ETH

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

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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

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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.
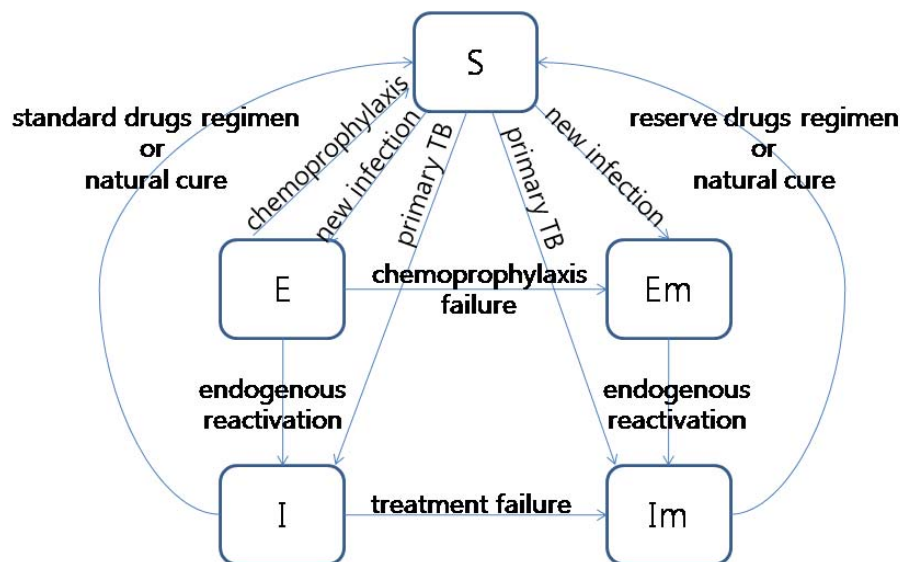

Figure 1. Structure of model. Population change due to birth and death from each compartments are not shown here.

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			
Im to S	inappropriate chemoprophylaxis	+/-	-	1-0.72 = 0.28	1-0.75 = 0.25	1-0.89 = 0.11	1-0.89 = 0.11
	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.
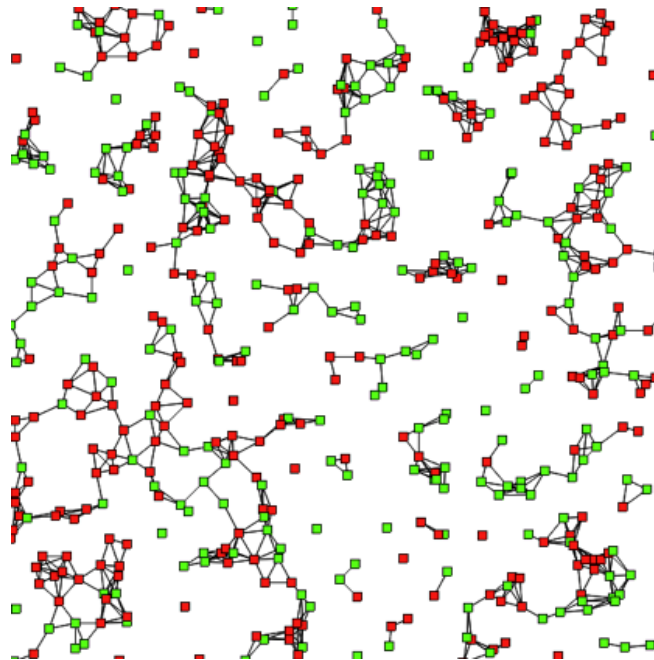

Figure 2. Initial graphical sketch of Agent Based Modelling
in Continuous Space

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.
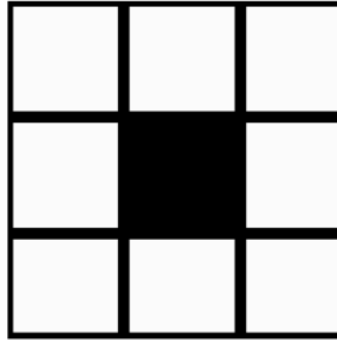
Figure 3. Grid based modelling and neighbours.

