Spread of Vector Borne Diseases in a Population with Spatial Structure

Dominique Chu and Jonathan Rowe

School of Computer Science, University of Birmingham
Birmingham B15 2TT, UK,
{dxc,jer}@cs.bham.ac.uk,
WWW home page: http://www.cs.bham.ac.uk

Abstract. Mathematical modeling of the spread of infectious diseases is a well established field with high practical importance. Underlying most analytical approaches is the assumption of "perfect mixing," that is the idea that the spatial structure of the population can be neglected. This assumption is crucial to the solvability of the models, but can be dropped when using computational models instead of analytical approaches. Using methods from Artificial Life, we investigate under which conditions the perfect mixing assumption becomes a good approximation to describe the spread of vector borne disease in a population with spatial structure.

1 Introduction

Understanding the spread of vector borne diseases is of great importance. Despite a global AIDS crisis, vector borne diseases (particularly but not exclusively Malaria) remain an important cause of premature deaths in tropical countries. Beside the human tragedy, premature deaths do of course also have economic implications. It is therefore of great interest for governments to set measures to eradicate or at least minimize the spread of these diseases.

Mathematical and computational modeling of the spread of these diseases can help gain an understanding of which measures might be effective before they are actually implemented (thus saving costs). A great advantage of mathematical (i.e. equation based) approaches is their great versatility and generality. Particularly analytic solutions to those models lead to an understanding of the various dynamical regimes of the system. However, analytical solutions are typically only possible under rather restrictive assumptions. In the context of infectious disease modeling, it is usually assumed that the spatial structure of the population can be ignored, that is that all participants of the system interact with one another. This assumption is usually referred to as "perfect mixing."

An important methodological tool of Artificial Life is agent-based modeling (ABM). ABMs allow for an easy representation of populations with spatial structure. At the same time they allow the precision of the control of assumptions as other formal modeling approaches; a drawback of ABMs is their lack of generality. In principle for every set of parameters, a simulation needs to be run.

In practice however, this is not necessary. A coarse grained exploration of the parameter space is usually sufficient, but might nevertheless necessitate a very large number of simulations.

One way to integrate equation and agent-based models is to use the latter as validation test-beds to guide the development of the former. In the present context of vector borne diseases, ABMs are particularly useful as test-beds that help create an understanding of the scope of the perfect mixing assumption. It is quite obvious that in the real world the perfect mixing assumption is probably never fulfilled exactly; an important question is thus to understand under which conditions a system starts to behave as though it was perfectly mixed.

2 Description of the Model

The model we describe in this article is not meant to be realistic with respect to the behavior of any real system. The main emphasis of the model is to maximize the simplicity, which then allows us to maximize the understanding of its dynamics. Once this basic understanding is reached, it will be possible to add effects to the model in order to make it more realistic.

ABMs are best described in order of their major components:

- Environment
- Agents
- Interactions

The environment of the model is a 2 dimensional continuous space of size $2L \times 2L$, where L is measured in some unit. The environment has no features other than that it provides a topology for the agents.

There are two types of agents in the model, "vectors" and "people". Those agents are mainly distinguished by their infection period, movement rules, and mode of infection transmission. An infection can only be transmitted between agents of different type. The number of agents of each type is held constant during a simulation run. Agents are thus characterized by their position in the environment and by their internal state, which can be either "infected" or "healthy".

At each time-step the agents take a random position within a square of linear size $2M$ centered around their current position. M is a parameter of the model and set independently for people and vectors; throughout this article we will refer to M as step-size of the agent. Movement is always subject to the constraint that the agents stay within the boundaries of the environment. A parameter of the model s called the *shrink factor* allows to restrict the space of the people agents to a square of size $2Ls \times 2Ls$ in the centre of the world. Vectors continue to occupy the entire world. This enables us to vary the population density of the people agents.

The only form of interaction between agents is transmission of an infection. At each time-step vectors interact simultaneously with all people that are at most one unit away from it. If the vector is infected then all agents it interacts with will also be infected from the following time-step on. If the vector is not infected,

but at least one of the people is infected, then the vector will be infected from the next time-step on. Throughout all simulations presented here, vectors keep their infection for two time steps and people keep their infection for 40 time-steps. However, the model has re-infection, that is whenever an agent interacts with another infected agent, while it is already infected, then its remaining infection period is reset to its full value. So, for example, if a people agent is re-infected 39 time-steps after it has been infected the last time, then it will still have to wait for 40 more time-steps until it loses its infection again.

