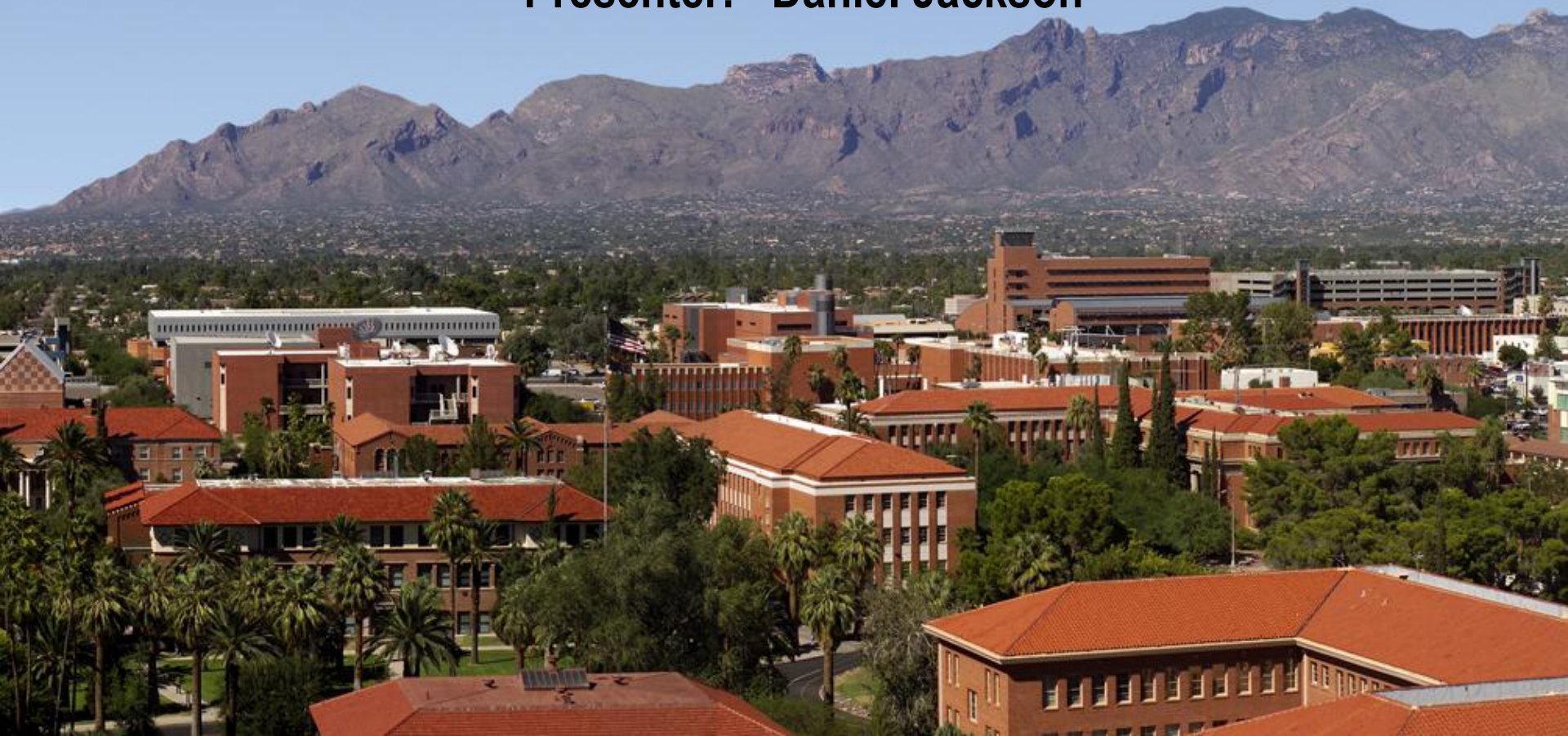


Epidemics with Pathogen Mutation on Small-World Networks

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Introduction to the Model



In 1918–1919, an estimated 40–50 million people died worldwide from the influenza pandemic.

- Epidemiology
 - Factors affecting health and illness of a population
 - Viral outbreaks
- What we are studying
 - Socio-spatial networks
 - Time-dependent dynamics
 - Immunity
 - Pathogen mutations

Why study this model?

