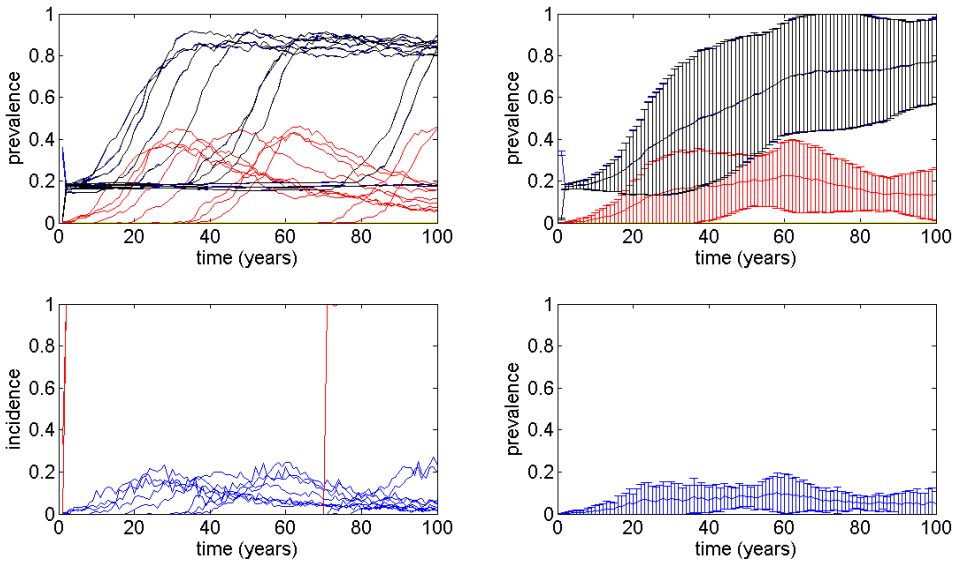

Figure 15. China with chemoprophylaxis: Top: prevalence of HIV(yellow), TB in all forms(blue), TB disease(red) and MDR-TB(black) follow up for 100 years, Bottom: incidence(blue) and ratio of MDR-TB to total TB(red). Left: each curve for one run. Right: average of every runs with error bars.

V. Summary and Outlook

We have realized couple of important remarks both in terms of an answer to our research question and in terms of implementation.

First of all, after all those simulations we conclude that Chemoprophylaxis eventually leads Tuberculosis bacteria to be more resistant, which means extremely high percentage of TB that survived Chemoprophylaxis becomes MDR-TB. This does not mean that number of people get infected increase, however, considering the hardships for curing MDR-TB (as discussed in the very beginning), this is a remarkable result on Chemoprophylaxis. Therefore it seems to us that having Chemoprophylaxis onto a large population would be careless and it should be conducted through limited target.

At the same time, our simulation strategy could not have thoroughly considered all the parameters about country environment and TB probabilities, due to the complexity of the realistic simulation. For the future, couple of strong limitations of this simulation should be reconsidered.

Secondly, about the way we structured the codes, we discovered that continuous space based simulation offers an elegant visualization, but depending on the final setup, it can make the execution extremely slow (due to checking numerous agents). This has to be studied further as a next step.

VI. References

[1] C.P. Bhunu, W. Garira, Z. Mukandavire, M. Zimba. *Tuberculosis Transmission Model with Chemoprophylaxis and Treatment,* Bulletin of Mathematical Biology 2008.

[2] C. Dye, B.G. Williams, *Criteria for the Control of Drug-Resistant Tuberculosis*, PNAS 2000.

[3] T.R. Frieden, T.R. Sterling, S.S. Munsiff, C.J. Watt, C. Dye, *Tuberculosis*, Lancet 2003.

[4] Global tuberculosis control, WHO report 2011.

