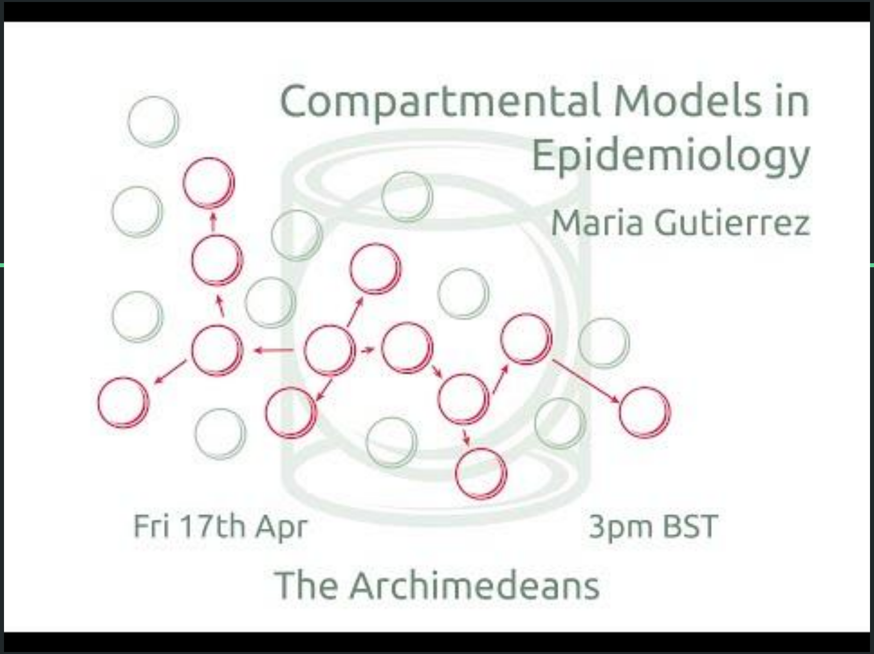
Mathematical Modelling of Infectious Diseases

A more mathematical to sequel to Compartmental Models in Epidemiology

Maria A Gutierrez

4th September 2020, The Archimedeans (Cambridge University Mathematical Society)

Previous talk:



Compartmental Models in Epidemiology

Maria Gutierrez

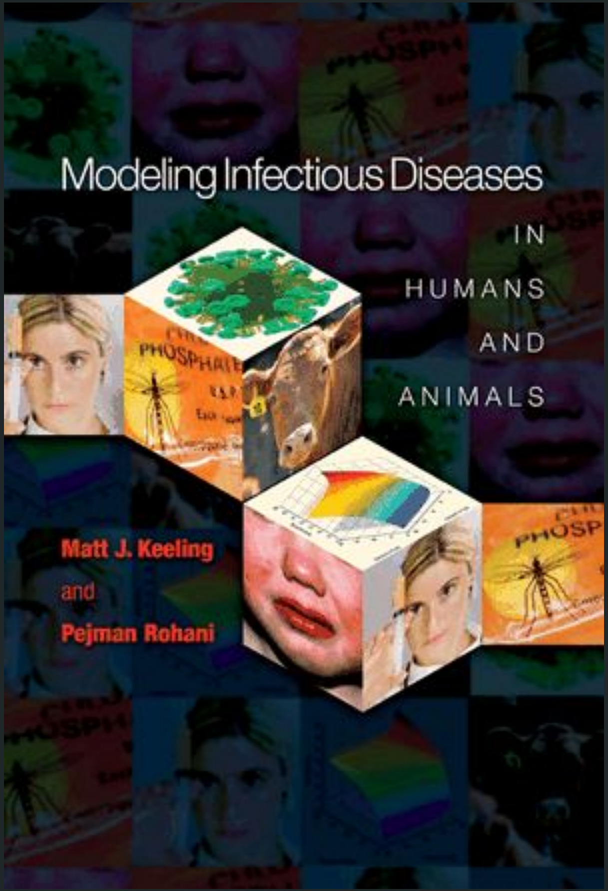
Fri 17th Apr

3pm BST

The Archimedeans

“Modelling Infectious Diseases in Humans and Animals”

By Keeling and Rohani



Outline

Questions are very welcomed at any point.

Chapters:

1. Simple Epidemic Models
2. Host Heterogeneities
3. Temporally Forced Models
4. Stochastic Dynamics
5. Spatial Models
6. Controlling Infectious Diseases

Chapter 1:

Simple Epidemic Models

The Basics

Notation

X: **number** of **susceptible** individuals

Y: **number** of **infectious** individuals

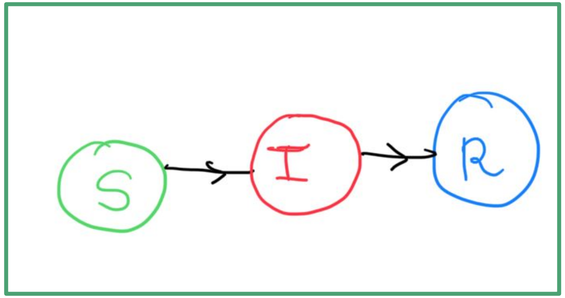
Z: **number** of **recovered** individuals

N: total **population size**

S: **fraction** of **susceptible** individuals = X/N

I: **fraction** of **infected** individuals = Y/N

R: **fraction** of **recovered** individuals = Z/N



Frequency vs Density Dependent Transmission

β (transmission rate): (contact rate) x (transmission probability)

λ (force of infection): per capita rate at which a susceptible individual contracts the infection.

So new infectedes are produced at a rate λX.

Frequency dependent transmission: $\boldsymbol{\lambda = \beta Y / N = \beta I}$

Density dependent transmission: $\boldsymbol{\lambda = \beta Y}$

SIR (frequency dependent) + natural dynamics

γ: recovery rate (could include deaths from disease)

μ: rate of natural births and deaths (constant population size)

$$\begin{aligned}
\dot{X} &= \mu N - \beta XY/N - \mu X \\
\dot{Y} &= +\beta XY/N - \gamma Y - \mu Y \\
\dot{Z} &= +\gamma Y - \mu Z \\
X + Y &+ Z = N
\end{aligned}$$

$$\begin{aligned}
\dot{S} &= \mu - \beta SI - \mu S \\
\dot{I} &= +\beta SI - (\gamma + \mu) I \\
\dot{R} &= +\gamma I - \mu R \\
S + I &+ R = 1
\end{aligned}$$

Basic Reproduction Number & Endemic Equilibrium

The **Basic Reproduction Number** is the number of secondary cases generated per infected individual in an otherwise susceptible population (S=1).

$$\boxed{R_0 = \frac{\beta}{\gamma+\mu} = (\text{transmission rate}) \times (\text{infectious period})}$$

Endemic Equilibrium

$$(S^*, I^*, R^*) = \left(\frac{1}{R_0}, \frac{\mu}{\beta}(R_0 - 1), 1 - I^* - R^*\right)$$