- Mathematical models can help predict the behavior of infectious agents on susceptible populations
- Predictions of mathematical models can help guide efficient and effective treatment for the eradication of disease
- Accounting for pathogen mutation and time-dependent immunity within the small-world paradigm leads to a more realistic model



Examples of infectious diseases

Measles:

- Highly infectious
- Short incubation period
- Short immunity duration
- Control policy is long-term

Smallpox:

- Less infectious
- Longer incubation period
- Long immunity duration
- “Herd Immunity” made eradication possible



Infection and Immunity

- Immune response is triggered by genetically similar pathogens (antigenicity)
- Measure of 'how similar' is the cross-immunity threshold, h_{thr}
- Individuals infected when a new viral strain is sufficiently different ($h_{min} > h_{thr}$) from any recently encountered
- Individuals, represented by nodes in the network, can infect others, represented by neighboring nodes, during the infectious stage (infection duration)
- Individuals, represented by nodes in the network, can become infected again after a sufficient amount of time has passed (immunity duration)



Deterministic vs. Probabilistic

SIR: Differential Equation Model

$$\frac{dS}{dt} = -\alpha S \frac{I}{N}$$

$$\frac{dI}{dt} = \alpha S \frac{I}{N} - \beta I$$

$$\frac{dR}{dt} = \beta I$$

SIRS: Agent Based Model

Consider node **n**

If **n** has a virus in the infectious stage

add to infected-population count

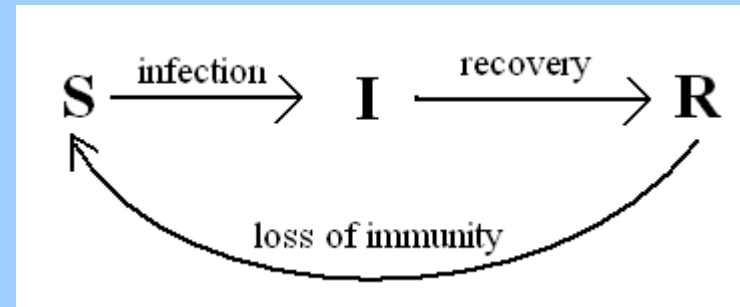
For each virus **v** in the viral history