[5] Country statistics from http://apps.who.int/ghodata/?vid=16300&theme=country (27.11.2011)

VII. Code

main.m

```
clear
% set the parameters varying dependent on countries
countrySetup
country=Country.empty(size(countries,2),0);
for i=1:size(countries,2)
    country(i).prevHIV=countries(2,i);
    country(i).prevTB=0.33;
    country(i).prevTBact=countries(3,i);
    country(i).incTB=countries(4,i);
    country(i).growth=countries(5,i);
    country(i).death=countries(6,i);
    country(i).deathTB=countries(7,i);
    country(i).deathHIV=countries(8,i);
    country(i).rateDet=countries(9,i);
    country(i).rateDetMDR=0.06;
    country(i).rateSuc=countries(10,i);
    country(i).rateSucMDR=0.6;
    country(i).ratioMDR=countries(11,i);
end

% set the pamameters about the TB itself
parameterSetup

% set the simulation conditions
N=200; % number of agents
M=100; % size of map
time=100; % time span in years
run=5; % number of simulations

countryID=1; % select a country to be simulated
chemo=1; % 1 if chemoprophylaxis is chosen as a strategy to control TB,
0 if not
rateChemSuc=0.5; % estimated success rate of chemoprophylaxis

% preallocate variables for epidemiological data concerned
rHIV=zeros(run,time+1);
rTBtot=zeros(run,time+1);rTBlat=zeros(run,time+1);rTBact=zeros(run,time+
1);
rMDRtot=zeros(run,time+1);rMDRlat=zeros(run,time+1);rMDRact=zeros(run,ti
me+1);
ratioMDR=zeros(run,time+1);
inc=zeros(run,time);

% initialize movie
mov = avifile('TB_movie.avi');

for j=1:run

% initialization of agents
agents=Agent.empty(N,0);

```

```
for i=1:N;
    agents(i).alive=1;
    agents(i).w=M;
    agents(i).h=M;
    agents(i).x=rand*M;
    agents(i).y=rand*M;
    % HIV and TB status of new born agents are determined according to
the
    % prevalences in the country chosen to be simulated
    if rand<country(countryID).prevHIV
        agents(i).HIVstatus=1;
    end
    if rand<country(countryID).prevTB
        agents(i).TBstatus=1;
        if rand<country(countryID).ratioMDR
            agents(i).MDRstatus=1;
        end
    end
    if rand<country(countryID).prevTBact
        agents(i).TBstatus=2;
        if rand<country(countryID).ratioMDR
            agents(i).MDRstatus=1;
        end
    end

end

% calculate the realized prevalence and incidence after initialization
[rHIV(j,1) rTBtot(j,1) rTBlat(j,1) rTBact(j,1) rMDRtot(j,1) rMDRlat(j,1)
rMDRact(j,1)]=realPrevalence(agents);
ratioMDR(j,1)=rMDRact(j,1)/rTBact(j,1);

figure()
for t=1:time
    % draw agents in the space
    drawAgentsInSpace

    % agent update
    agents2=agents;order=randperm(length(agents));
    for i=1:length(agents)
        % agents update in regard to the endogenous reactivation

inc(j,t)=inc(j,t)+agents2(order(i)).endoReact(probRct,probRctHIV);
        % agents update in regard to the natural cure
        agents2(order(i)).natCure(naturalCure);
        % agents update in regard to new infection by contact

inc(j,t)=inc(j,t)+agents2(order(i)).infection(agents,probInf,probInfHIV,
probPrm,probPrmHIV,probPrmMDR);
        % agents update in regard to standard therapies

agents2(order(i)).stdTherapy(country(countryID).rateDet,country(countryI
D).rateDetMDR,country(countryID).rateSuc,country(countryID).rateSucMDR);
        % agents update in regard to chemoprophylaxis only if the
strategy
        % is chosen
        if chemo==1

agents2(order(i)).chemoProphylaxis(rateChemSuc,country(countryID).rateDe
t);
        end
    end
    agents=agents2;
```

```
115
116         % birth and death of agents
117         for i=1:length(agents)
118
119     agents(i).mortality(country(countryID).death,country(countryID).deathTB,
120     country(countryID).deathHIV);
121         end
122         N2=round(country(countryID).growth*length(agents)+0.1*(rand-0.5));
123         if N2>0
124             for i=N+1:N+N2
125                 agents(i)=Agent;
126             end
127             N=N+N2;
128         end
129         % initialization of new born agents
130         for i=1:length(agents)
131             if agents(i).alive==0
132                 agents(i).alive=1;
133                 agents(i).w=M;
134                 agents(i).h=M;
135                 agents(i).x=rand*M;
136                 agents(i).y=rand*M;
137                 agents(i).HIVstatus=0;
138                 agents(i).TBstatus=0;
139                 agents(i).MDRstatus=0;
140                 if rand<country(countryID).prevHIV
141                     agents(i).HIVstatus=1;
142                 end
143                 if rand<country(countryID).prevTB
144                     agents(i).TBstatus=1;
145                     if rand<country(countryID).ratioMDR
146                         agents(i).MDRstatus=1;
147                     end
148                 end
149                 if rand<country(countryID).prevTBact
150                     agents(i).TBstatus=2;
151                     if rand<country(countryID).ratioMDR
152                         agents(i).MDRstatus=1;
153                     end
154                 end
155             end
156         end
157
158         % move agents
159         for i=1:length(agents)
160             agents(i)=agents(i).move();
161         end
162
163         % calculate the realized prevalence of HIV, TB and MDR-TB every year
164         [rHIV(j,t+1) rTBtot(j,t+1) rTBlat(j,t+1) rTBact(j,t+1)
165     rMDRtot(j,t+1) rMDRlat(j,t+1) rMDRact(j,t+1)]=realPrevalence(agents);
166         pause(0.01);
167         inc(j,t)=inc(j,t)/length(agents);
168
169         % create movie
170         F = getframe(gca);
171         mov=addframe(mov,F);
172     end
173
174     end
175     % close video file
176     mov=close(mov);
177     % save the result
```

```
save('','rHIV','rTBtot','rTBlat','rTBact','rMDRtot','rMDRlat','rMDRact',
'ratioMDR','inc')

plotResult
```