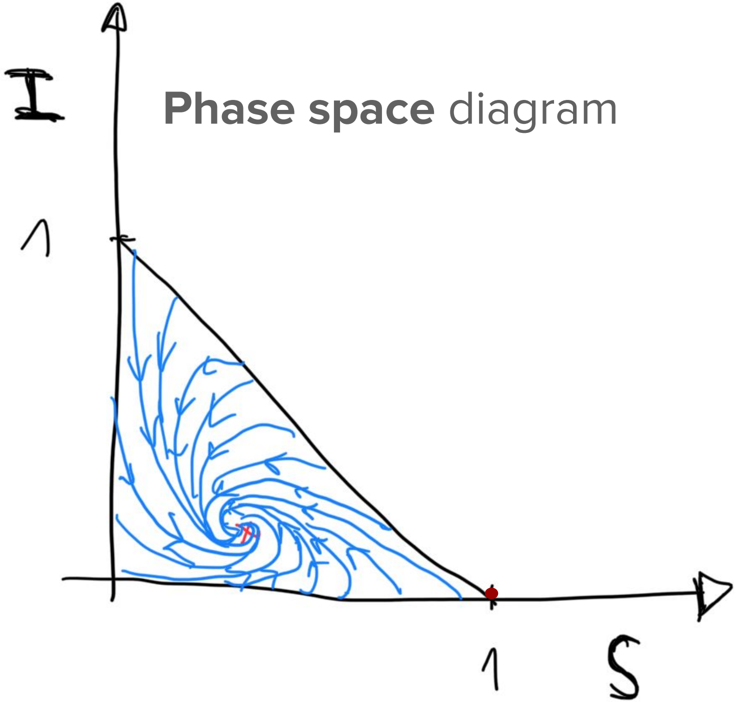
requires

$$R_0 > 1$$

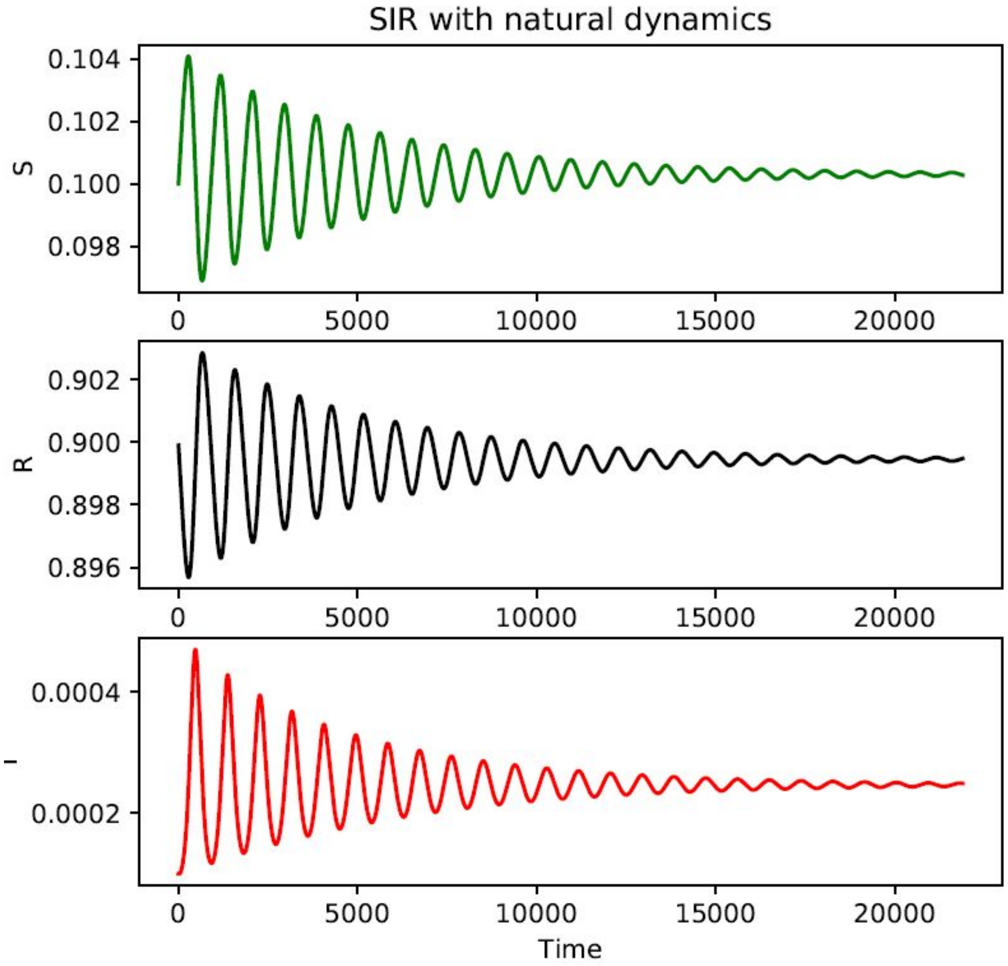
making the Endemic Equilibrium **stable**

Oscillations

Jacobian has **complex eigenvalues**



Phase space diagram



Parameter Estimation

Estimating R_0 from reported cases

In the **early stages** of an epidemic,

$$I(t) \approx I(0)\exp\left([R_0 - 1](\gamma + \mu)t\right)$$

so could use this to **fit the reported data.**

Mean Age at Infection (A)

Average period spent in the susceptible class is approximately the inverse of the force of infection:

$$A \approx \frac{1}{\beta I^*} = \frac{1}{\mu(R_0 - 1)} \Rightarrow R_0 - 1 \approx \frac{L}{A}$$

where L=1/μ is the host's life expectancy

Maximum Likelihood Estimator

Probability individual of age a is susceptible is $P(a) \approx \exp\left(-a\mu(R_0 - 1)\right)$

Data: n seronegative individuals of ages $a_1, a_2, \ldots, a_n$ and m seropositive individuals of ages $b_1, b_2, \ldots, b_m$

Likelihood

$$L(R_0) = f_{\mathbf{X}}(\mathbf{x}|R_0)$$
$$L(R_0) = \prod_{i=1}^{n} \exp(-a_i\mu(R_0 - 1)) \prod_{i=1}^{m} [1 - \exp(-b_i\mu(R_0 - 1))]$$

Choose the basic reproduction number to **maximize the likelihood function** (mle)

Chapter 2:

Host Heterogeneities

Continuous Vs Discrete Heterogeneities

Age Structure - PDE model

$$\frac{\partial S(a,t)}{\partial t} = \mu\delta(a) - S(a,t)\int_0^\infty \beta(a,a')I(a',t)da' - \mu S(a,t) - \frac{\delta S(a,t)}{\delta a}$$

$$\frac{\partial I(a,t)}{\partial t} = S(a,t)\int_0^\infty \beta(a,a')I(a',t)da' - \mu I(a,t) - \gamma I(a,t) - \frac{\delta I(a,t)}{\delta a}$$

Hard to estimate the transmission rate (continuous function of two variables)

Hard to get analytical results

In practice use **numerical solutions**

-> **partition population** into age groups.