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.
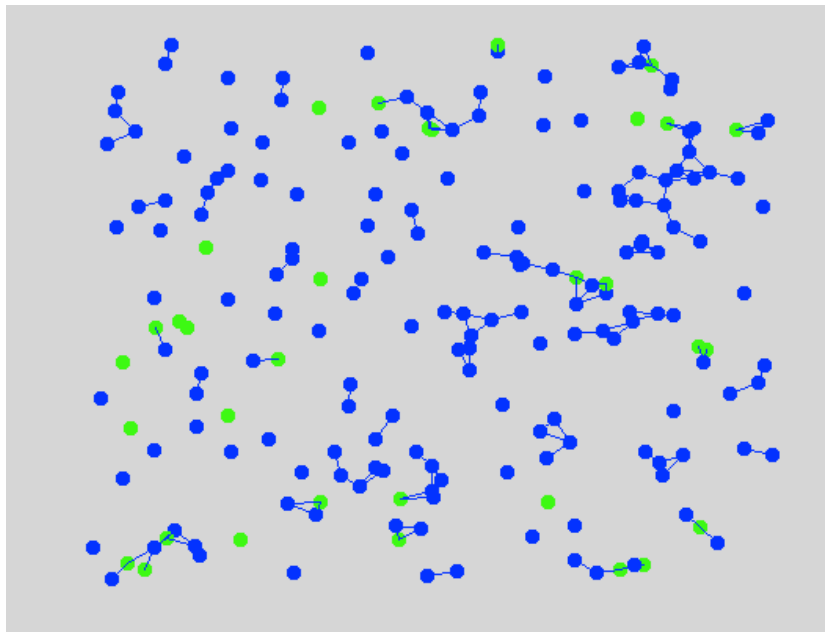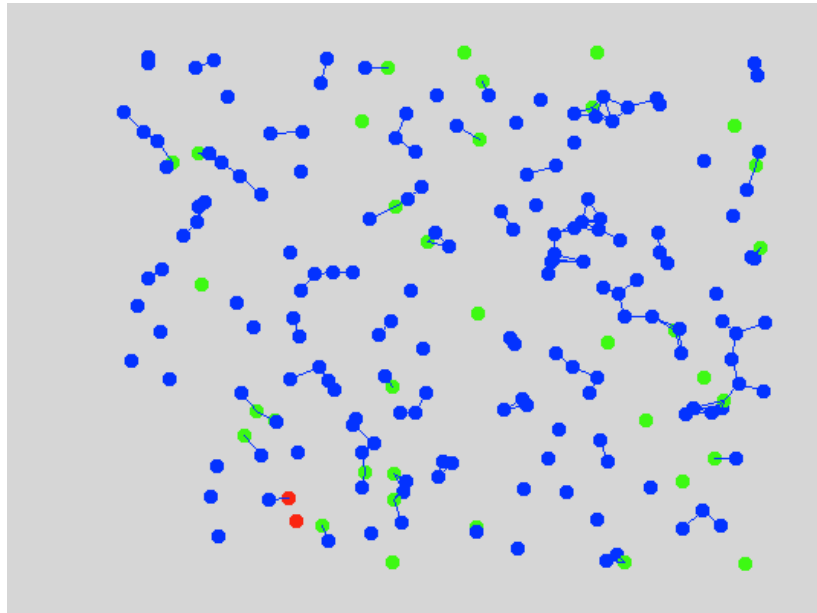

Figure 4. When the simulation has just begun

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
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.)
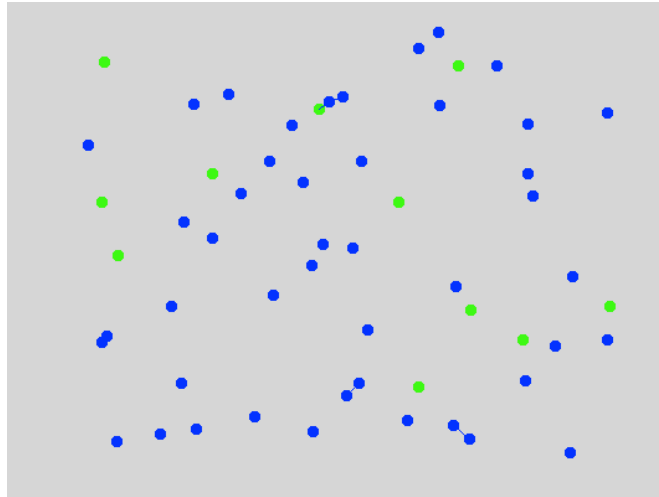

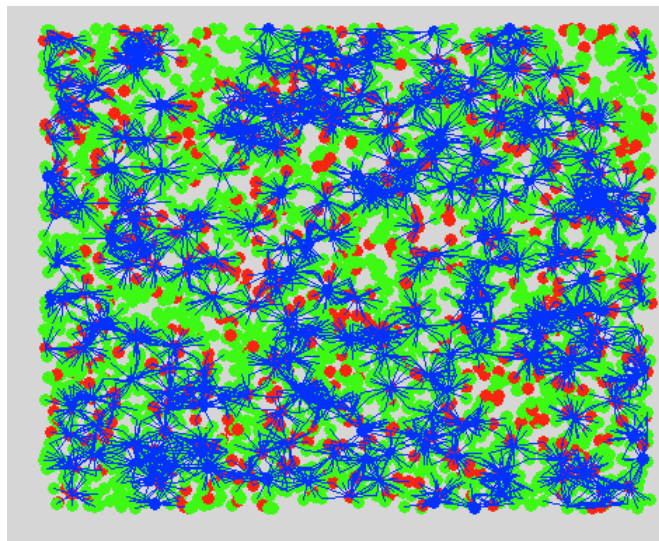
Figure 7. Number of agents less than 100