Agent.m

```
classdef Agent < handle
    % an agent is equivalent to an individual which belongs to
    % S(susceptible),E(latently infected),I(active disease),Em(latently
    % infected with MDR-TB strains) or Im(active disease with MDR-TB
    % strains)

    properties
        alive=0; % 0:dead, 1:alive
        x;y;w;h; % coordinates
        HIVstatus=0; % 0:HIV-negative, 1:HIV-positive
        TBstatus=0; % 0:susceptible, 1:latently infected, 2:active
disease
        MDRstatus=0; % 0:drug-susceptible TB, 1:MDR-TB
        speed=2.0;
        angle=0.0;
        maxD=25; % distance up to which contagion may occur
    end

    methods
        function newcase=endoReact(agent,probRct,probRctHIV)
            % determine whether the latently infected individual will
            % progress into the active TB
            % probability is dependent on the individual's HIV status
            newcase=0;
            if (agent.TBstatus==1)&&(agent.HIVstatus==0)
                if rand<probRct
                    agent.TBstatus=2;newcase=newcase+1;
                end
            end
            if (agent.TBstatus==1)&&(agent.HIVstatus==1)
                if rand<probRctHIV
                    agent.TBstatus=2;newcase=newcase+1;
                end
            end
        end

        function agent=natCure(agent,rate)
            % determine whether the active TB will be cured naturally
            if (agent.TBstatus==2)&&(rand<rate)
                agent.TBstatus=0;agent.MDRstatus=0;
            end
        end

        function
newcase=infection(agent,agents,probInf,probInfHIV,probPrm,probPrmHIV,pro
bPrmMDR)
            % determine whether the susceptible individual will be
infected
            % by contact with the neighbors who have TB disease
            % newly infected individuals could develop primary TB
disease,
```

```
            % instead of entering latency
            % the probabilities depend on the HIV status and drug
            % susceptibility of the TB strain infected
            newcase=0;
            if agent.TBstatus==0
            for i=1:length(agents)
                dx=agent.x-agents(i).x;
                dy=agent.y-agents(i).y;
                if (dx<agent.maxD)&&(dy<agent.maxD)
                d=(dx*dx+dy*dy);
                if d<agent.maxD
                    patch([agent.x agents(i).x],[agent.y
agents(i).y],'k','EdgeColor','b')
                    if agent.HIVstatus==0
                        if (agents(i).TBstatus==2)&&(rand<probInf)
                            agent.TBstatus=1;
                            agent.MDRstatus=agents(i).MDRstatus;
                            if (agent.MDRstatus==0)&&(rand<probPrm)
                                agent.TBstatus=2;newcase=newcase+1;
                            elseif
(agent.MDRstatus==1)&&(rand<probPrmMDR)
                                agent.TBstatus=2;newcase=newcase+1;
                            end
                        end
                    elseif agent.HIVstatus==1
                        if (agents(i).TBstatus==2)&&(rand<probInfHIV)
                            agent.TBstatus=1;
                            agent.MDRstatus=agents(i).MDRstatus;
                            if (agent.MDRstatus==0)&&(rand<probPrmHIV)
                                agent.TBstatus=2;newcase=newcase+1;
                            elseif
(agent.MDRstatus==1)&&(rand<probPrmMDR)
                                agent.TBstatus=2;newcase=newcase+1;
                            end
                        end
                    end
                end
                 end

            end
            end
        end

        function
agent=stdTherapy(agent,rateDet,rateDetMDR,rateSuc,rateSucMDR)
            % determine whether the individual with active TB will be
cured
            % by standard drug therapy
            % TB can be cured only when the disease is correctly
diagnosed
            % and the drug regimen succeeds
            % if the drug regimen fails, the originally drug-susceptible
TB
            % strains become resistant
            if (agent.TBstatus==2)&&(agent.MDRstatus==0)
                if (rand<rateDet)
                    if (rand<rateSuc)
                        agent.TBstatus=0;agent.MDRstatus=0;
                    else
                        agent.MDRstatus=1;
                    end
                end
            elseif (agent.TBstatus==2)&&(agent.MDRstatus==1)
                if (rand<rateDetMDR)&&(rand<rateSucMDR)
```

```
                    agent.TBstatus=0;agent.MDRstatus=0;
                end
            end

        end

        function agent=chemoProphylaxis(agent,rate,rateDet)
            % determine whether the TB in latency will be eliminated
from
            % the individual by chemoprophylaxis
            % if the regimen fails, the originally drug-susceptible TB
            % strains become resistant
            % if the indivual is infected with MDR-TB strains, it won't
be
            % eliminated
            if (agent.TBstatus==1)&&(agent.MDRstatus==0)
                if rand<rate
                    agent.TBstatus=0;
                else
                    agent.MDRstatus=1;
                end
            elseif
(agent.TBstatus==2)&&(agent.MDRstatus==0)&&(rand>rateDet)
                agent.MDRstatus=1;
            end
        end

        function agent=move(agent)
            % agents move once a year in a continuous space
            agent.angle=agent.angle+(rand-0.5)*pi;

            agent.x=agent.x+agent.speed*cos(agent.angle);
            agent.y=agent.y+agent.speed*sin(agent.angle);

            if agent.x>agent.w
                agent.x=agent.x-agent.w;
            end
            if agent.y>agent.h
                agent.y=agent.y-agent.h;
            end
            if agent.x<0
                agent.x=agent.w+agent.x;
            end
            if agent.y<0
                agent.y=agent.h+agent.y;
            end

        end

        function agent=mortality(agent,death,deathTB,deathHIV)
            % determine whether the individual will die in this year
            % mortality depends on TB and HIV status of the individual
            rate=death;
            if agent.TBstatus==2
                rate=rate+deathTB;
            end
            if agent.HIVstatus==1
                rate=rate+deathHIV;
            end
            if rand<rate
                agent.alive=0;
            end
        end
```

```
179
180         end
181
182     end
```