3 Analysis of the Perfect Mixing Case

In this particular model, each agent is associated with a bite area, that is a circle of radius one centered around it; in general this circle defines the bite area of the agents. Vectors and people agents will only interact with one another if they are within each other's bite area. If the area of the world is $W = 4L^2$, then the possibly overlapping bite areas of n agents in the system will a fraction $q(n)$ of the entire space.

$$q(n, s) = 1 - s^2 \exp(-bn/(s^2 W)) \tag{1}$$

The additional variable s allows to take into account that people agents might be restricted to a particular fraction s^2 of the overall space (the shrink factor — see below).

If P and p are the total number of people agents and the number of infected agents respectively, and M and m are the analogous values for vectors, then we can write down a set of equations describing the behavior of the people and vector population in equilibrium.

Assume R_m and R_p are the number of time steps necessary for the vectors and people agents to recover. According to eq. **??**, in perfect mixing the probability for a particular people agent not to be within the bite area of a vector is given by $1 - q(m, 1)$. People agents are not infected if they have not been within the bite area of an infected vector during the last R_p time steps. A similar reasoning holds for vectors, with the additional complication that we also want to account for the case that people are restricted to a fraction s of the overall space. In this case we have to take into account that the density of people agents within their area is increase (because they are crammed into smaller space), but the probability for a vector to land within the space of occupied by the agents is only s^2.

The fraction of infected people (vector) agents is then given by the probability that the people (vector) agent has been within the bite area of a vector (people agent) within the last R_p (R_m) time steps at least once.

$$\begin{aligned} \frac{m}{M} &= 1 - \left(1 - s^2 q(p, s)\right)^{R_m} \\ \frac{p}{P} &= 1 - \left(1 - q(m, 1)\right)^{R_p} \end{aligned} \tag{2}$$

M	total number of vectors
P	total number of people
m	number of infected vectors
p	number of infected people
R_m	time for vector to recover
R_p	time for person to recover
b	biting area of a vector
W	world size (area)

Table 1. Meaning of the variables used in the model of section **??**.

We could not find an analytical solution for this set of equations; instead we obtain all theoretical predictions reported in this article by numerically solving the equations for m and p.

An approximation to eqn. **??** allows us to find the minimal system size at which the infection will be sustained within the population. Suppose the system is at time step t. Again, a people agent will not be infected at the next time step if it has not been bitten for the last R_p time steps. So similar to eqn. **??** we write:

$$\frac{p(t+1)}{P} = 1 - \exp\left(\frac{-m(t)bR_p}{W}\right) \tag{3}$$

A vector is not infected at time $t+1$ if they have not bitten an infected person for the last R_m steps. Assume that the density of agents is not very high, such that the overlapping between the bite areas can be ignored. If a vector is dropped into the area occupied by people agents, then the probability of landing within the bite area of a people agent is $b/(s^2W)$; in order to obtain the correct result, this probability needs to be multiplied with the probability of actually being dropped into the occupied area s^2. Altogether the fraction of infected vectors at time $t+1$ equals the fraction probability that a vector has been bitten at least once during the previous R_m time steps by any of the infected people agents. Assuming that the system is close to or at equilibrium, we can write

$$\begin{aligned}\frac{m(t+1)}{M} &= 1 - \prod_{i=t-R_m}^{t}\left(1 - s^2\frac{b}{s^2W}\right)^{p(t)} \\ &= 1 - \left(1 - s^2\frac{b}{s^2W}\right)^{p(t)R_m} \approx \frac{bR_m p(t)}{W}\end{aligned} \tag{4}$$

where the approximation is good if b is much smaller than W. Because we are at equilibrium, $m(t+1) = m(t) = m$. Combining those results gives

$$p(t+1) = P - P\exp\left(-\frac{MR_mR_pb^2p(t)}{W^2}\right)$$

One solution is $p = 0$. This corresponds to all people agents being uninfected. To find when this is stable, we proceed as follows: Write