Discrete version

Transmission matrix between different subgroups (eg, children and adults)

$$\frac{dS_i}{dt} = -\sum\nolimits_j \beta_{ij} S_i I_j$$

$$\frac{dI_i}{dt} = \sum\nolimits_j \beta_{ij} S_i I_j - \gamma_i I_i$$

(Here no natural dynamics)

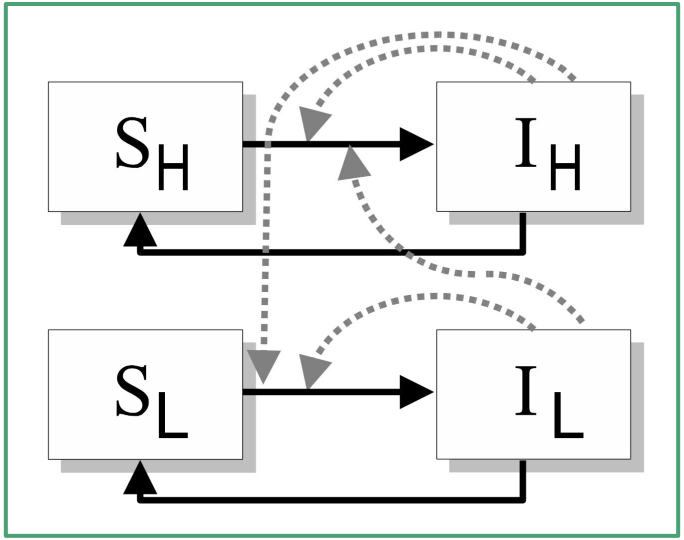
Number of parameters quadratic in number of subgroups

Risk Structure

High & Low Risk Groups

Transmission matrix between groups

$$\underline{\underline{\beta}} = \begin{pmatrix} \beta_{HH} & \beta_{HL} \\ \beta_{LH} & \beta_{LL} \end{pmatrix}$$



$$\beta_{HH} > \beta_{LL} > \beta_{HL} = \beta_{LH}$$

Basic reproduction number:

- Found by eigenvalue approach
- Higher than without risk substructure

Random Partnership Model

Useful for STIs: **partition population according to number of sexual partners**

$$\boxed{\beta_{ij} = \beta \frac{ij}{\sum_k k n_k}} \qquad \frac{I_i}{I} \rightarrow \frac{i n_i}{\sum_k k n_k}$$

where $n_i = N_i / N, I = \sum_i I_i$

$$\boxed{R_0 = \frac{1}{\gamma} \sum_{i,j} \beta_{ij} S_i I_j / I = \frac{\beta}{\gamma} \frac{M^2 + V}{M}}$$

is the *expected* number of secondary cases per primary case, where **M, V** are the **mean** and **variance** of the number of sexual partners

Super-Shedders and Super-Spreaders

Super-shedder: an individual who once infected secretes large amounts of the infectious agent

$$\underline{\underline{\beta}} = \begin{pmatrix} f\beta & \beta \\ f\beta & \beta \end{pmatrix}, f > 1$$

Super-spreader: an individual with a very high number of contacts.

$$\underline{\underline{\beta}} = \begin{pmatrix} f^2\beta & f\beta \\ f\beta & \beta \end{pmatrix}, f > 1$$

Chapter 3:
Temporally Forced Models

Resonance

Take system to be SIR
(ignore natural deaths in X,Y:
everyone gets the disease)

$$\dot{X} = \mu N - \beta(t) XY/N$$
$$\dot{Y} = \beta(t) XY/N - \gamma Y$$

with **time-dependent transmission rate**:

$$\beta(t) = \beta_0(1 + \beta_1 \cos \omega t), |\beta_1| \ll 1$$

Expand around fixed points:

$$X = X^*(1 + x), Y = Y^*(1 + y), |x|, |y| \ll 1$$

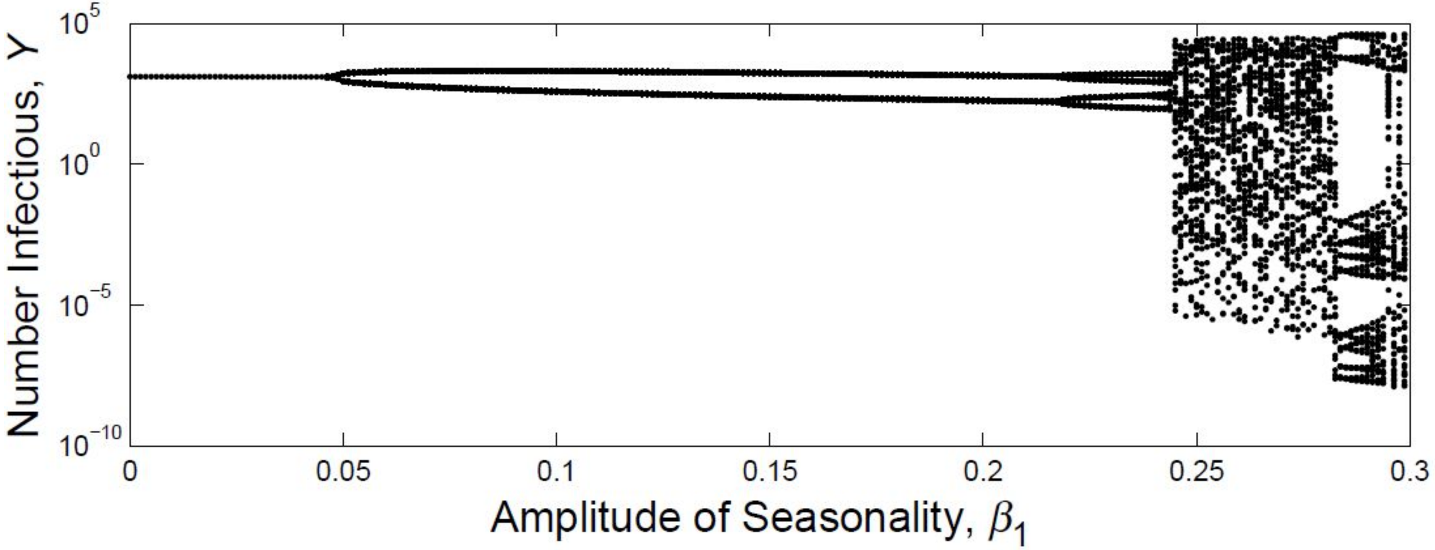
To linear order in small quantities,

$$\boxed{\ddot{y} + \mu R_0 \dot{y} + \mu \beta_0 y = -\beta_1 \omega \gamma \sin \omega t}$$

- Small variations in transmission rate -> significant **amplitude fluctuations**
- Can have **resonance** if forcing at system's natural frequency