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.
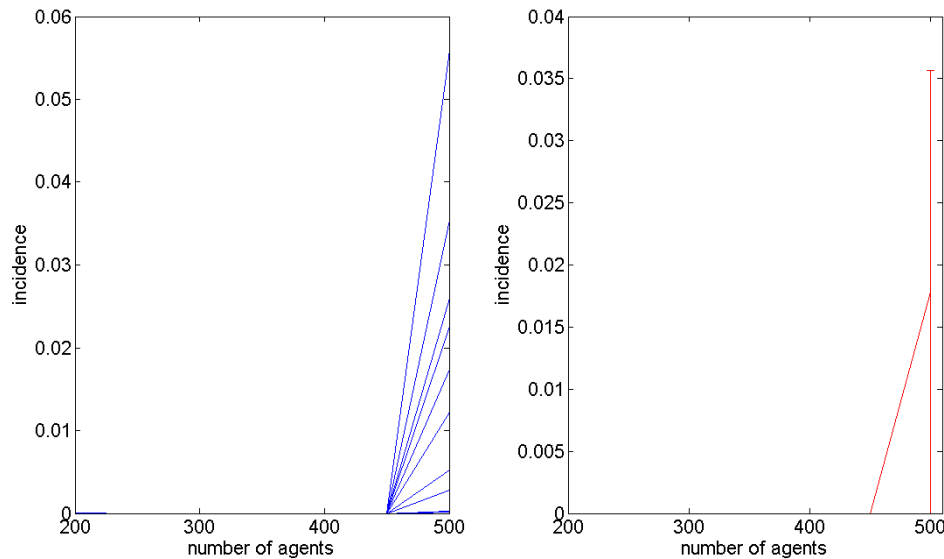

Figure 10. Preliminary simulation in China: incidence in average of 30 years as a function of the number of agents for 10 different simulation runs. Left: each curve for one run. Right: average of every runs with error bars.

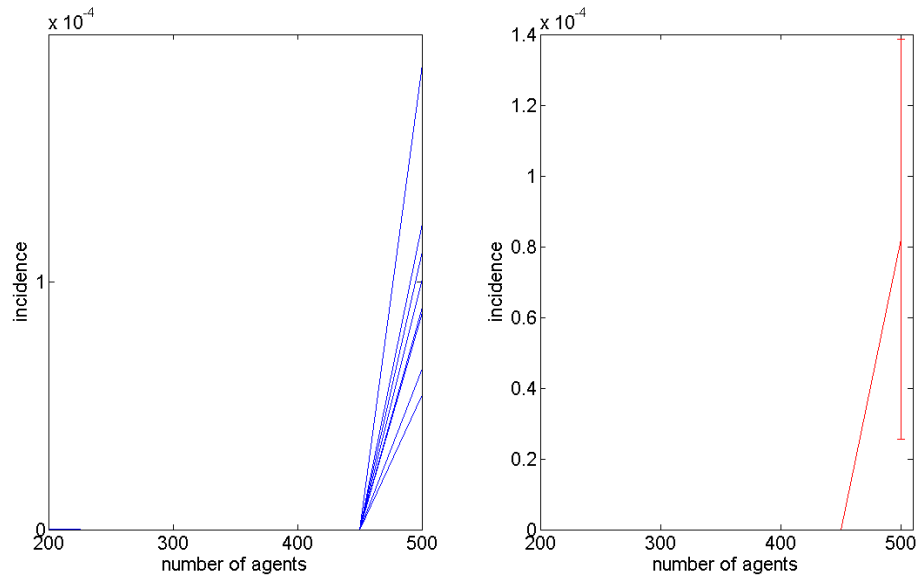**Figure 11. Second preliminary simulation in China:** incidence in average of 30 years as a function of the number of agents for 10 different simulation runs. Left: each curve for one run. Right: average of every runs with error bars.
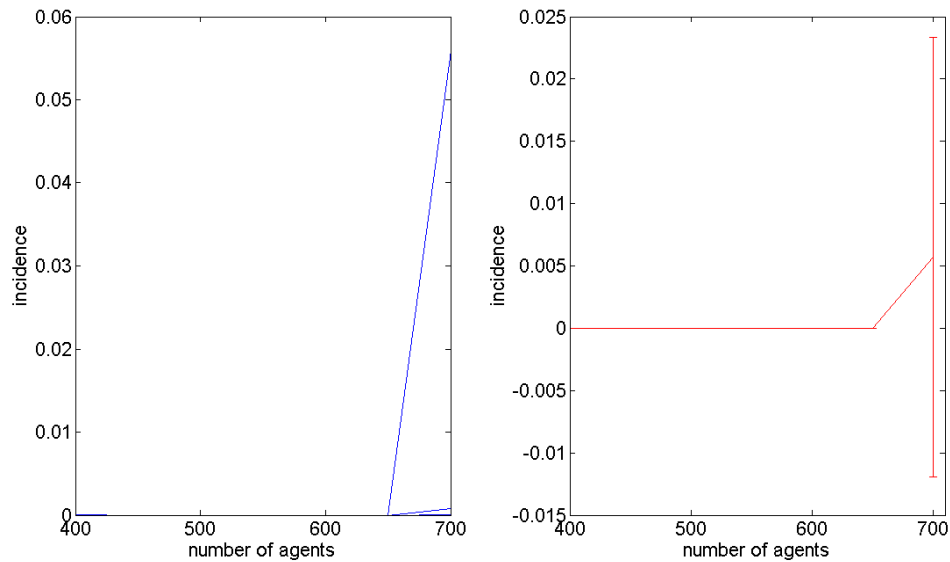
16