If **v** is in infectious stage

send challenge strain to neighboring nodes

If **n** has been immune to **v** longer than the immunity duration

remove **v** from the viral history

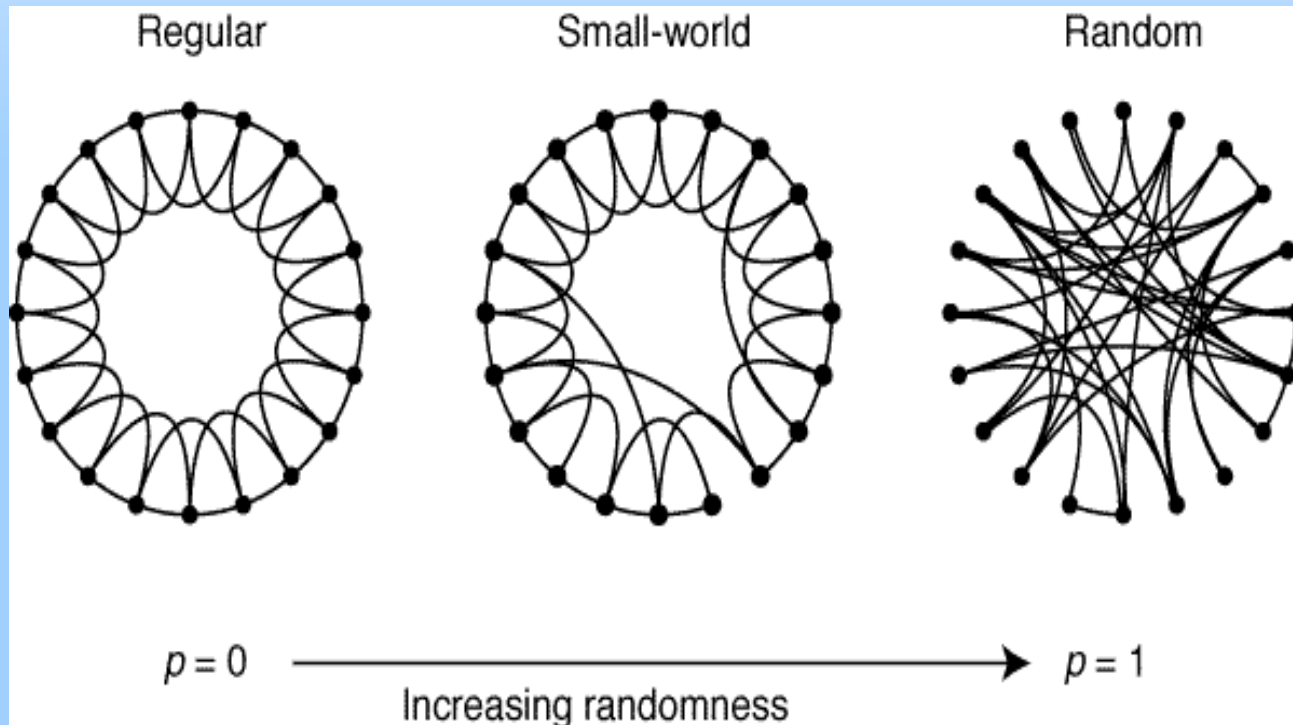


Stochastic: Data averaged to account for probabilistic factors

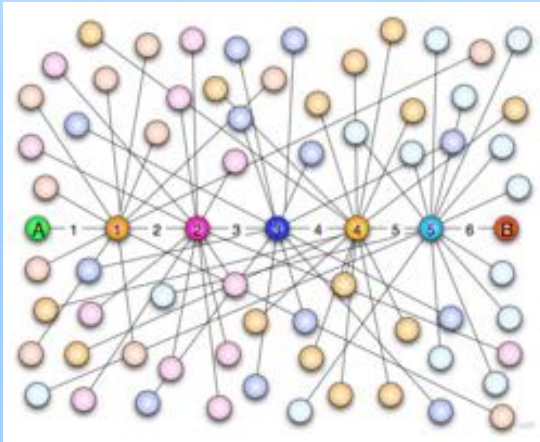
- Many network realizations account for rewiring variability
- Many runs per network account for mutation variability

Small-World Networks

- Connected graph, highly regular but with clustering
- Better depicts realistic socio-spatial networks
- Purely regular and purely random networks are not realistic
- Rewiring networks increases disorder
- Small-World behavior emerges for $p > \frac{1}{N}$



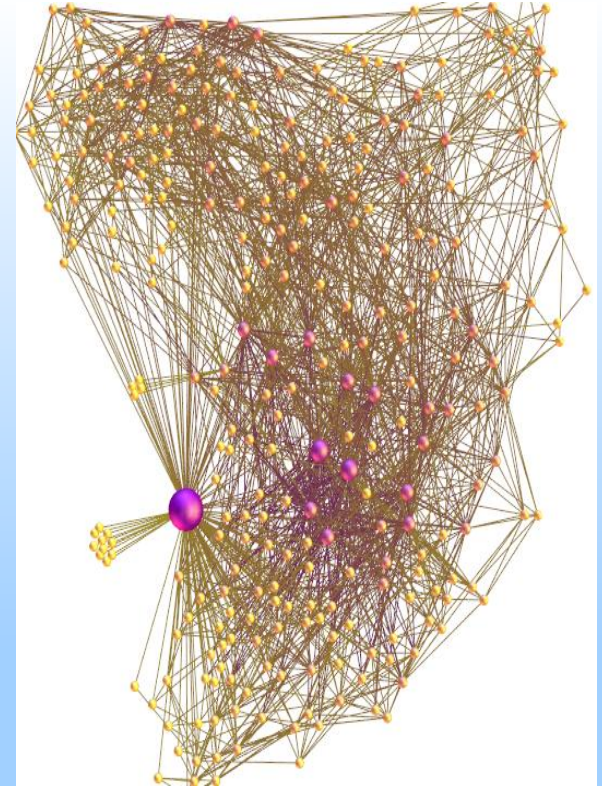
Examples of small world networks



Collaboration graph of
film actors



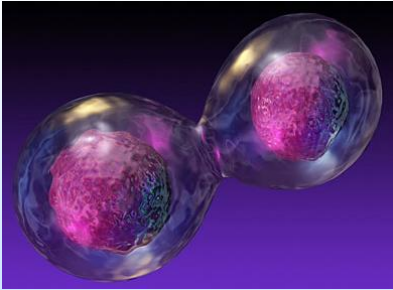
Power Grid of
Western U.S.