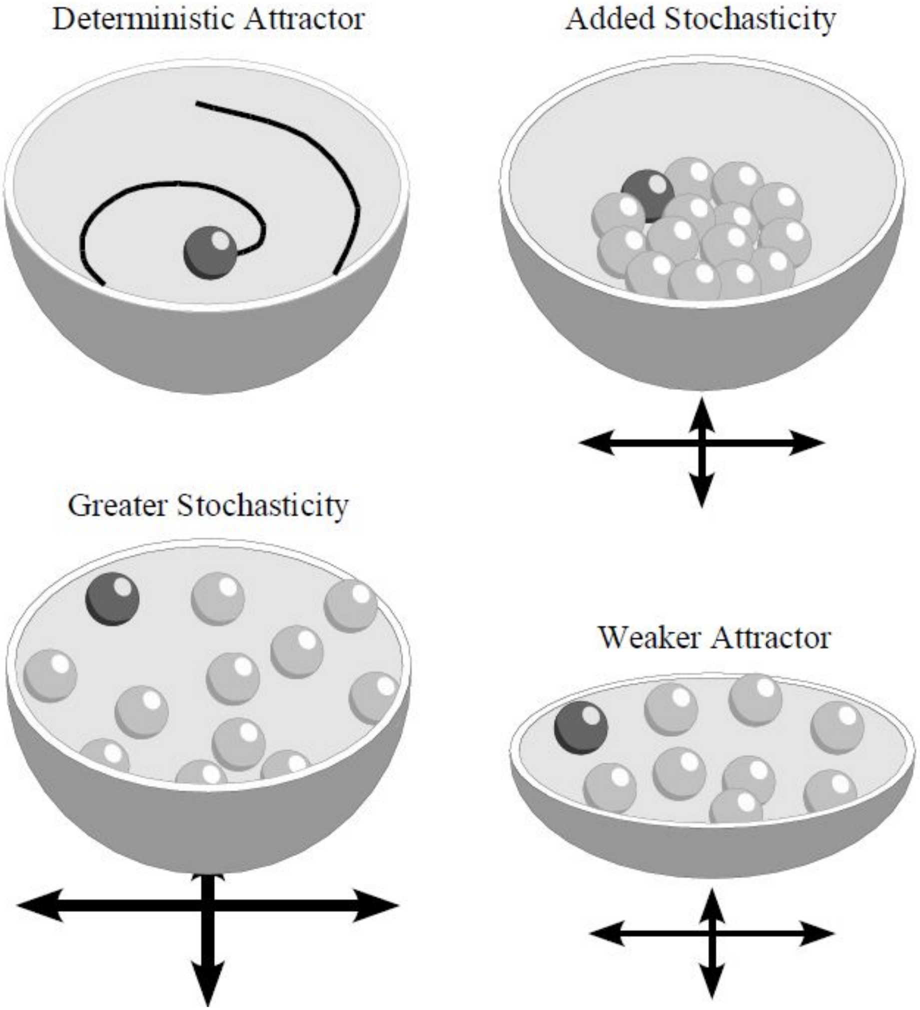
Bifurcation Diagrams

Period-doubling cascade to **chaos**!



Choice of forcing function also important

Chapter 4:
Stochastic Dynamics

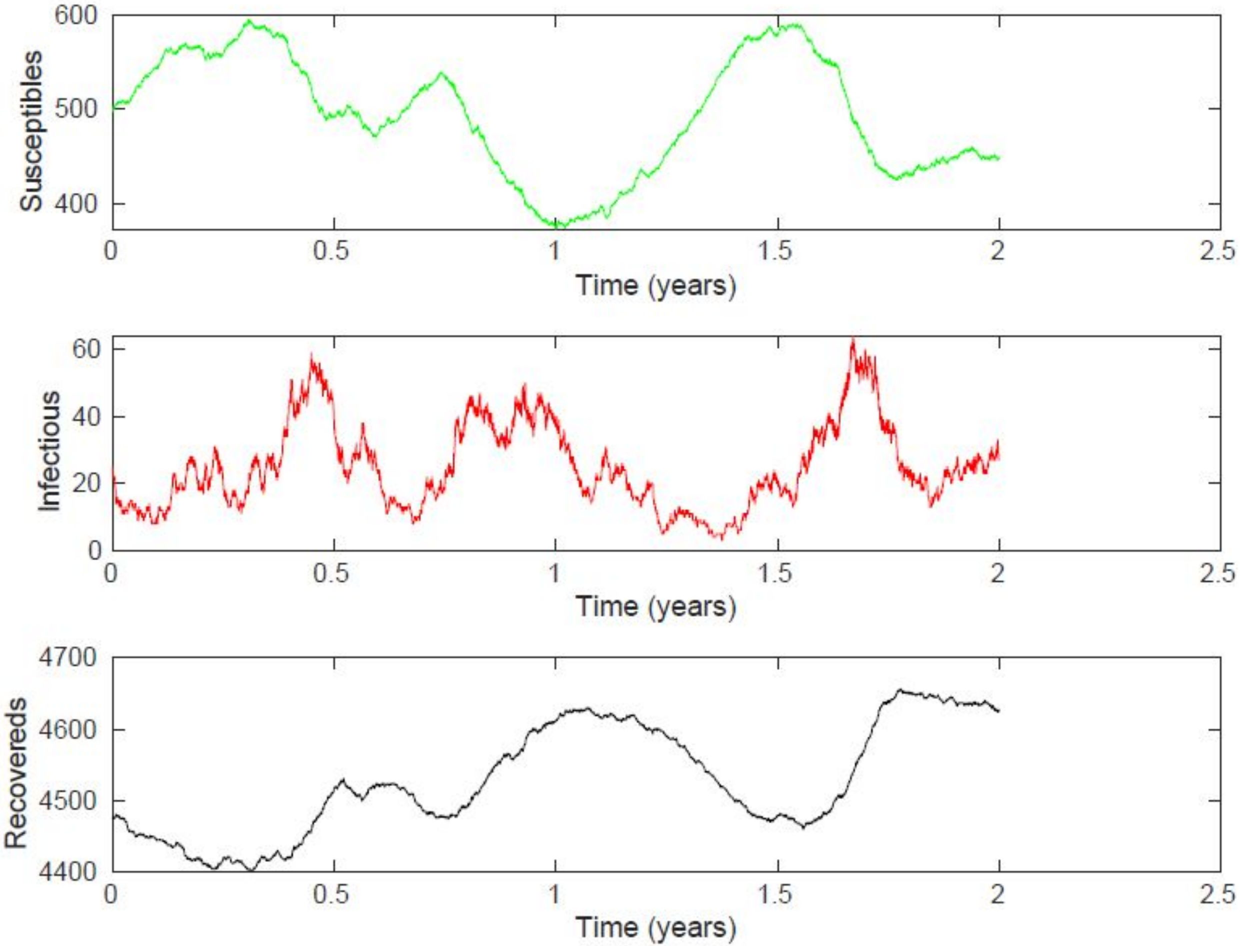

Deterministic Attractor
Added Stochasticity
Greater Stochasticity
Weaker Attractor

Event-Driven Approaches

Gillipsie’s First Reaction Method

1. Label all possible events $E_1, E_2, \ldots, E_n$
2. For each event, determine the rate at which it occurs $R_1, R_2, \ldots, R_n$
   Example (SIR):
   a. Births occurs at rate μN, result is X -> X+1
   b. Transmission occurs at rate βXY/N, result is X->X-1, Y->Y+1
   c. Recovery occurs at rate γY, result is Y->Y-1, Z->Z+1
   d. Deaths of A (where A=X, Y or Z) occur at a rate μA, result is A -> A-1
3. For each event m, calculate the time until it next occurs $$\delta t_m = -\frac{\log RAND_m}{R_m}$$
4. Find the event p that happens first (has the smallest δt)
5. Perform event p and update the time
6. Return to Step 2