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).
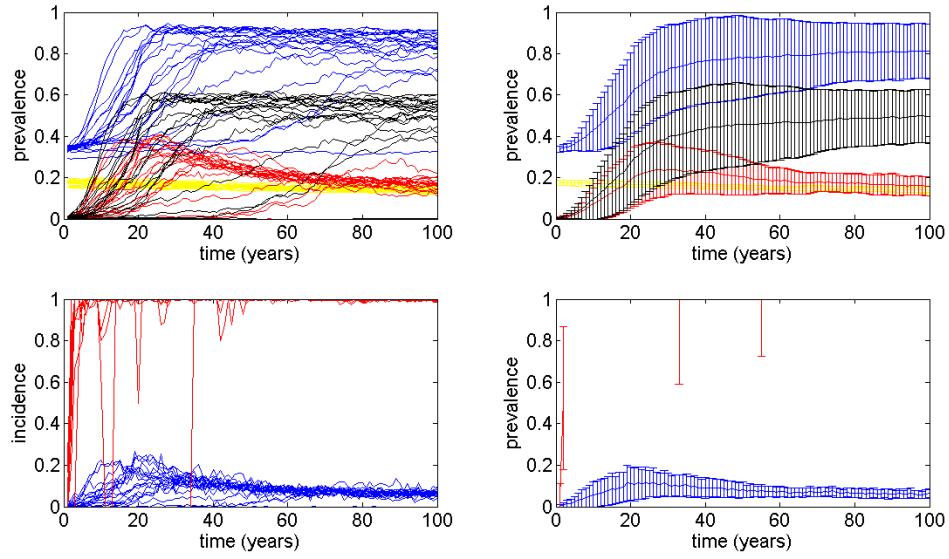