Neural network of worm
(*Caenorhabditis elegans*)

Variables

- N Population size
- $2k$ Average number of neighbors
- ρ Network randomness (probability of node connections rewiring)
- τ_i Infection time
- τ_R Immunity duration
- μ Mutation probability
- h_{thr} Cross-immunity threshold (antigenicity)
- L Pathogen representation length



How Infections Spread In a Small World Network

- Bitstring model:
 - Abstract representation of a pathogen's genetic code
 - Choose bitstring of length ten. e.g. 0000000000
 - Mutations are single random bit flips: e.g. 0000010000
- Cross-immunity:
 - Hamming-distance: l^1 -norm of pathogen representations
e.g. 0110001 and 0100011 have hamming-distance 2
 - Minimum hamming distance, h_{\min} : smallest distance between challenge strain and all strains in the viral history
 - Individual becomes infected if $h_{\min} > h_{\text{thr}}$
- Mutation:
 - Survival mechanism of pathogen
 - The mutation probabilities (μ) of pathogens are generally small

Model Realizations

(Parameters Studied)

Immunity Duration

$\tau_R = 50, 150, 450$

$N = 10^5$

$k = 2$

$\rho = 0.01$

$\tau_I = 1$

$\mu = 0.01$

$h_{thr} = 2$

Cross-Immunity Threshold

$h_{thr} = 0, 2, 4, 10$

$N = 10^5$

$k = 2$

$\rho = 0.01$

$\tau_I = 1$

$\tau_R = 150$

$\mu = 0.01$

Network Size

$N = 10^4, 10^5, 10^6$

$k = 2$

$\rho = 0.01$

$\tau_I = 1$

$\tau_R = 150$

$\mu = 0.01$

$h_{thr} = 2$

Model Implementation

```

(Global Scope)
// Adds a virus if Hamming-distance between it and any other virus is less than nHammingDistThreshold
bool CVirusList::AddVirus(CVirus* pChallengeVirus, unsigned int nHammingDistThreshold, float fMutationProbability)
{
    // Compute min hamming distance
    unsigned int h_min = VIRUS_MAX_LENGTH;
    CVirus* pThis = m_pVirusRoot;
    while(pThis)
    {
        unsigned int h = pThis->ComputeHammingDistance(pChallengeVirus->getStrain());
        if (h < h_min) h_min = h;
        pThis = pThis->getNext();
    }

    // Infect if h_min > h_thr
    if (h_min > nHammingDistThreshold)
    {
        CVirus* pNewVirus = new CVirus(pChallengeVirus->getStrain()); // Create a copy to add to the list
        pNewVirus->Mutate(fMutationProbability);
        AddVirus(pNewVirus);
        return true;
    }
}
    
```

C++

Matlab

Typical runtime (per network per run)