Use U(0,1) to generate RAND


Susceptibles
600
500
400
0
0.5
1
1.5
2
2.5
Time (years)
Infectious
60
40
20
0
0
0.5
1
1.5
2
2.5
Time (years)
Recovereds
4700
4600
4500
4400
0
0.5
1
1.5
2
2.5
Time (years)

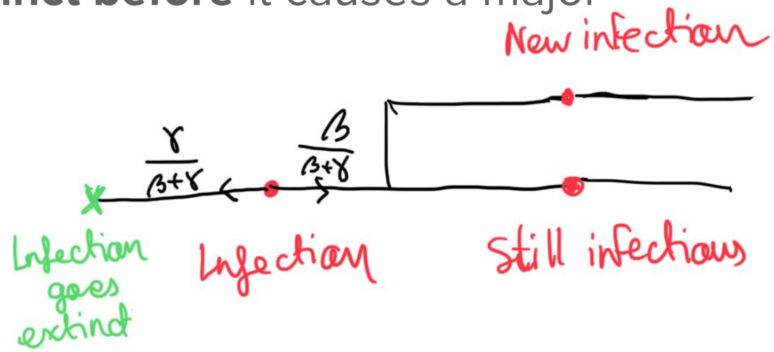
Probability of Extinction - Branching Process

Suppose that one infectious individual arrives at large totally susceptible population.

Let P be the **probability** that the disease goes **extinct before** it causes a major **epidemic**.

$$P = \frac{\gamma}{\beta+\gamma} + \frac{\beta}{\beta+\gamma} P^2$$

$$\Rightarrow P = \min\{1/R_0, 1\}$$



Stochasticity can stop an epidemic (despite having basic reproductive ratio > 1)

Analytical Methods

Stochastic Differential Equations

$$\frac{dx}{dt} = F(x) + f(x)\xi \qquad \xi \sim N(0,1)$$

For a general DE with additive “white noise”, the **exact** probability distribution P is given by the **Fokker-Plank Equation**:

$$\boxed{\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x}(F(x)P(x,t)) + \frac{1}{2}\frac{\partial^2}{\partial x^2}(f(x)^2 P(x,t))}$$

$$\frac{dY}{dt} = [\beta XY/N + \sqrt{\beta XY/N}\xi_1] - [\gamma Y + \sqrt{\gamma Y}\xi_2]$$

$$\frac{dY}{dt} = \beta XY/N - \gamma Y + \sqrt{\beta XY/N + \gamma Y}\xi$$

(the two independent normal random variables add their variances and means)

Fokker-Plank equation (continuation)

$$\frac{\partial P(Y)}{\partial t} = -\frac{\partial}{\partial Y}([\beta XY/N - \gamma Y]P(Y)) + \frac{1}{2}\frac{\partial^2}{\partial Y^2}([\beta XY/N + \gamma Y]P(Y))$$

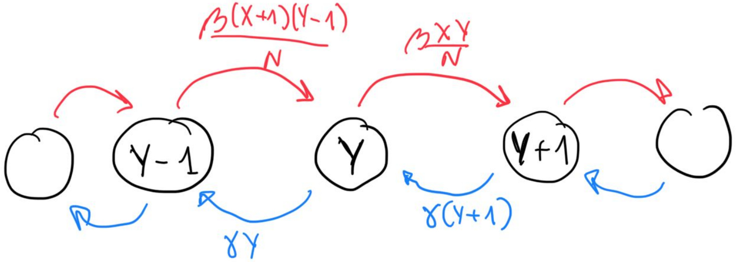
Equilibrium P*(Y) is given by RHS=0 so

$$\boxed{\frac{\partial P(Y)}{\partial Y} = \left[\frac{2\beta XY - 2\gamma YN - \beta(N-2Y) + \gamma N}{\beta XY + \gamma YN}\right] P(Y)}$$

where X=N-Y (for SIS)

-Can **integrate** (at least numerically)

Master Equations: SIS dynamics



P_Y : probability that Y individuals are infectious

$$\frac{dP_Y}{dt} = -P_Y \gamma Y - P_Y \beta \frac{(N-Y)Y}{N} + P_{Y+1}\gamma(Y+1) + P_{Y-1}\beta \frac{(N-Y+1)(Y-1)}{N}$$

BCs: $P_{-1} = 0 = P_{N+1}$

Equilibrium has $\dot{P}_Y = 0 \; \forall Y = 0, 1, \ldots, N$ so flow from Y to Y+1 is the same as the flow from Y+1 to Y

$$\Rightarrow P^*_{Y+1}\gamma(Y+1) = P^*_Y(\beta(N-Y)Y/N) \text{ s.t. } \textstyle\sum_{Y=1}^{N} P^*_Y = 1$$

$$\boxed{P^*_Y = P^*_1 \frac{(N-1)!}{(N-Y)!Y}\left(\frac{\beta}{\gamma N}\right)^{Y-1}}$$

Break!

Chapter 5:

Spatial Models

Levins-Type Metapopulations

Each **subpopulation** is **either infected or disease-free**.

Global coupling: P is probability a subpopulation is infected, **e** is **extinction rate** (of the disease in each subpopulation), **ρ** gives the **coupling** between subpopulations

$$\frac{dP}{dt} = \rho(1-P)P - eP$$

General case:

$$\frac{dP_i}{dt} = \sum_j \rho_{ij}(1-P_i)P_j - e_i P_i$$

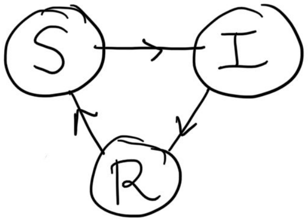
Lattice-Based Models

Eg: ‘Forest-Fire’ Model simulation for SIRS dynamics

S to I at rate $\tau n+\varepsilon$ where n is the number of infected neighbours

I to R at rate γ (recovery rate)

R to S at rate ν (at which immunity wanes)



τ: transmission rate between contacts

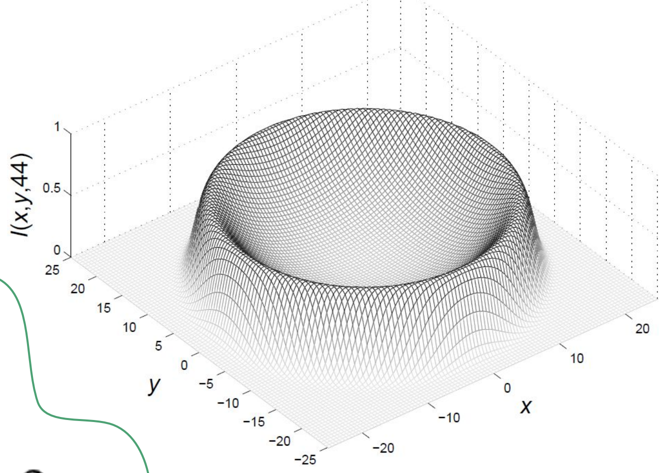
ε: **import** rate into susceptible sites