$$G(p) = P - P\exp\left(-\frac{MR_mR_pb^2p}{W^2}\right)$$

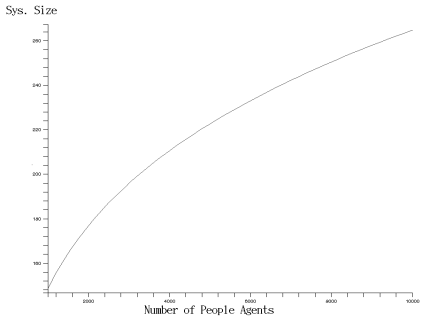

Fig. 1. Assuming a fixed vector population of 10000, this graph shows the points at which the infection gains foothold in a system according to equation **??**

so that $p(t+1) = G(p)$ at equilibrium. Then the state $p = 0$ is stable if $|dG/dp| < 1$ when $p = 0$.

$$\frac{dG}{dp} = \frac{PMR_mR_pb^2}{W^2} \exp\left(-\frac{MR_mR_pb^2p}{W^2}\right)$$

At $p = 0$ we have

$$\frac{dG}{dp}|_{p=0} = \frac{PMR_mR_pb^2}{W^2}$$

So the equilibrium is stable if

$$\frac{PMR_mR_pb^2}{W^2} < 1$$

or, alternatively,

$$\frac{b}{W} < \frac{1}{\sqrt{MPR_mR_p}} \tag{5}$$

This equation enables us to predict the minimal world-size for which the infection gets established in the the system (see figure **??**). Note that equation **??** predicts that the shrink factor does not seem to influence the minimal world size.

4 Results

In all simulation runs presented in this article, the infection period for vectors and people agents is kept constant at 2 and 40 respectively. This choice is to a large degree arbitrary, but reflects the idea that the life-time of the vectors is shorter than the infection period of the people. In all simulations shown, we varied the linear size L of the system in discrete steps of 10 from 10 to 400; this corresponds to system of area between 400 and 640000 square units. For each linear system size setting we simulated the system for 5000 time steps and recorded the fraction of the infected people and vector agents averaged over the

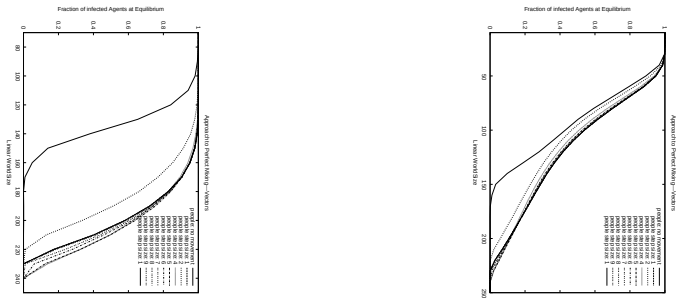

Fig. 2. The left (right) graph shows the fraction of infected people agents (vectors) versus the linear system size. The recorded data points are not shown here, but replaced by connecting line segments for better viewing. Increasing the mobility of people initially has a dramatic effect on the infection levels in the population, but further increases show less dramatic increases.

last 1000 time steps. At this time the system has reached its steady state. For all simulations presented here we keep the number of agents and vectors in the system at 5000 and 10000 respectively.

In the first series of simulations we kept the step size of the vectors constant at one, whereas the step size of the people agents steps varied from from 0 to 9. The results of those simulations are summarized in figure **??**. The graphs show clearly that already a slight increase of the movement leads to a dramatic change of the behavior of the system. When the step zise is zero (no movement for people) the infection gets established at a linear system size of 180. Howver, in the case of a step size of 1, the infection can establish itself at considerably lower densities, namely at a linear system size of about 230. The graph shows clearly that this is already the same density as in the case of a step size of 9. Note that for intermediate step sizes the infection is actually slightly more severe, (i.e. higher infection rates at similar densities) than for the large step sizes.

Figure **??** shows a comparison between the theoretical prediction for the perfect mixing case and experimental results from an implementation of the perfect mixing scenario. This graph shows that when the people agents' step size is nine, then the model behaves like in perfect mixing, even if the vectors' step size is only 1.