Figure 14. China without chemoprophylaxis: Top: prevalence of HIV(yellow), TB in all forms(blue), TB disease(red) and MDR-TB(black) follow up for 100 years, Bottom: incidence(blue) and ratio of MDR-TB to total TB(red). Left: each curve for one run. Right: average of every runs with error bars.
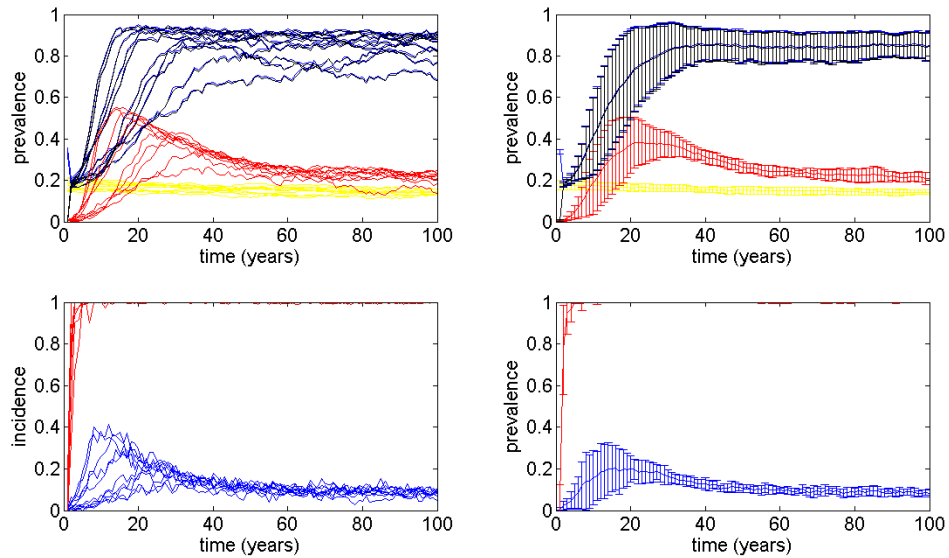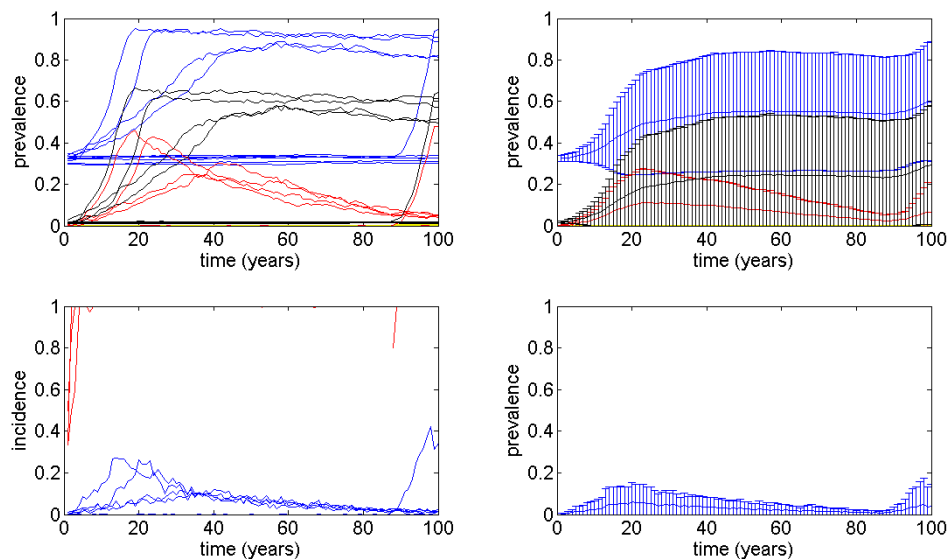
Figure 15. China with chemoprophylaxis: Top: prevalence of HIV(yellow), TB in all forms(blue), TB disease(red) and MDR-TB(black) follow up for 100 years, Bottom: incidence(blue) and ratio of MDR-TB to total TB(red). Left: each curve for one run. Right: average of every runs with error bars.
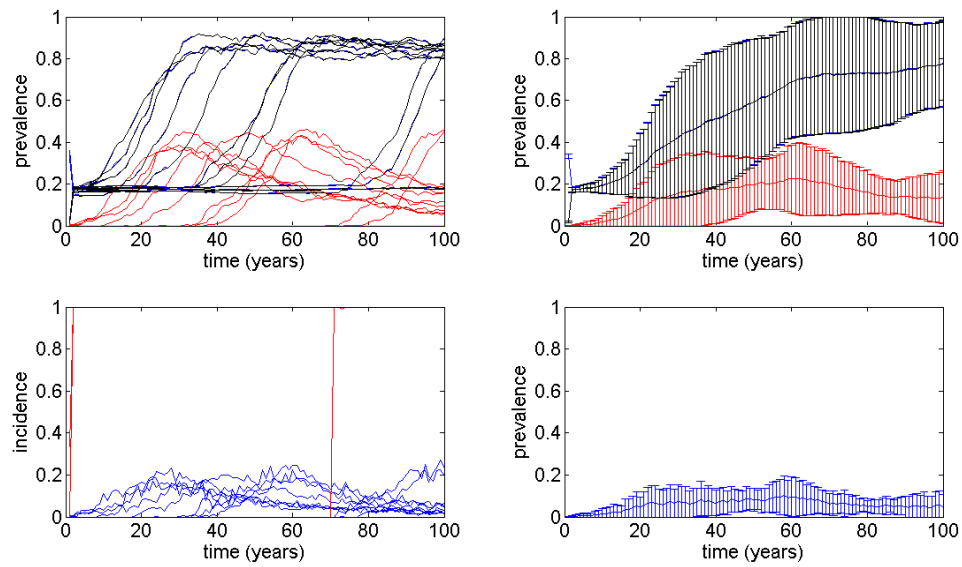
V. Summary and Outlook