Simulation! The MATLAB code for this simulation (and for many other models) is here:

https://github.com/meryjoy99/mathematical_modelling_infectious_diseases

Continuous-Space Models

Reaction-Diffusion Equation



$$\begin{aligned}
\frac{\partial X(t,\mathbf{x})}{\partial t} &= -\beta XY/N + D_X \nabla^2 X \\
\frac{\partial Y(t,\mathbf{x})}{\partial t} &= \beta XY/N - \gamma Y + D_Y \nabla^2 Y \\
\frac{\partial Z(t,\mathbf{x})}{\partial t} &= \gamma Y + D_Z \nabla^2 Z
\end{aligned}$$

Transient dynamics: **travelling wave** at the origin $Y(t, x, y) = \hat{Y}(r - ct)$

If same diffusion, **speed** is $\boxed{c = 2\sqrt{D(R_0 - 1)\gamma}}$

Integro-Differential Equations

K(d) transmission kernel: how infectivity decreases with distance

$$\frac{dX(\mathbf{x},t)}{dt} = -\lambda(\mathbf{x},t)X(\mathbf{x},t)$$

$$\frac{dY(\mathbf{x},t)}{dt} = \lambda(\mathbf{x},t)X(\mathbf{x},t) - \gamma Y(\mathbf{x},t)$$

$$\lambda(\mathbf{x},t) = \beta \int Y(\mathbf{y},t)K(\mathbf{x}-\mathbf{y})d^2y$$

(density dependent)

Basic Reproduction Ratio:

$$R_0 = \beta \int_{\mathbb{R}^2} N(\mathbf{x})K(\mathbf{x})d^2x = 2\pi\beta N \int_0^\infty K(r)rdr$$

for uniform population density

Individual-Based Models

An Example

$$\lambda_i = \beta \sum_{j \in \text{infectious}} K(d(i,j))$$

Force of infection to a susceptible individual i is where K is the transmission kernel and d(i,j) is the distance between i and an infectious individual j.

Hard to parameterize

Computationally expensive (cubic order in population size)

Shortcuts: discrete time, discrete space

Simulation! The MATLAB code for this simulation (and for many other models) is here:

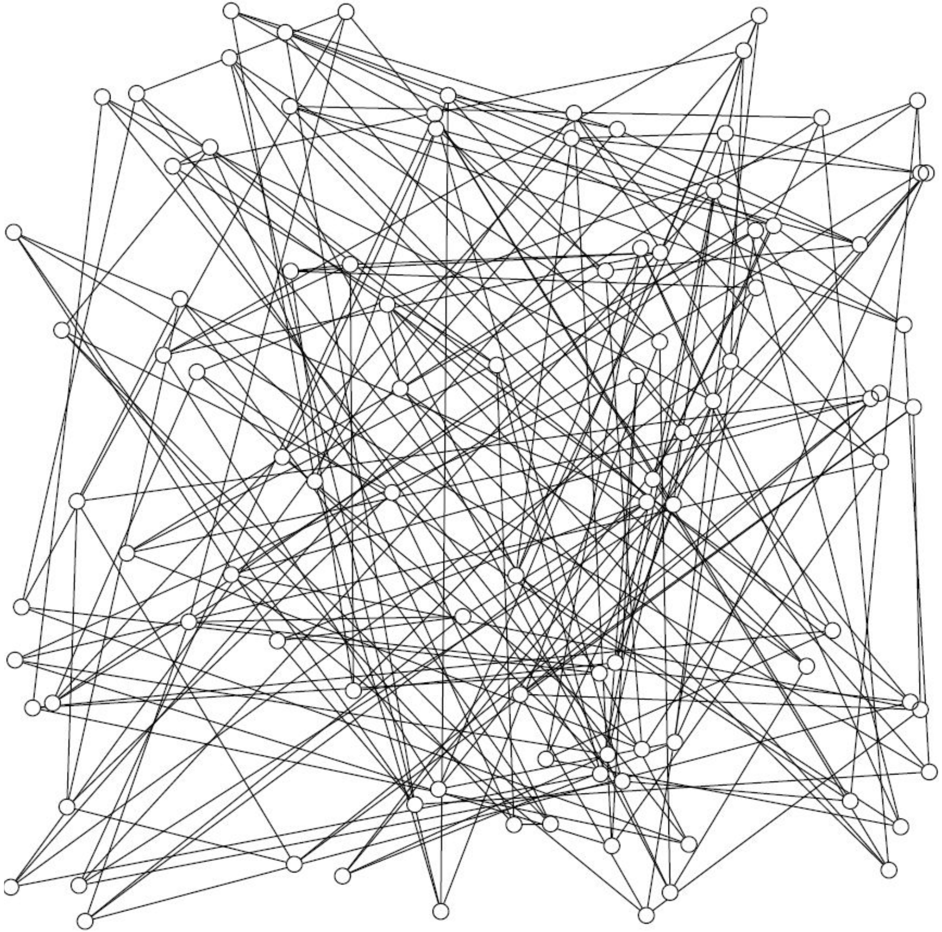
https://github.com/meryjoy99/mathematical_modelling_infectious_diseases

