

# Review of Epidemics with Pathogen Mutation on Small World Networks for future testing of control strategies

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Epidemics of mutating pathogens on human networks are a major concern to both public health and economics. The outbreak of a contagious novel virus into a population can cause large number of individuals to get sick--shutting down a society and causing the deaths of large numbers of people. Recent outbreaks of disease such as SARS, and the recent H1N1 flu outbreak indicate how rapidly a potentially deadly virus can spread around the world and infect many millions of people despite control efforts. This model helps predict the outbreak and spread of a mutating pathogen based on parameters for the spread of the disease across a small world network.

## **Introduction**

Epidemiology is the study of infections over a network of people. And epidemic is the wide-spread infection of a group of individuals in contact with each other and people not yet infected. It is important to study both the history and potential future of epidemics as diseases such as AIDS and Pandemic Flu, which have killed millions worldwide, is critical to public health. In 2009, Influenza A(H1N1/09) emerged. Though not as catastrophic as initially feared, Influenza A(H1N1/09) was genetically close to the Spanish Flu strain of the early 20<sup>th</sup> Century that killed millions worldwide. It demonstrated how a highly contagious novel virus could rapidly spread to all nations on Earth in less than one year. Studying disease spread across socio-spatial networks is an important aspect in understanding disease-contraction dynamics and determining methods to limit outbreak [1].

Creating accurate and effective models of pathogen-spread and containment is an important asset in determining the danger of an infectious strain. Programs such as childhood-immunization [2], have benefited from effective models. Rapidly mutating diseases present some of the most dangerous cases for natural pandemic or bio-terrorist attack [1].

Many models have been created to map the spread of a disease for these purposes. However, there are few models that incorporate both pathogen mutation and a realistic socio-spatial network [1]. Societal realities, such as stronger links between family members than strangers, are important aspects for the spread of a pathogen. The interaction between immunity and pathogen mutation also affects the dynamics. Models based on uniform mixing of a network are not realistic. Individuals spend more time with their families, coworkers, and friends than with strangers. Though not true representations of social-spatial networks, small-world networks capture two key features of true social networks. They are highly clustered; two nodes which share a neighbor are likely to themselves be neighbors. Furthermore the diameter, the minimum number of vertices between any two nodes, of the graph increases only logarithmically with network size [3].

The paper Epidemics with pathogen mutation on small-world networks written by Zhi-Gang Shao, Zhi-Jie Tan, Xian-Wu Zhou, Zhun-Zhi Jin, all faculty in the physics department of Wuhan University, was the original source for this type of model. We replicated their model and results with the intention of engaging in future studies into this area. The authors created their model as a more realistic study of disease outbreak on society [1].

## **Review of Author's Model**

### *SIRS Model*

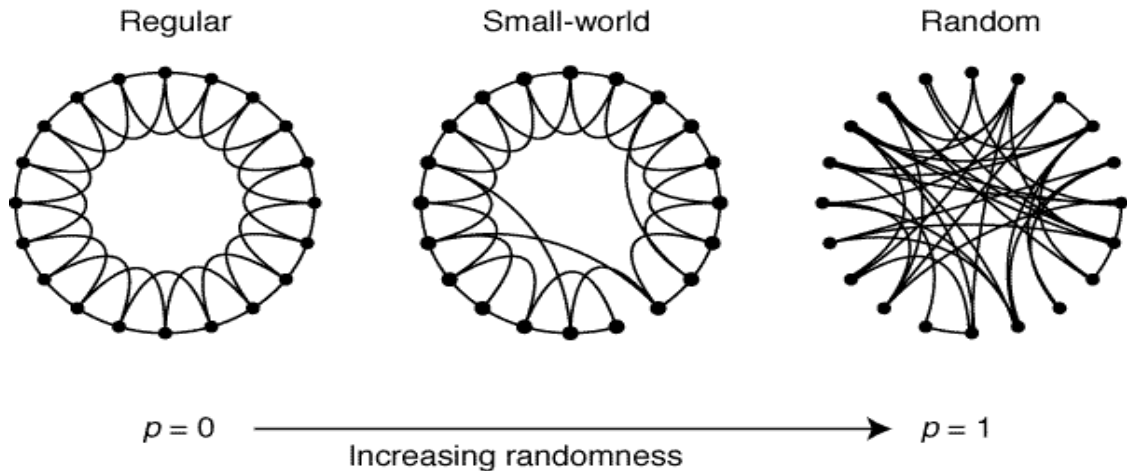
The model being proposed is an S(susceptible)I(infected)R(immune)S(susceptible) model. Any node in the network progresses from susceptible to infection, to infected, to immune, and back to susceptible as time progresses. The model also includes pathogen mutation meaning that immunity to all the strains moving through the system at a time step is less likely. Simpler models are SIS, and SIR models. In SIS models there is no immunity stage and an individual can become infected immediately after it has recovered. In SIR models once infected an individual retains immunity for the rest of time. And SIRS model is a better model for studying the pathogens with higher epidemic risk.