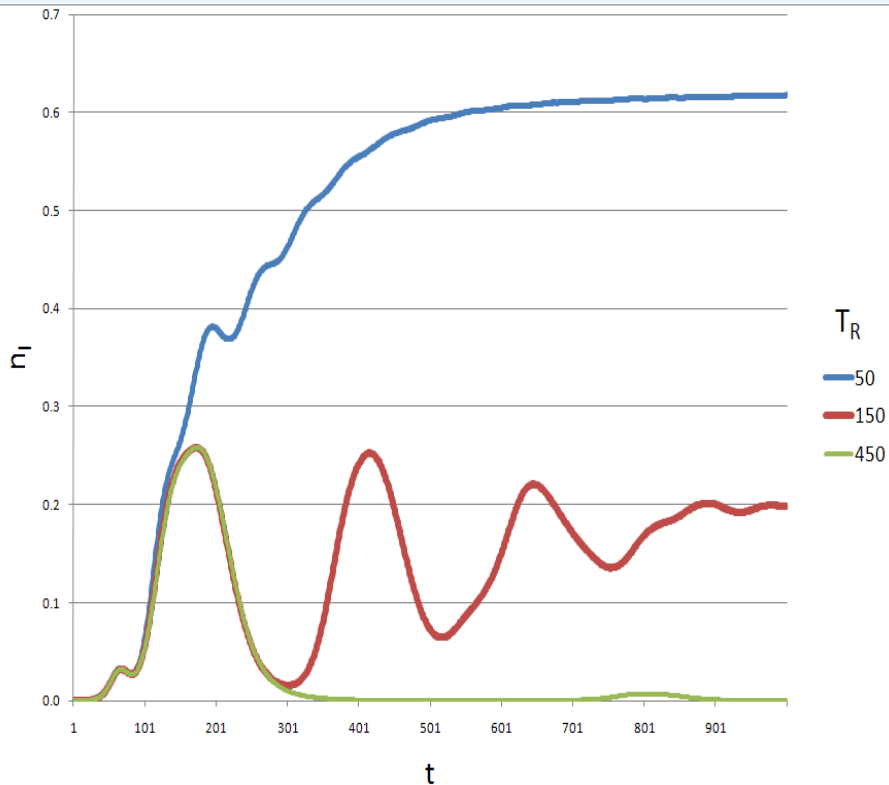
Parameter	MATLAB implementation	C++ implementation
$\tau = 50$	Unknown (>34 hours)	15 min
$\tau = 150$	10 hours	3 min
$\tau = 450$	1.5 hours	0.35 min
$N = 10^4$	2 hours	0.50 min
$N = 10^5$	10 hours	3 min
$N = 10^6$	Unknown (not attempted)	55 min

```

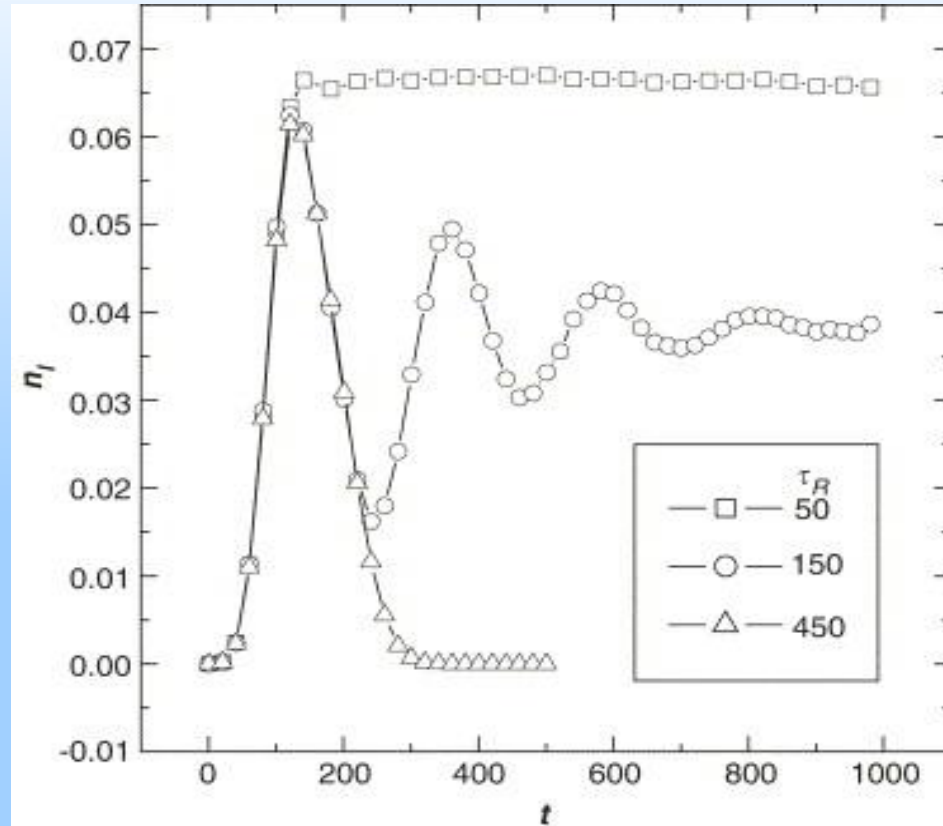
function Nodes = increment_tau( Nodes , Params )
% and counts and returns the number of infected nodes and the
% updated network.
Nodes = increment_tau(Nodes, Params);
num_infected = 0;

% For each node, determine if it's infected and try to infect
% neighboring nodes if it is
for n=1:Params.N
    is_infected = 0;
    ThisNode=Nodes(n);
    num_viruses = length(ThisNode.Virus);
    if (num_viruses>0)
        for v=1:num_viruses
            % If this virus is in the infected stage,
            % then infect neighboring nodes
            ThisVirus = ThisNode.Virus(v);
            if (ThisVirus.tau >= 0)
                if (ThisVirus.tau < Params.tau_1)
                    is_infected = 1;
                    % Send the virus challenge-strain to each neighbor node
                    for nbr = 1:length(ThisNode.Neighbors)
                        Neighbor = Nodes(ThisNode.Neighbors(nbr));
                        Nodes(ThisNode.Neighbors(nbr)) = infect(Neighbor, ThisVirus.strain, Params);
                    end
                end
            end
        end
    end
    num_infected = num_infected + is_infected;
end
end
    
```