parameterSetup.m

```
1   probInf=0.35; % probability of infection
2   probInfHIV=0.4; % probability of infection in HIV positive individuals
3   probPrm=0.14; % probability of development into primary TB in newly
4   infected
5   probPrmHIV=0.67; % probability of development into primary TB in HIV
6   positive individuals
7   probPrmMDR=0.88; % probability of development into primary TB in the
8   infected with MDR-TB strains
9   probRct=0.000113; % probability of endogenous reactivation
10  probRctHIV=0.003; % probability of endogenous reactivation in HIV
11  positive individuals
12  naturalCure=0.2; % natural cure rate
```

Country.m

```
1   classdef Country
2       % a country is defined by several parameters that are taken into
3       % account in evaluation of TB epidemiology
4
5       properties
6           prevHIV; % prevalence of HIV
7           prevTB; % prevalence of all forms TB
8           prevTBact; % prevalence of TB disease
9           incTB; % incidnece of TB disease
10          growth; % annual population growth rate
11          death; % death rate per yr, estimated from adult mortality rate
12          deathTB; % additional death rate due to TB per yr
13          deathHIV; % additional death rate due to HIV
14          rateDet; % case detection rate for all forms of TB
15          rateDetMDR; % case detection rate in case of MDR-TB strains
16          rateSuc; % TB treatment success rate
17          rateSucMDR; % TB treatment success rate in case of MDR-TB
18  strains
19          ratioMDR; % ratio of the MDR-TB cases among new TB cases
20      end
21
22      methods
23      end
24
25  end
```