### *Small World Networks*

A small world network is a collection of  $N$  nodes, which act as individuals. The nodes each have a history which records the strains they have been infected with or are currently infected with. The nodes are connected together creating the network. The model requires that we create multiple different networks to run it on. To create the networks each node starts out in a linear sequence connected to its  $2k$  nearest neighbors, the first and last nodes being next to each other. To turn this from a fully symmetric network to a small world network the model goes from node to node and rewires each of the  $k$ , clockwise connections to a random node, with a probability  $p$ , and maintains the connection with probability  $1-p$ . The model prevents both self-connections and multiple connections between two nodes. Small-world behavior occurs when the probability of rewiring a connection is larger than  $1/N$

[3] The authors had network sizes vary from  $10^4$  to  $10^6$  and took  $p = 0.01$ , well within the small world range [1].

Example of small world network with increasing  $p$  the randomness of the network increases.



D.J. Watts and S.H. Strogatz, *Nature* 393 (1998), p. 440.

### *Mutating pathogen*

Each node can be in one of three states. S-susceptible to infection, I-infected, and R-immune. Once an individual in state S is infected it passes into the immune-state after the infection time  $\tau_i$ . The individual stays immune until the end of the immunity duration  $\tau_R$ . This is referred to a SIRS model. Including mutation into the model causes new strains to appear in the system, these new strains can infect individuals immune to previous strains. However, immunity is conferred if the new strain is similar enough to old strains in the immune response memory.

Pathogens are represented using a bit-string model, in which each pathogen strain is represented by a unique bit-string of length  $l$ , i.e. 1010000011. These bit-strings serve as abstract representations of the genetic code of the pathogen [1]. Mutation is carried out by flipping a single digit in the bit string representation. Mutations can occur only during an infection event, and do so with probability  $\mu = 0.01$ . An individual will be immune to any pathogens similar to ones in its immunity repertoire [1]. The similarity between strains is measured by the  $l^1$  norm, the hamming-distance. Since each bit-string

is length  $l$ , the total number of possible strains is  $2^l$  and with  $10^5$  nodes it is likely that mutations will cause a large number of strains to be present at any one time.

The epidemic is started by randomly choosing one node to be infected with the initial strain 000...000. At each time-step, infected nodes send challenge-strains to their nearest neighbors, simulating contact with infectious individuals. The challenge-strain is then compared to the immunity repertoire of the neighboring node. If the minimum hamming-distance between the challenge-strain and all the strains in the repertoire of the neighboring node is greater than  $h_{\text{thr}}$ , the cross-immunity threshold, then the neighboring node becomes infected.

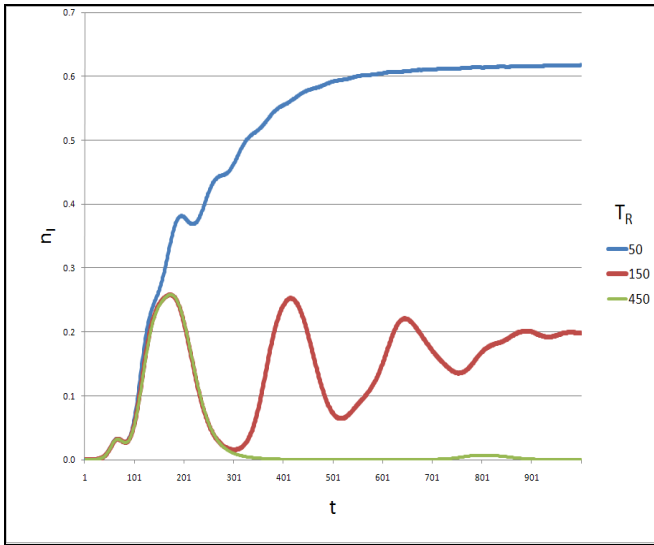
To simplify the model each strain has the same immunity duration, infection time, mutation probability and cross-immunity threshold. The length of the bit string is set to  $l = 10$  and the infection time is set to  $\tau_i = 1$  for all variations of the parameters studied [1].