Our Results

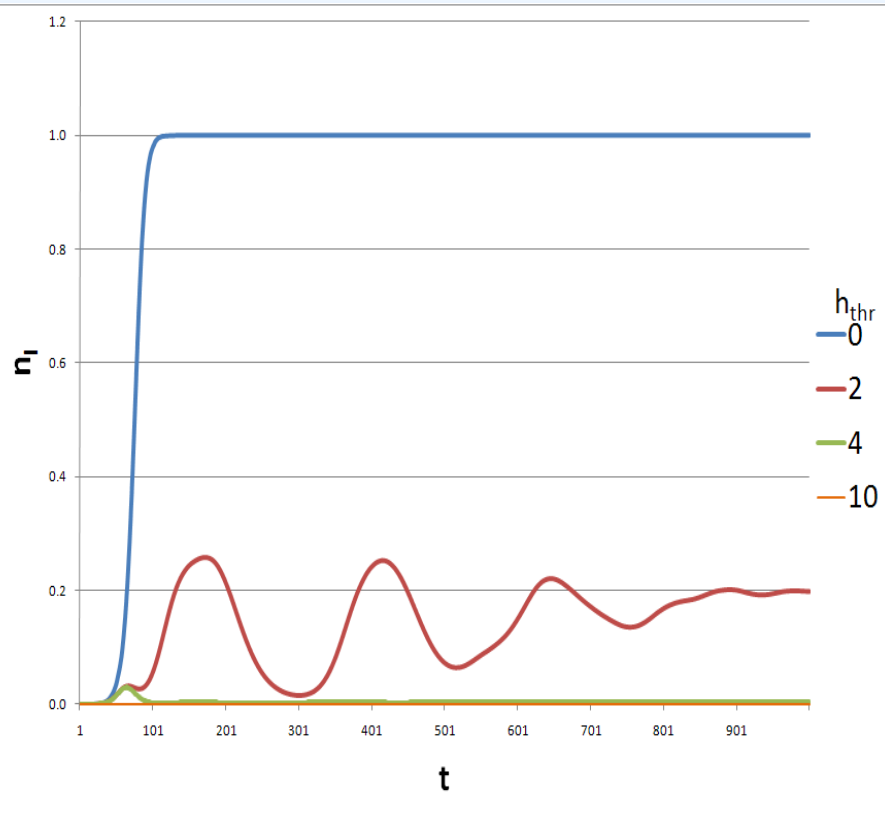


Source Results

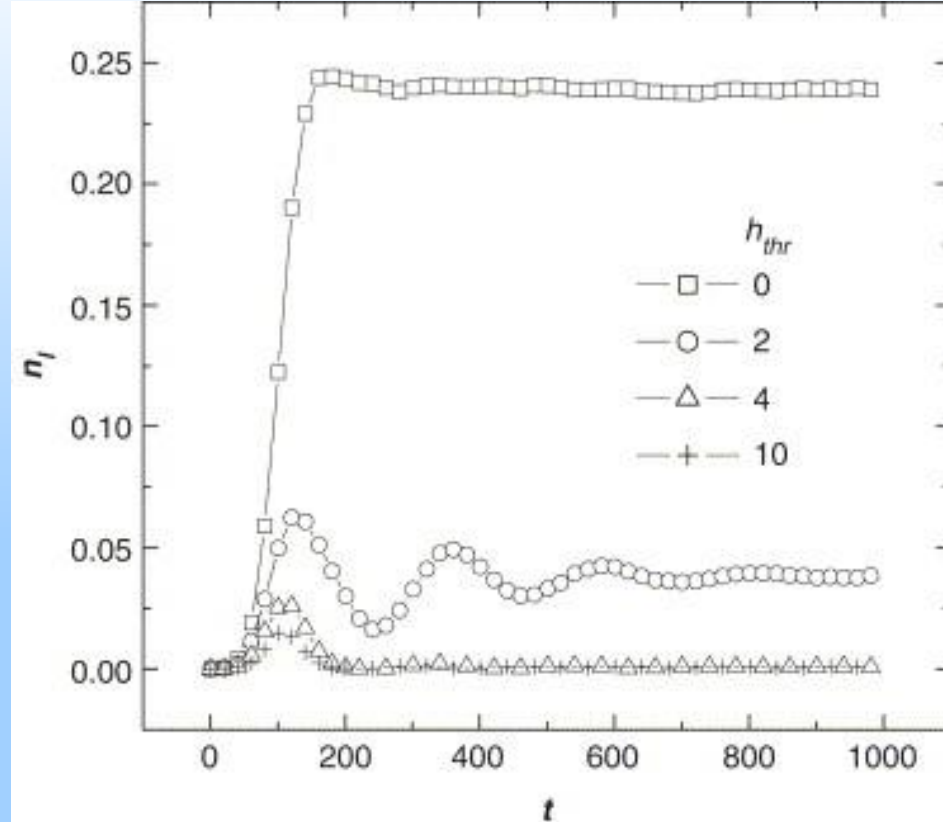


Fraction of infectious individuals n_i as a function of time step t for a set of variations of the immunity duration τ_R . Cross-immunity threshold $h_{\text{thr}} = 2$. Network size $N=10^5$.