countrySetup.m

```
% country profiles from WHO
% 1: SouthAfrica, 2: China, 3: Republic of Korea, 4: Switzerland
countries=[1 2 3 4
    0.178 0.001 0.0005 0.004  % prevalence of HIV, 0.05 is estimated
    0.00808 0.00138 0.00114 0.00006 % prevalence of TB disease
    0.00971 0.00096 0.00090 0.000049 % incidence of TB per yr
    0.001 0.001 0 0 % annual population growth rate
    0.015111 0.002736 0.001803 0.001327 % death rate per yr, estimated
from adult mortality rate
    0.00052 0.00012 0.000083 0.0000017 % additional death rate due to TB
per yr
    0.00627 0.000019 0 0 % additional death rate due to HIV
    0.72 0.75 0.89 0.89 % case detection rate for all forms of TB
    0.76 0.94 0.84 0.85 % TB treatment success rate, 0.85 is estimated
    0.018 0.057 0.027 0.012 % ratio of the MDR-TB cases among new TB
cases
    ];
```

preSearch.m

```
clear
% set the parameters varying dependent on countries
countrySetup
country=Country.empty(size(countries,2),0);
for i=1:size(countries,2)
    country(i).prevHIV=countries(2,i);
    country(i).prevTB=0.33;
    country(i).prevTBact=countries(3,i);
    country(i).incTB=countries(4,i);
    country(i).growth=countries(5,i);
    country(i).death=countries(6,i);
    country(i).deathTB=countries(7,i);
    country(i).deathHIV=countries(8,i);
    country(i).rateDet=countries(9,i);
    country(i).rateDetMDR=0.06;
    country(i).rateSuc=countries(10,i);
    country(i).rateSucMDR=0.6;
    country(i).ratioMDR=countries(11,i);
end

% set the pamameters about the TB itself
parameterSetup

% set the simulation conditions
M=100; % size of map
time=30; % time span in years
run=10; % number of simulations

countryID=3; % select a country to be simulated
chemo=0; % 1 if chemoprophylaxis is chosen as a strategy to control TB,
0 if not
rateChemSuc=0.5; % estimated success rate of chemoprophylaxis

k=0;
for N=400:50:700
k=k+1;
inc=zeros(7,run,time);
N
for j=1:run
j
```

```
% initialization of agents
agents=Agent.empty(N,0);

for i=1:N;
    agents(i).alive=1;
    agents(i).w=M;
    agents(i).h=M;
    agents(i).x=rand*M;
    agents(i).y=rand*M;
    % HIV and TB status of new born agents are determined according to
the
    % prevalences in the country chosen to be simulated
    if rand<country(countryID).prevHIV
        agents(i).HIVstatus=1;
    end
    if rand<country(countryID).prevTB
        agents(i).TBstatus=1;
        if rand<country(countryID).ratioMDR
            agents(i).MDRstatus=1;
        end
    end
    if rand<country(countryID).prevTBact
        agents(i).TBstatus=2;
        if rand<country(countryID).ratioMDR
            agents(i).MDRstatus=1;
        end
    end

end

for t=1:time

    % agent update
    agents2=agents;order=randperm(length(agents));
    for i=1:length(agents)
        % agents update in regard to the endogenous reactivation

inc(k,j,t)=inc(k,j,t)+agents2(order(i)).endoReact(probRct,probRctHIV);
        % agents update in regard to the natural cure
        agents2(order(i)).natCure(naturalCure);
        % agents update in regard to new infection by contact

inc(k,j,t)=inc(k,j,t)+agents2(order(i)).infection(agents,probInf,probInf
HIV,probPrm,probPrmHIV,probPrmMDR);
        % agents update in regard to standard therapies

agents2(order(i)).stdTherapy(country(countryID).rateDet,country(countryI
D).rateDetMDR,country(countryID).rateSuc,country(countryID).rateSucMDR);
        % agents update in regard to chemoprophylaxis only if the
strategy
        % is chosen
        if chemo==1

agents2(order(i)).chemoProphylaxis(rateChemSuc,country(countryID).rateDe
t);
        end
    end
    agents=agents2;

    % birth and death of agents
    for i=1:length(agents)

agents(i).mortality(country(countryID).death,country(countryID).deathTB,
```

```
country(countryID).deathHIV);
    end
    N2=round(country(countryID).growth*length(agents)+0.1*(rand-0.5));
    if N2>0
        for i=N+1:N+N2
            agents(i)=Agent;
        end
        N=N+N2;
    end
    % initialization of new born agents
    for i=1:length(agents)
        if agents(i).alive==0
            agents(i).alive=1;
            agents(i).w=M;
            agents(i).h=M;
            agents(i).x=rand*M;
            agents(i).y=rand*M;
            agents(i).HIVstatus=0;
            agents(i).TBstatus=0;
            agents(i).MDRstatus=0;
            if rand<country(countryID).prevHIV
                agents(i).HIVstatus=1;
            end
            if rand<country(countryID).prevTB
                agents(i).TBstatus=1;
                if rand<country(countryID).ratioMDR
                    agents(i).MDRstatus=1;
                end
            end
            if rand<country(countryID).prevTBact
                agents(i).TBstatus=2;
                if rand<country(countryID).ratioMDR
                    agents(i).MDRstatus=1;
                end
            end
        end
    end

    % move agents
    for i=1:length(agents)
        agents(i)=agents(i).move();
    end

    % calculate the incidence
    inc(k,j,t)=inc(k,j,t)/length(agents);

end

end
end
save('SouthKorea_preliminary','inc')
averInc=zeros(run,7);
for k=1:7
    for j=1:run
        for t=1:time
            averInc(j,k)=averInc(j,k)+inc(k,j,t);
        end
        averInc(j,k)=averInc(j,k)/time;
    end
end
subplot(1,2,1)
plot(400:50:700,averInc,'b')
set(gca,'FontSize',16)
xlabel('number of agents','FontSize',16)
```

```
168 ylabel('incidence','FontSize',16)
169 xlim([400 700])
170 subplot(1,2,2)
171 errorbar(400:50:700,mean(averInc),std(averInc),'r')
172 set(gca,'FontSize',16)
173 xlabel('number of agents','FontSize',16)
174 ylabel('incidence','FontSize',16)
175 xlim([400 710])
```