The numerical model was implemented in C++. Since this is a stochastic model, data gathered for each variation of network parameters was run over ten different networks with at least fifty runs per network. This was to account for the randomness inherent in the construction of the networks and in mutation events (parameters  $p$  and  $\mu$ , respectively). The resulting data was then averaged to a single data set. The original authors averaged data for ten networks with one hundred runs each. Time-constraints and the limitations of our computing power prevented exact replication of the previous effort.

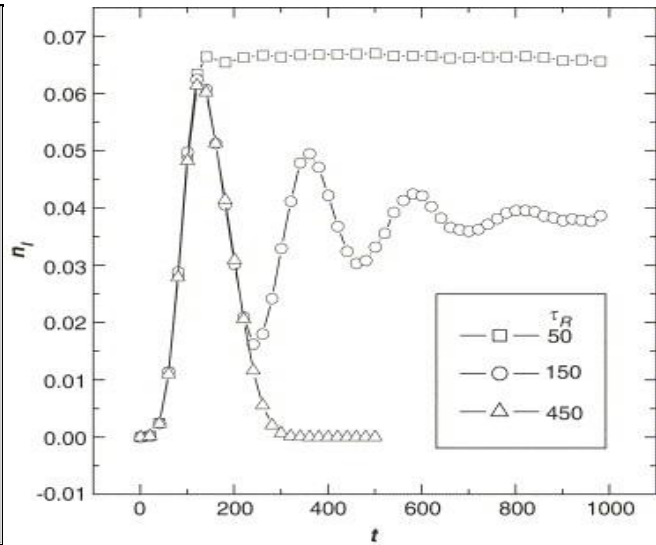
## **Results**

### *Case 1: Effect of immunity duration*

The simulation was run for immunity duration,  $\tau_R = 50, 150, 450$ . The cross-immunity threshold  $h_{\text{thr}} = 2$ . The network size was set to  $N = 10^5$ . The figure shows the fraction of infectious individuals as a function of the time step.



Replicated model results

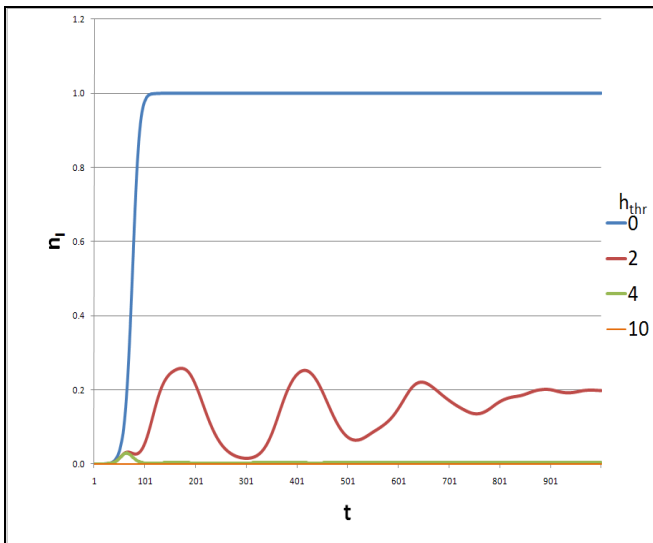


Physica A 363 (2006) 561-566 by Zhi-Gang Shao, Zhi-Jie Tan, Xian-Wu Zhou, Zhun-Zhi Jin

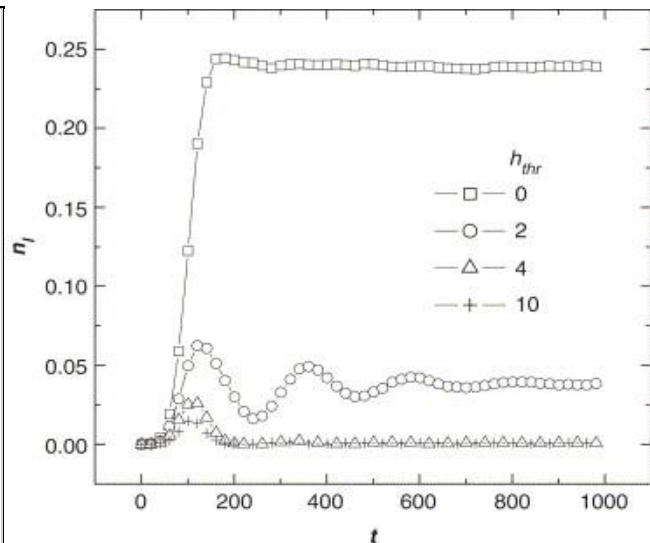
**Figure 1: Plots of fraction infected against time, for immunity duration  $\tau_R$ , Cross-immunity threshold  $h_{thr} = 2$ , and population  $N = 10^5$ .**

*Case 2: Effect of cross-immunity threshold*

The simulation was run for  $h_{thr} = 0, 2, 4$ , and  $10$ . The immunity duration,  $\tau_r = 150$ , and the population size was again  $N = 10^5$ . Figure 2 shows the fraction of infected individuals as a function of dimensionless time.