Our Results

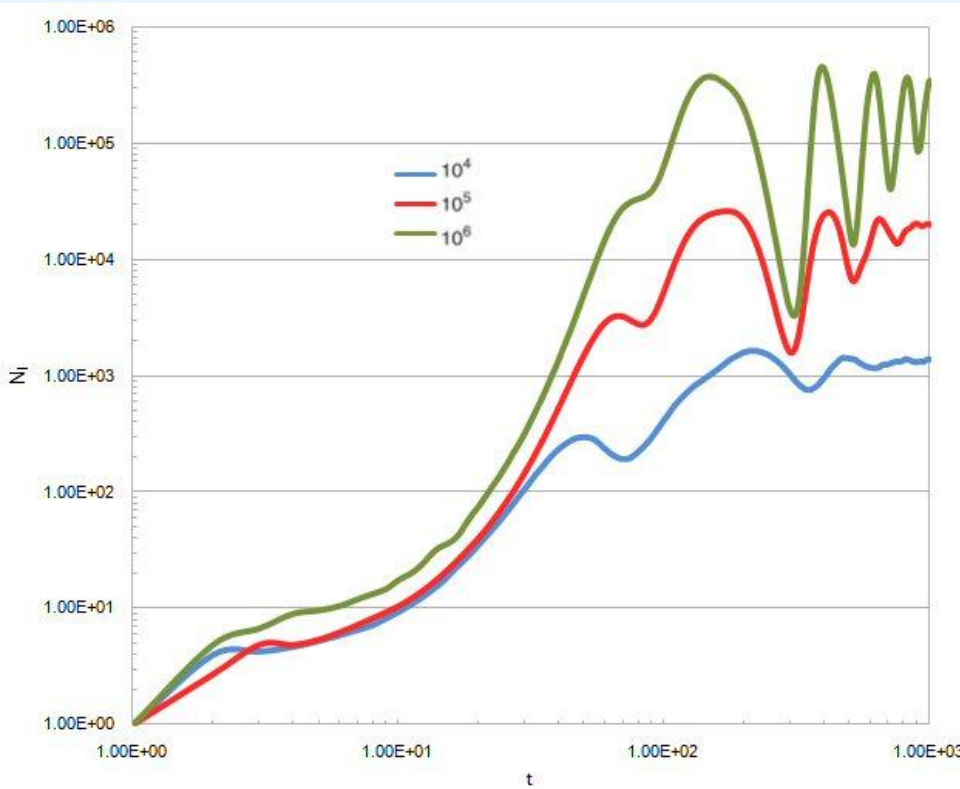


Source Results

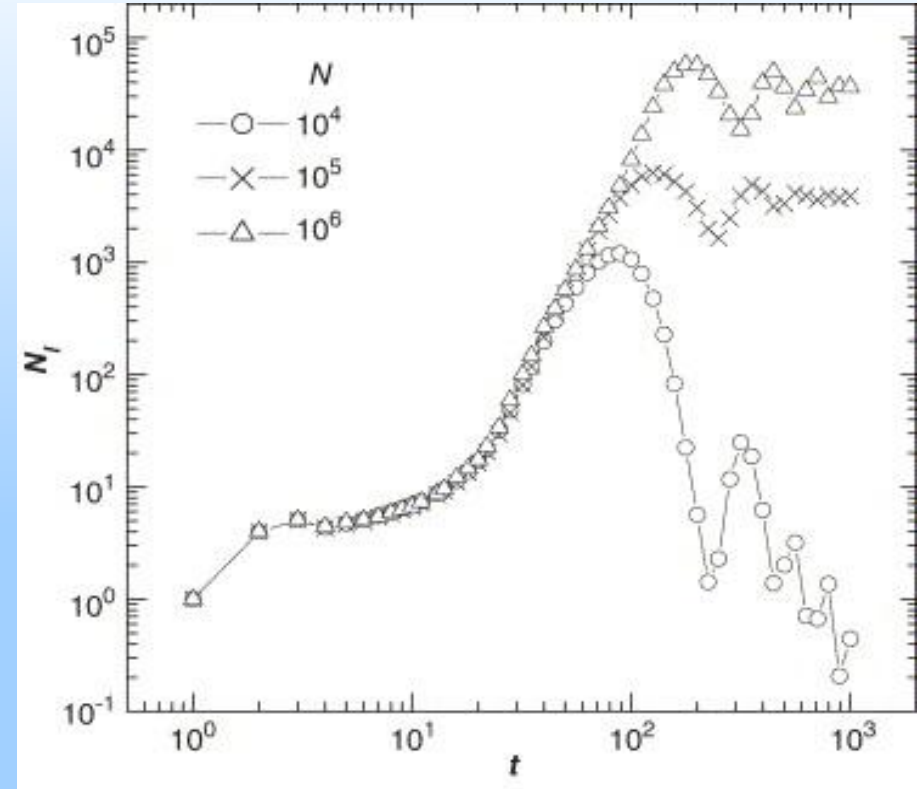


Fraction of infectious individuals n_i as a function of time step t for a set of variations of the cross-immunity threshold h_{thr} . Immunity duration $T_R = 150$. Network size $N = 10^5$.

Our Results



Source Results



Number of infectious individuals N_I as a function of time step t for networks of size $N = 10^4$, 10^5 , and 10^6 . Immunity duration $\tau_R = 150$. Cross-immunity threshold $h_{thr} = 2$.

Summary of results

- Implementation captured behavior very similar to the original work
 - Long immunity durations, high cross-immunity thresholds, and small networks lead to rapid viral extinction
 - Moderate immunity duration and moderate cross-immunity thresholds lead to persistent oscillatory behavior
 - Short immunity durations and low cross-immunity thresholds rapidly lead to systemic infection (potential for pandemic)
- Discrepancies
 - Implemented $h_{\min} > h_{\text{thr}}$ test for immunity, as outlined in the paper, but authors implemented $h_{\min} \geq h_{\text{thr}}$
 - Scaling factor

Future Work

Vaccinations

Policy

Quarantine/isolation

Quarantine and isolation of suspect and confirmed cases.

Movement restrictions

For example, quarantine of neighbourhoods or closure of schools, airports or other transport systems.

'Ring' vaccination

Contacts of suspect smallpox cases are traced and vaccinated when found. Can be coupled with policy of isolation of identified contacts.

Targeted vaccination

For example, vaccination of whole population in affected neighbourhood or city.

Mass vaccination

Vaccination of whole population of a country experiencing or threatened by an outbreak.

Prophylactic vaccination

Vaccination before a smallpox release.

Demographic Variations in Immunity



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