realPrevalence.m

```
1  function [ rHIV,rTBtot,rTBlat,rTBact,rMDRtot,rMDRlat,rMDRact ] =
2  realPrevalence( agents )
3  % calculate the realized prevalence of HIV, TB and MDR-TB
4  HIV=zeros(length(agents),1);
5  TBtot=zeros(length(agents),1);
6  TBlat=zeros(length(agents),1);
7  TBact=zeros(length(agents),1);
8  MDRtot=zeros(length(agents),1);
9  MDRlat=zeros(length(agents),1);
10 MDRact=zeros(length(agents),1);
11 for i=1:length(agents)
12     HIV(i)=agents(i).HIVstatus==1;
13     TBtot(i)=(agents(i).TBstatus==1)||(agents(i).TBstatus==2);
14     TBlat(i)=agents(i).TBstatus==1;
15     TBact(i)=agents(i).TBstatus==2;
16     MDRtot(i)=agents(i).MDRstatus==1;
17     MDRlat(i)=(agents(i).TBstatus==1)&&(agents(i).MDRstatus==1);
18     MDRact(i)=(agents(i).TBstatus==2)&&(agents(i).MDRstatus==1);
19 end
20 rHIV=sum(HIV)/length(agents);
21 rTBtot=sum(TBtot)/length(agents);
22 rTBlat=sum(TBlat)/length(agents);
23 rTBact=sum(TBact)/length(agents);
24 rMDRtot=sum(MDRtot)/length(agents);
25 rMDRlat=sum(MDRlat)/length(agents);
26 rMDRact=sum(MDRact)/length(agents);
27
28 end
```

drawAgents.m

```
1    % draw agents in the space
2      drawAgents=zeros(length(agents),3);
3      for i=1:length(agents)
4          drawAgents(i,1)=agents(i).x;
5          drawAgents(i,2)=agents(i).y;
6          drawAgents(i,3)=agents(i).TBstatus;
7      end
8
9  scatter(drawAgents(:,1),drawAgents(:,2),50,drawAgents(:,3),'filled');
10     box on
11     axis off
12     colormap([0 0 1;0 1 0.5;1 0 0]);
```