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

```matlab
1   clear
2   % set the parameters varying dependent on countries
3   countrySetup
4   country=Country.empty(size(countries,2),0);
5   for i=1:size(countries,2)
6       country(i).prevHIV=countries(2,i);
7       country(i).prevTB=0.33;
8       country(i).prevTBact=countries(3,i);
9       country(i).incTB=countries(4,i);
10      country(i).growth=countries(5,i);
11      country(i).death=countries(6,i);
12      country(i).deathTB=countries(7,i);
13      country(i).deathHIV=countries(8,i);
14      country(i).rateDet=countries(9,i);
15      country(i).rateDetMDR=0.06;
16      country(i).rateSuc=countries(10,i);
17      country(i).rateSucMDR=0.6;
18      country(i).ratioMDR=countries(11,i);
19  end
20
21  % set the pamameters about the TB itself
22  parameterSetup
23
24  % set the simulation conditions
25  N=200; % number of agents
26  M=100; % size of map
27  time=100; % time span in years
28  run=5; % number of simulations
29
30  countryID=1; % select a country to be simulated
31  chemo=1; % 1 if chemoprophylaxis is chosen as a strategy to control TB,
32  0 if not
33  rateChemSuc=0.5; % estimated success rate of chemoprophylaxis
34
35  % preallocate variables for epidemiological data concerned
36  rHIV=zeros(run,time+1);
37  rTBtot=zeros(run,time+1);rTBlat=zeros(run,time+1);rTBact=zeros(run,time+
38  1);
39  rMDRtot=zeros(run,time+1);rMDRlat=zeros(run,time+1);rMDRact=zeros(run,ti
40  me+1);
41  ratioMDR=zeros(run,time+1);
42  inc=zeros(run,time);
43
44  % initialize movie
45  mov = avifile('TB_movie.avi');
46
47  for j=1:run
48
49  % initialization of agents
50  agents=Agent.empty(N,0);
51
```

```matlab
52      for i=1:N;
53          agents(i).alive=1;
54          agents(i).w=M;
55          agents(i).h=M;
56          agents(i).x=rand*M;
57          agents(i).y=rand*M;
58          % HIV and TB status of new born agents are determined according to
59      the
60          % prevalences in the country chosen to be simulated
61          if rand<country(countryID).prevHIV
62              agents(i).HIVstatus=1;
63          end
64          if rand<country(countryID).prevTB
65              agents(i).TBstatus=1;
66              if rand<country(countryID).ratioMDR
67                  agents(i).MDRstatus=1;
68              end
69          end
70          if rand<country(countryID).prevTBact
71              agents(i).TBstatus=2;
72              if rand<country(countryID).ratioMDR
73                  agents(i).MDRstatus=1;
74              end
75          end
76
77      end
78
79      % calculate the realized prevalence and incidence after initialization
80      [rHIV(j,1) rTBtot(j,1) rTBlat(j,1) rTBact(j,1) rMDRtot(j,1) rMDRlat(j,1)
81      rMDRact(j,1)]=realPrevalence(agents);
82      ratioMDR(j,1)=rMDRact(j,1)/rTBact(j,1);
83
84      figure()
85      for t=1:time
86          % draw agents in the space
87          drawAgentsInSpace
88
89          % agent update
90          agents2=agents;order=randperm(length(agents));
91          for i=1:length(agents)
92              % agents update in regard to the endogenous reactivation
93
94      inc(j,t)=inc(j,t)+agents2(order(i)).endoReact(probRct,probRctHIV);
95              % agents update in regard to the natural cure
96              agents2(order(i)).natCure(naturalCure);
97              % agents update in regard to new infection by contact
98
99      inc(j,t)=inc(j,t)+agents2(order(i)).infection(agents,probInf,probInfHIV,
100     probPrm,probPrmHIV,probPrmMDR);
101             % agents update in regard to standard therapies
102
103     agents2(order(i)).stdTherapy(country(countryID).rateDet,country(countryI
104     D).rateDetMDR,country(countryID).rateSuc,country(countryID).rateSucMDR);
105             % agents update in regard to chemoprophylaxis only if the
106     strategy
107             % is chosen
108             if chemo==1
109
110     agents2(order(i)).chemoProphylaxis(rateChemSuc,country(countryID).rateDe
111     t);
112             end
113         end
114         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
```

```
178    save('','rHIV','rTBtot','rTBlat','rTBact','rMDRtot','rMDRlat','rMDRact',
179    'ratioMDR','inc')
180
181    plotResult
```