In the next set of experiments the people agents are distributed on a smaller area than the vectors. In the specific simulations we performed, the agents are distributed on a square in the center of the environment. The linear size of the square is half the size of entire world. Equation **??** predicts that that the shrinkage of the agent area does not have any influence on the minimal world size where the infection gets established in the world. Theoretical predictions (that is numerical solutions of eqn. **??**) could confirm this for a number of example simulations (data not shown); furthermore, this result is also confirmed by actual simulation of the system as can be seen in figure **??**. The $s < 1$ case is a good approximation for the symmetric case, when the total area of the world is large,

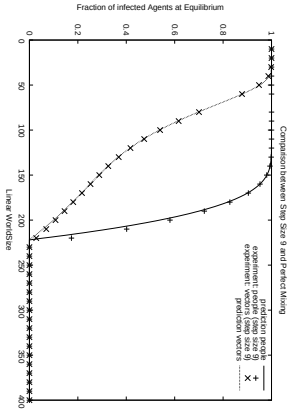

Fig. 3. This graph compares the predicted behavior of a perfect mixing model with the actual simulation results obtained from a simulations of people with step size nine and vectors with a step size of 1.

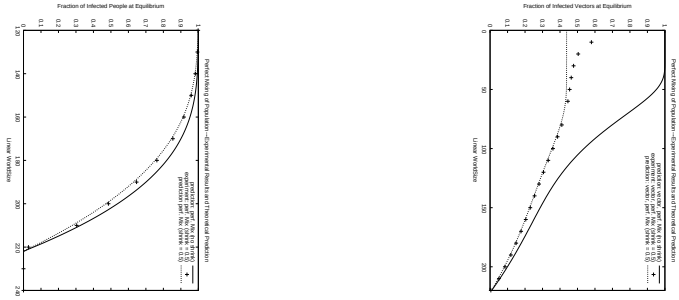

Fig. 4. Those graphs show a comparison of the perfect mixing case with and without shrinkage of the agent-area. The lhs shows the infection levels in the people population; the rhs analogous results for the vector agent population.

but still supports the infection. This approximation becomes progressively worse, as the linear size of the world L and s decrease. Figure **??** shows that the approximation is only good for the people agent population, whereas the vector populations has infection levels very different from the $s = 1$ case.

As shown above, when $s = 1$ then increasing the step size of people agents quickly approximates the perfect mixing case, even though the agents retain a maximal step size. Simulations show that this is not the case any more when $s < 1$. Figure **??** shows that agent movement can not approximate the perfect mixing case of the population any more, if the people agents are restricted to a shrunk area. Instead the people population seems to approximate the behavior of an $s = 1$ system with the same density of agents. This is only true for the people agents; for not too small world-sizes, the vector population has s^2 times the infection level of the scaled-up system.

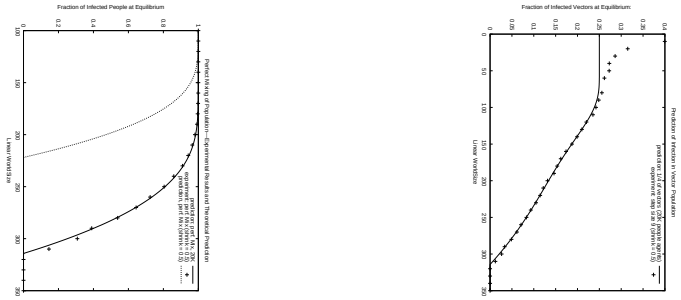

Fig. 5. When only the people agents are allowed to move, then this does not lead to perfect mixing any more. The crosses represent data points won from the actual simulation. The dotted curve is the theoretical prediction for the perfect mixing case of the shrunk population. The solid curve is the theoretical prediction for an $s = 1$ system, but with the same people density as the shrunk system in the shrunk area; in this case this is 20K people agents.

5 Discussion

and the influence of s on the perfect mixing. An extreme case of spatial structure in the population is reached when the step size of people agents is zero. In this case it is useful to think the system as consisting of a number of separated clusters. A cluster is defined as a group of connected people agents. Two such agents are connected if there exists a possibility that a vector can catch an infection from one agent and infect the second one. By this definition it is thus impossible to have cross-infection between agents of two separate clusters.

An important factor for the understanding of the dynamics of infections in clusters is that an infection might not be very stable in small clusters if the density of vectors is low. In order to sustain the infection within one cluster it is necessary that at least once every 40 time-steps a vector vector infects itself from a people agent and either re-infects this people agent or carries the infection to another agent in the cluster. Clearly, there are a number of important factors influencing whether or not an infection will be sustained. Shape and density of the clusters have an important influence on the likelihood of cross-infection between agents. Similarly, the density of vectors across every cluster is a crucial factor and can be assumed to be approximate well the average density M/W.