Replicated model results

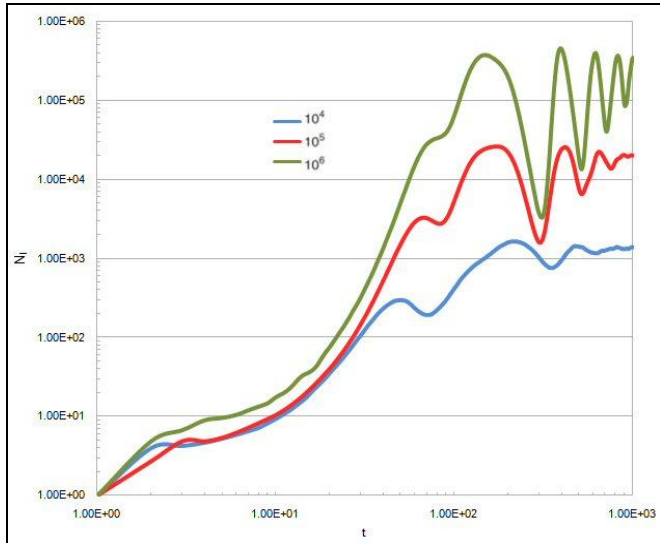


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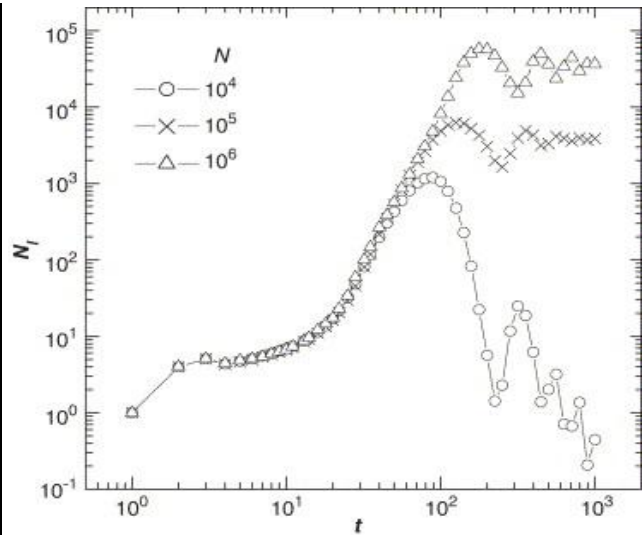
**Figure 2: Fraction of infected individuals as a function of time step  $t$  for cross immunity threshold  $h_{thr}$ , immunity duration  $\tau_R = 150$ .**

### Case 3: Effect of population size

The simulation was run for network sizes,  $N = 10^4, 10^5, 10^6$ . The immunity duration  $\tau_r = 150$ , and the Cross-Immunity Threshold  $h_{thr} = 2$ . The figures 3a and 3b show the number of infected nodes as a function of time.



Replicated model results



Physica A 363 (2006) 561-566 by Zhi-Gang Shao, Zhi-Jie Tan, Xian-Wu Zhou, Zhun-Zhi Jin

**Figure 3: Number of infected individuals as a function of time step  $t$  for population  $N = 10^5$ , immunity duration  $\tau_r = 150$ , and population  $N = 10^5$ .**

## Discussion

### Case 1(Effect of immunity duration)

(Figure 1) In both the original results and the replicated models up to the 100<sup>th</sup> time step the three simulations have the same fraction of individuals infected. Furthermore, immunity durations of 150 and 450 have the same time dependent dynamics up to the 200<sup>th</sup> time step.

For large  $\tau_R$  values, e.g.  $\tau_R = 450$ , the infection spreads quickly initially but then dies out. Moderate values of  $\tau_R$ , e.g.  $\tau_R = 150$ , a decaying oscillation occurs. Small values of  $\tau_R$ , e.g.  $\tau_R = 50$  the infection rapidly spreads then becomes persistent, this case will be hard to contain and control, and represents the greatest threat for pandemic [1].