Agent.m

```
1    classdef Agent < handle
2        % an agent is equivalent to an individual which belongs to
3        % S(susceptible),E(latently infected),I(active disease),Em(latently
4        % infected with MDR-TB strains) or Im(active disease with MDR-TB
5        % strains)
6
7        properties
8            alive=0; % 0:dead, 1:alive
9            x;y;w;h; % coordinates
10           HIVstatus=0; % 0:HIV-negative, 1:HIV-positive
11           TBstatus=0; % 0:susceptible, 1:latently infected, 2:active
12   disease
13           MDRstatus=0; % 0:drug-susceptible TB, 1:MDR-TB
14           speed=2.0;
15           angle=0.0;
16           maxD=25; % distance up to which contagion may occur
17       end
18
19       methods
20           function newcase=endoReact(agent,probRct,probRctHIV)
21               % determine whether the latently infected individual will
22               % progress into the active TB
23               % probability is dependent on the individual's HIV status
24               newcase=0;
25               if (agent.TBstatus==1)&&(agent.HIVstatus==0)
26                   if rand<probRct
27                       agent.TBstatus=2;newcase=newcase+1;
28                   end
29               end
30               if (agent.TBstatus==1)&&(agent.HIVstatus==1)
31                   if rand<probRctHIV
32                       agent.TBstatus=2;newcase=newcase+1;
33                   end
34               end
35           end
36
37           function agent=natCure(agent,rate)
38               % determine whether the active TB will be cured naturally
39               if (agent.TBstatus==2)&&(rand<rate)
40                   agent.TBstatus=0;agent.MDRstatus=0;
41               end
42           end
43
44           function
45   newcase=infection(agent,agents,probInf,probInfHIV,probPrm,probPrmHIV,pro
46   bPrmMDR)
47               % determine whether the susceptible individual will be
48   infected
49               % by contact with the neighbors who have TB disease
50               % newly infected individuals could develop primary TB
51   disease,
```

```matlab
52                    % instead of entering latency
53                    % the probabilities depend on the HIV status and drug
54                    % susceptibility of the TB strain infected
55                    newcase=0;
56                    if agent.TBstatus==0
57                    for i=1:length(agents)
58                        dx=agent.x-agents(i).x;
59                        dy=agent.y-agents(i).y;
60                        if (dx<agent.maxD)&&(dy<agent.maxD)
61                        d=(dx*dx+dy*dy);
62                        if d<agent.maxD
63                            patch([agent.x agents(i).x],[agent.y
64   agents(i).y],'k','EdgeColor','b')
65                            if agent.HIVstatus==0
66                                if (agents(i).TBstatus==2)&&(rand<probInf)
67                                    agent.TBstatus=1;
68                                    agent.MDRstatus=agents(i).MDRstatus;
69                                    if (agent.MDRstatus==0)&&(rand<probPrm)
70                                        agent.TBstatus=2;newcase=newcase+1;
71                                    elseif
72   (agent.MDRstatus==1)&&(rand<probPrmMDR)
73                                        agent.TBstatus=2;newcase=newcase+1;
74                                    end
75                                end
76                            elseif agent.HIVstatus==1
77                                if (agents(i).TBstatus==2)&&(rand<probInfHIV)
78                                    agent.TBstatus=1;
79                                    agent.MDRstatus=agents(i).MDRstatus;
80                                    if (agent.MDRstatus==0)&&(rand<probPrmHIV)
81                                        agent.TBstatus=2;newcase=newcase+1;
82                                    elseif
83   (agent.MDRstatus==1)&&(rand<probPrmMDR)
84                                        agent.TBstatus=2;newcase=newcase+1;
85                                    end
86                                end
87                            end
88                        end
89                         end
90
91            end
92            end
93        end
94
95        function
96   agent=stdTherapy(agent,rateDet,rateDetMDR,rateSuc,rateSucMDR)
97                % determine whether the individual with active TB will be
98   cured
99                % by standard drug therapy
100               % TB can be cured only when the disease is correctly
101  diagnosed
102               % and the drug regimen succeeds
103               % if the drug regimen fails, the originally drug-susceptible
104  TB
105               % strains become resistant
106               if (agent.TBstatus==2)&&(agent.MDRstatus==0)
107                   if (rand<rateDet)
108                       if (rand<rateSuc)
109                           agent.TBstatus=0;agent.MDRstatus=0;
110                       else
111                           agent.MDRstatus=1;
112                       end
113                   end
114               elseif (agent.TBstatus==2)&&(agent.MDRstatus==1)
115                   if (rand<rateDetMDR)&&(rand<rateSucMDR)
```

```matlab
116                             agent.TBstatus=0;agent.MDRstatus=0;
117                     end
118                 end
119
120             end
121
122             function agent=chemoProphylaxis(agent,rate,rateDet)
123                 % determine whether the TB in latency will be eliminated
124     from
125                 % the individual by chemoprophylaxis
126                 % if the regimen fails, the originally drug-susceptible TB
127                 % strains become resistant
128                 % if the indivual is infected with MDR-TB strains, it won't
129     be
130                 % eliminated
131                 if (agent.TBstatus==1)&&(agent.MDRstatus==0)
132                     if rand<rate
133                         agent.TBstatus=0;
134                     else
135                         agent.MDRstatus=1;
136                     end
137                 elseif
138     (agent.TBstatus==2)&&(agent.MDRstatus==0)&&(rand>rateDet)
139                     agent.MDRstatus=1;
140                 end
141             end
142
143             function agent=move(agent)
144                 % agents move once a year in a continuous space
145                 agent.angle=agent.angle+(rand-0.5)*pi;
146
147                 agent.x=agent.x+agent.speed*cos(agent.angle);
148                 agent.y=agent.y+agent.speed*sin(agent.angle);
149
150                 if agent.x>agent.w
151                     agent.x=agent.x-agent.w;
152                 end
153                 if agent.y>agent.h
154                     agent.y=agent.y-agent.h;
155                 end
156                 if agent.x<0
157                     agent.x=agent.w+agent.x;
158                 end
159                 if agent.y<0
160                     agent.y=agent.h+agent.y;
161                 end
162
163             end
164
165             function agent=mortality(agent,death,deathTB,deathHIV)
166                 % determine whether the individual will die in this year
167                 % mortality depends on TB and HIV status of the individual
168                 rate=death;
169                 if agent.TBstatus==2
170                     rate=rate+deathTB;
171                 end
172                 if agent.HIVstatus==1
173                     rate=rate+deathHIV;
174                 end
175                 if rand<rate
176                     agent.alive=0;
177                 end
178             end
```