If we assume that the internal structure of clusters of a given size tend to be similar to each other, then the vector density is the crucial factor. At small densities (i.e. large W) small clusters will tend to lose their infection within relatively short times through random fluctuation of vector densities. We can thus assume that only clusters of a minimum size A will contribute to the overall infection rate., where A is a function of the vector density.

Once the people agents start to move around, the clustering effect disappears. The agents can move around thus increasing contact between agents and facilitation infection across larger areas of the world. The speed of agent movement

(the step size) still causes temporal clusters: The maximum distance between people agents so that an infection can be transmitted from one to the other is 83 units if the step size is 1. This number increases with the step sizes. The simulations indicate for a step size of 2 (163 units maximal distance between people) perfect mixing is very well approximated, particularly for smaller linear system sizes. At a step size of 9 the system behaves like the perfect mixing case over all linear system sizes.

If we restrict the linear size of the agent area to a fraction s of the overall area, then, the density of agents within this area will increase by s^2. Thus whenever a vector is within the area populated by people, then it will have a dramatically increased chance of actually being near an agent and catching/transmitting an infection. However, at every time step the probability of actually being within the populated area is only s^2. Figure **??** shows that in the perfect mixing case $s = 1$ system is well approximated by the $s = 1/2$ system. Further decreasing the factor will result in increasingly bad approximations.

The situation is very different for vectors. While in the shrunk case people agents still behave similarly to the $s = 1$ case (if the shrinkage factor is not too large), the infection levels in the vector population remain consistently lower in the shrunk case than in the $s = 1$ case. This effect is easily explained if one considers that the vectors will only have a chance to interact with people no more than every s^2-th time step. Thus in the limit of a very densely populated people area, the probability for a vector being infected is equal to $2(1 - \frac{1}{s^2})\frac{1}{s^2} + (\frac{1}{s^2})^2$. For the shown case of $s = (1/2)$ this yields an infection level for the vectors of .4375. This theoretical prediction is only partially confirmed by the simulation in figure **??**, however, where the fraction of the infected vector population seems to converge to 1 as the world size gets smaller. This discrepancy is easily explained by considering that while the people are restricted to the shrunk area, a vector can still catch an infection if it is outside this area, but still within 1 unit of an agent. As W decreases this edge effect becomes increasingly important and in the limit of very small systems every part of the world will be within 1 unit of a people agent.

In the case of the $s = 1$ system, perfect mixing is reached if the agents' step size is sufficiently large, even though the step size of the vectors is not. In the case of $s < 1$ this is no longer the case. The dynamics in this case can be easily understood by considering that the vector population splits up into two weakly connected sub-populations, those vectors inside the people agents' area and the one outside. One characteristic of perfect mixing is that the internal state of the system at time t is nearly independent of the system state at time $t - 1$. If $s = 1$ a sufficiently large agent-step size can ensure that the correlation between system states at various times become quickly un-correlated. If on the other hand the space occupied by people agents is smaller than the space occupied by vectors, then perfect mixing requires two things to hold. Firstly, within the area occupied by the people agent, people agents need to mix well with vectors. Secondly, there needs to be rapid mixing between the two vector sub-populations inside and outside the people agent area.

6 Conclusions

We have used agent-based simulations and corresponding mathematical analysis to help understand the conditions under which a perfect mixing assumption is a good approximation to the dynamics of a vector-borne disease in a spatially distributed population. We find that perfect mixing is a reasonable approximation under the following conditions:

- People and vectors spread over same area, with modest movement for all agents. Perfect mixing is a good approximation for both vectors and people.
- People distributed over a restricted area, with modest movement for all agents. Perfect mixing (with the same *density* of agents) is a good approximation for the people, but not for the vectors.

However, if the movement of people is very small compared to the world size, then the population breaks up into clusters, which require a critical density to be able to maintain the infection. This seems to be a reasonable model of large-scale population distributions (for example, consider across whole countries or continents), whereas the perfect mixing model may better approximate the disease dynamics in a smaller area (e.g. a cities or isolated rural area).