### *Case 2(Effect of cross-immunity threshold)*

(Figure 2) In the original and replicated models the dependence on the cross-immunity threshold is dramatic. For  $h_{thr} = 0$  any challenge strain will infect the node the system rapidly tends towards a constant infection rate of 100%. This is a reduction to the SIS model. For a  $h_{thr} = 10$ , the bit string length the model reduces to an SIR model. Lower cross immunity between strains leads to more rapid outbreak and greater public health threat. This can be seen with seasonal influenza, the new strain arriving each flu season is outside the cross-immunity threshold of the previous year's influenza virus, and therefore annual inoculation is required.

### *Case 3(Effect of population size)*

(Figure 3) In both models the size of the network does not affect the initial dynamics of the system. The number of infected in all three cases grows towards a maximum before the effect of the immunity duration comes into play. These simulations run with  $\tau_R = 150$ , display the damped oscillations for moderate immunity duration lengths. The dynamics for population size only vary at later time. The smaller networks reach equilibrium quicker than the large networks. Not repeated in the replicated results but in the authors model for the smallest population size, the number of infected reduces with time, ultimately resulting in the elimination of the pathogen from the system.

### *SIRS Model on a small-world network*

The SIRS model with pathogen mutation on small-world networks presents special results not present in other models. As shown SIRS models with pathogen mutation have parameter sets where oscillations can occur in the fraction of individuals infected. Mutation leads to an increase in the number of nodes infected, while immunity leads to a decrease in the fraction infected. The small world network affects the dynamics because the rewiring creates long-range connections [1]. A long range connection allows infection to spread across the network to previously uninfected areas of the graph. These long range connections increase the spread of pathogen strains.

## *Discrepancies*

In repeating the work of the previous authors, we ran into a few discrepancies that future work should attempt to explain. First, in all three cases the fraction of the number infected in our work was higher than the original work. When testing the cross-immunity threshold our averages were exactly four times larger than the authors. Secondly, for network size  $N = 10^4$ , the authors reported that the number of infected decayed to zero for larger times. In our results the number infected displayed the same damped oscillations as the larger networks.

## **Conclusion**

Mutating pathogens are a major threat to public health. The interaction of the immune response and disease mutation leads to oscillations in the number of infected when the outbreak is on a small world network. In real socio-spatial networks this is also the case as novel pathogens can rapidly spread across a network if a majority of individuals are immune. Understanding when a pathogen will not naturally be eliminated from the network, as in the saturation and oscillation cases, forces societies to take steps to reduce its impact and attempt to eradicate it. In the 20<sup>th</sup> century the eradication of Small Pox from circulation due to a massive immunization effort represents the lone success in truly eliminating a harmful pathogen from the planet. Novel pathogens created by random chance mutations such as the case of the H1N1/2009 pandemic will always be a scourge on society. This model can be used to assess effectiveness of countermeasures to epidemics such as H1N1/2009. Being better prepared to deal with the next pandemic could save millions of lives.

## **Future Work**

Having successfully replicated the fundamental behavior of the previous work, we now focus our attention on expanding the model to more accurately reflect the susceptibility of various individuals to infectious agents. We will then ask certain questions of our model, comparing our results to real-world data.

To that end, our objectives are two-fold. Firstly, we would like to enhance the model to reflect variable susceptibility. Not all individuals are equally susceptible to infection. The elderly, infants, those being treated with immuno-suppressant drugs and persons with immune-deficiencies caused by diseases such as HIV, are more likely to contract a virus if an outbreak occurs. We will be studying how populations with diverse demographics (age, health, etc.) handle an outbreak of a mutating pathogen. We also intend to compare our results to real world data, from the World Health Organization and others.

Our second objective is to examine how to best go about stopping an outbreak once it has occurred. Much time and money is expended in trying to quell outbreaks. Sometimes these efforts produce large amounts of waste, as evidenced by the recent dumping of vast amounts of H1N1 vaccine. To combat this waste and stop an outbreak we would like to know who and how many people to inoculate, and when to inoculate them. In particular we will look at vaccinating a proportion of a random sampling of the population, at vaccinating certain susceptible individuals such as the elderly, and at vaccinating those who come in contact with large segments of the public (represented by highly connected nodes in our small-world network model), such as taxi drivers, bus drivers, mail-persons, and teachers.

## **References**

- [1] Zhi-Gang Shao, Zhi-Jie Tan, Xian-Wu Zhou, Zhun-Zhi Jin, *Physica A* 363 (2006) 561-566.
- [2] B.T. Grenfell, O.N. Bjornstad, J. Kappey, *Nature* 414 (2001) 716.
- [3] R. Albert, A.-L. Barabási, *Rev. Mod. Phys.* 74 (2002) 47.