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

parameterSetup.m

```matlab
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

```matlab
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

```
1   % country profiles from WHO
2   % 1: SouthAfrica, 2: China, 3: Republic of Korea, 4: Switzerland
3   countries=[1 2 3 4
4       0.178 0.001 0.0005 0.004  % prevalence of HIV, 0.05 is estimated
5       0.00808 0.00138 0.00114 0.00006 % prevalence of TB disease
6       0.00971 0.00096 0.00090 0.000049 % incidence of TB per yr
7       0.001 0.001 0 0 % annual population growth rate
8       0.015111 0.002736 0.001803 0.001327 % death rate per yr, estimated
9   from adult mortality rate
10      0.00052 0.00012 0.000083 0.0000017 % additional death rate due to TB
11  per yr
12      0.00627 0.000019 0 0 % additional death rate due to HIV
13      0.72 0.75 0.89 0.89 % case detection rate for all forms of TB
14      0.76 0.94 0.84 0.85 % TB treatment success rate, 0.85 is estimated
15      0.018 0.057 0.027 0.012 % ratio of the MDR-TB cases among new TB
16  cases
17      ];
```

preSearch.m

```
1   clear
2   % set the parameters varying dependent on countries
3   countrySetup
4   country=Country.empty(size(countries,2),0);
5   for i=1:size(countries,2)
6       country(i).prevHIV=countries(2,i);
7       country(i).prevTB=0.33;
8       country(i).prevTBact=countries(3,i);
9       country(i).incTB=countries(4,i);
10      country(i).growth=countries(5,i);
11      country(i).death=countries(6,i);
12      country(i).deathTB=countries(7,i);
13      country(i).deathHIV=countries(8,i);
14      country(i).rateDet=countries(9,i);
15      country(i).rateDetMDR=0.06;
16      country(i).rateSuc=countries(10,i);
17      country(i).rateSucMDR=0.6;
18      country(i).ratioMDR=countries(11,i);
19  end
20
21  % set the pamameters about the TB itself
22  parameterSetup
23
24  % set the simulation conditions
25  M=100; % size of map
26  time=30; % time span in years
27  run=10; % number of simulations
28
29  countryID=3; % select a country to be simulated
30  chemo=0; % 1 if chemoprophylaxis is chosen as a strategy to control TB,
31  0 if not
32  rateChemSuc=0.5; % estimated success rate of chemoprophylaxis
33
34  k=0;
35  for N=400:50:700
36  k=k+1;
37  inc=zeros(7,run,time);
38  N
39  for j=1:run
40  j
```

```matlab
% 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,
```

```matlab
104             country(countryID).deathHIV);
105             end
106         N2=round(country(countryID).growth*length(agents)+0.1*(rand-0.5));
107         if N2>0
108             for i=N+1:N+N2
109                 agents(i)=Agent;
110             end
111             N=N+N2;
112         end
113         % initialization of new born agents
114         for i=1:length(agents)
115             if agents(i).alive==0
116                 agents(i).alive=1;
117                 agents(i).w=M;
118                 agents(i).h=M;
119                 agents(i).x=rand*M;
120                 agents(i).y=rand*M;
121                 agents(i).HIVstatus=0;
122                 agents(i).TBstatus=0;
123                 agents(i).MDRstatus=0;
124                 if rand<country(countryID).prevHIV
125                     agents(i).HIVstatus=1;
126                 end
127                 if rand<country(countryID).prevTB
128                     agents(i).TBstatus=1;
129                     if rand<country(countryID).ratioMDR
130                         agents(i).MDRstatus=1;
131                     end
132                 end
133                 if rand<country(countryID).prevTBact
134                     agents(i).TBstatus=2;
135                     if rand<country(countryID).ratioMDR
136                         agents(i).MDRstatus=1;
137                     end
138                 end
139             end
140         end
141
142         % move agents
143         for i=1:length(agents)
144             agents(i)=agents(i).move();
145         end
146
147         % calculate the incidence
148         inc(k,j,t)=inc(k,j,t)/length(agents);
149
150     end
151
152     end
153 end
154 save('SouthKorea_preliminary','inc')
155 averInc=zeros(run,7);
156 for k=1:7
157     for j=1:run
158         for t=1:time
159             averInc(j,k)=averInc(j,k)+inc(k,j,t);
160         end
161         averInc(j,k)=averInc(j,k)/time;
162     end
163 end
164 subplot(1,2,1)
165 plot(400:50:700,averInc,'b')
166 set(gca,'FontSize',16)
```

```
167    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]);
```