Networks

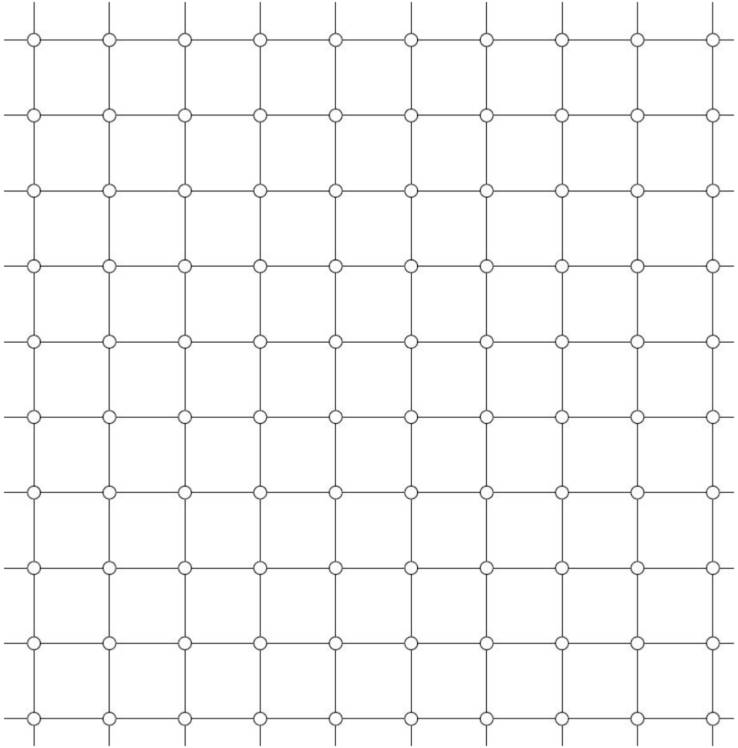
Random Networks

Ignores spatial position of individuals

Connections formed at random

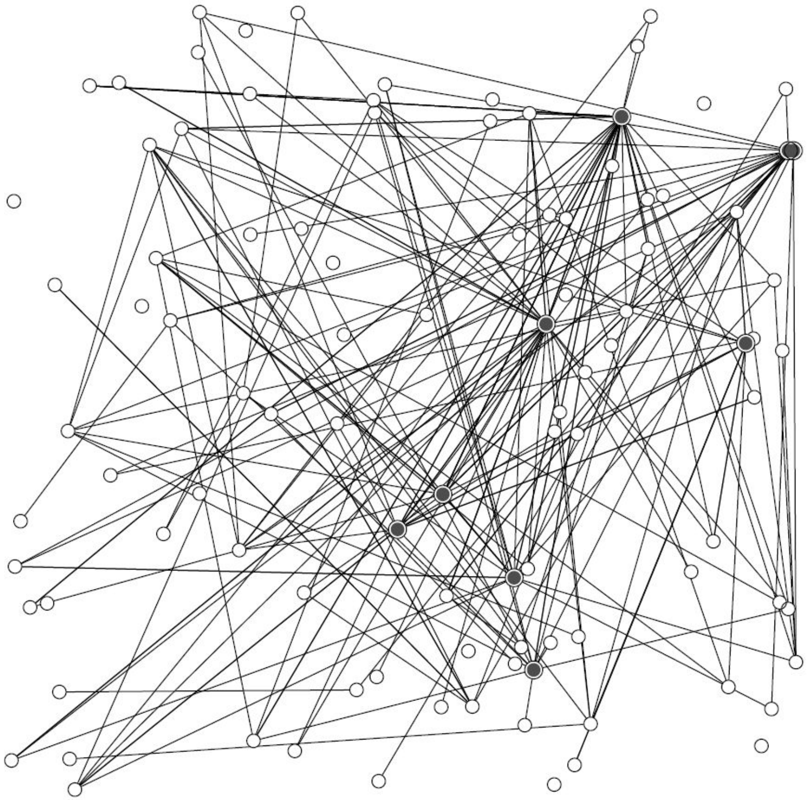


Lattices

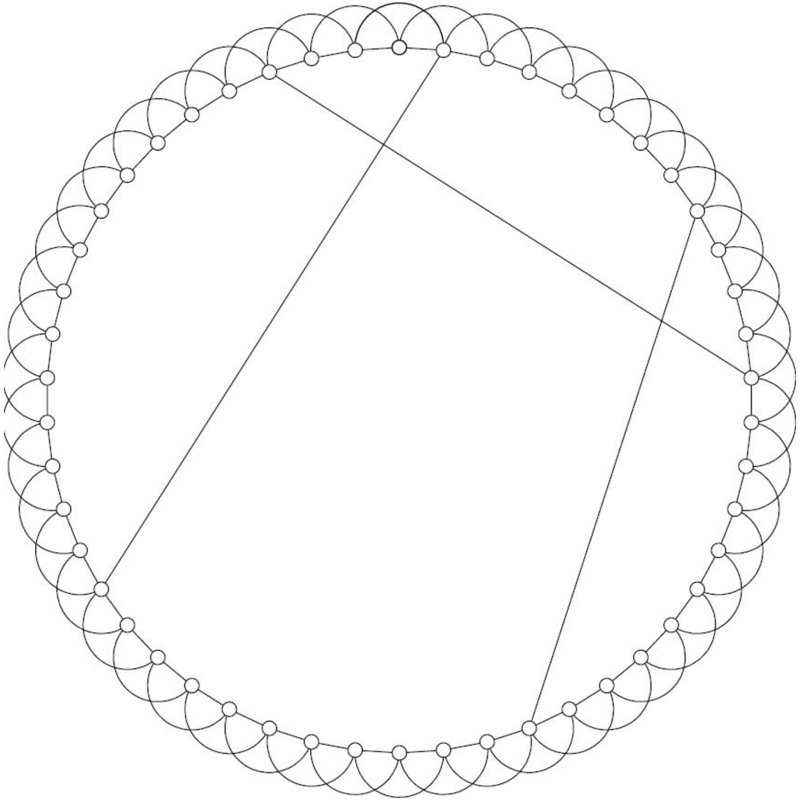


Spatial Networks

Scale-Free Networks



Small World Networks



Pair-Wise Models for Networks

Notation

For A,B,C ∈ {X,Y,Z}

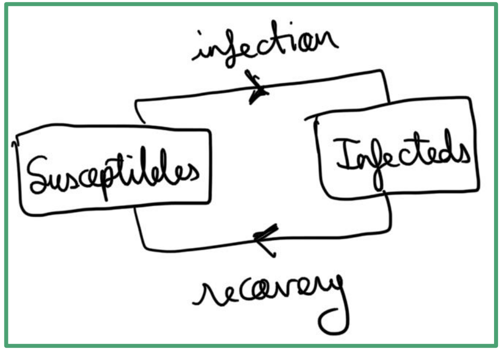
[AB]: Number of pairs in the network with an individual in class A connected to another individual in class B.

[ABC]: Number of triples in the network with an individual in A connected to someone in B connected to somebody else in C.

τ transmission probability: between infected-susceptible contacts

Rate of new infection= τ[YX]

SIS Pair-Wise Equations



$$\frac{dX}{dt} = \gamma Y - \tau[Y\overrightarrow{X}]$$

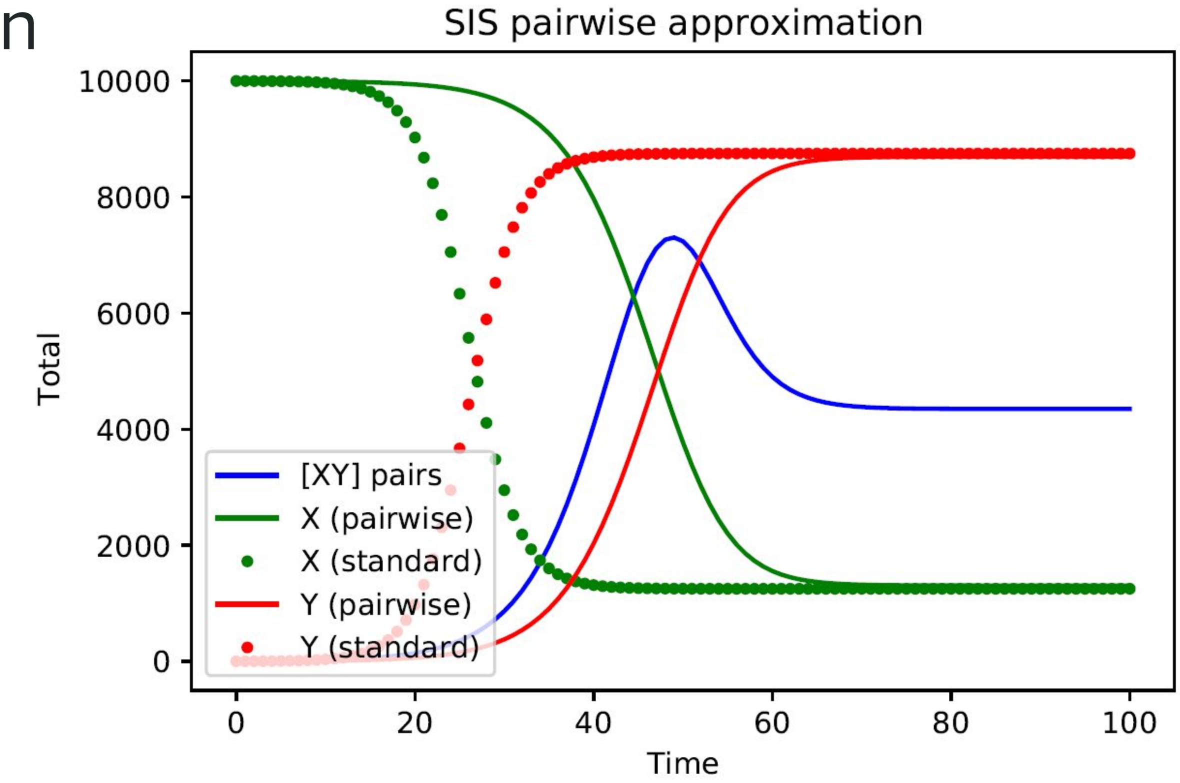
$$\frac{d[XY]}{dt} = \tau[Y\overrightarrow{X}X] + \gamma[YY] - \tau[Y\overrightarrow{X}] - \tau[Y\overrightarrow{X}Y] - \gamma[XY]$$

$$[ABC] \approx \frac{(n-1)}{n}\frac{[AB][BC]}{[B]}$$

$$Y = N - X$$
$$[XX] = nX - [XY]$$

where **n** is the average number of contacts of each individual.

Solution



Python **code** obtain to obtain numerical solutions + graphics at github repository: https://github.com/meryjoy99/mathematical_modelling_infectious_diseases

Chapter 6:

Controlling Infectious Diseases

Pulsed Vaccination

Model

p: fraction of susceptibles that get vaccinated

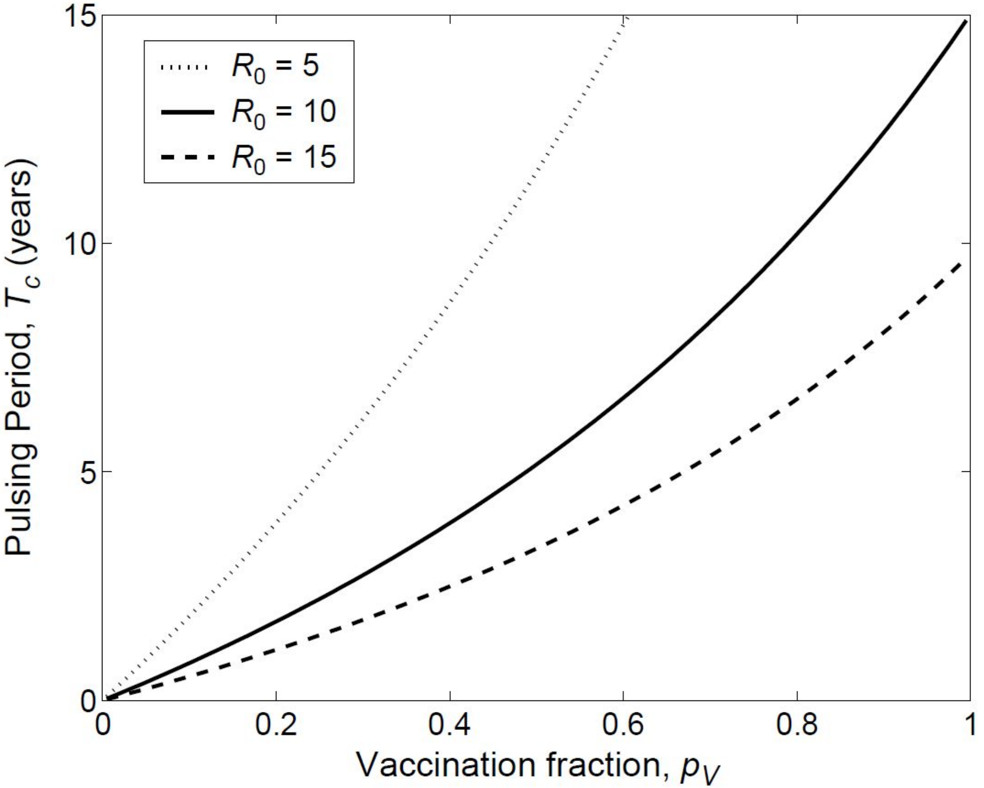
T: time gap between vaccinations

$$\frac{dS}{dt} = \mu - \beta SI - \mu S - p\sum_{n=0}^{\infty} S(nT^-)\delta(t - nT)$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I$$

Optimal time gap (Shulgin et al. 1998)

$$\boxed{\frac{(\mu T-p)(e^{\mu T}-1)+\mu pT}{\mu T(p-1+e^{\mu T})} < \frac{1}{R_0}}$$



Age-Structured Vaccination

Model

A: age of vaccination

p: vaccination fraction

$$\frac{\partial S(a,t)}{\partial t} = -\beta S(a,t)\hat{I}(t) - \mu S(a,t) - \frac{\delta S(a,t)}{\delta a}$$

$$\frac{\partial I(a,t)}{\partial t} = \beta S(a,t)\hat{I}(t) - \mu I(a,t) - \gamma I(a,t) - \frac{\delta I(a,t)}{\delta a}$$

$$\hat{I}(t) = \int_0^\infty I(a,t)da$$

$$S(0,t) = \mu, I(0,t) = 0$$

$$S(A^+,t) = (1-p)S(A^-,t)$$

$$I(A^+,t) = I(A^-,t)$$

Equilibrium

$$0 = \frac{\partial S}{\partial t} \Rightarrow S^*(a) = \begin{cases} \mu \exp\left(-(\beta \hat{I}^* + \mu)a\right) & \text{for } a < A \\ \mu(1-p)\exp\left(-(\beta \hat{I}^* + \mu)a\right) & \text{for } a > A \end{cases}$$

$$0 = \frac{d\hat{I}}{dt} = \int_0^\infty \frac{\partial I(a,t)}{\partial t} da = \hat{I}\ \left(\beta \int_0^\infty S(a,t)da - \gamma - \mu\right)$$

$$\Rightarrow \quad \boxed{\frac{1 - p\exp\left(-(\beta \hat{I}^* + \mu)A\right)}{\beta \hat{I}^* + \mu} = \frac{\beta + \mu}{\beta \mu}}$$

Total number of infecteds, Î* , minimised when A=0

Questions?

Feedback form: https://forms.gle/CZj4TJXqazohsaPE8

Resources: www.mariaalegriagutierrez.wordpress.com/epi-talk-2

Including:

- Links to **code** and **figures**
- **Slides** for this talk (and the previous one)
- Recommended papers, books, courses, etc

Figures: http://homepages.warwick.ac.uk/~masfz/ModelingInfectiousDiseases/index.html

Contact: mag84@cam.ac.uk

THANK YOU!