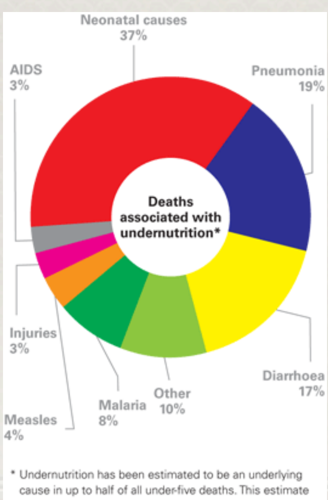
Mathematical Models of Infectious Diseases

Pej Rohani
Department of Ecology & Evolutionary Biology
University of Michigan

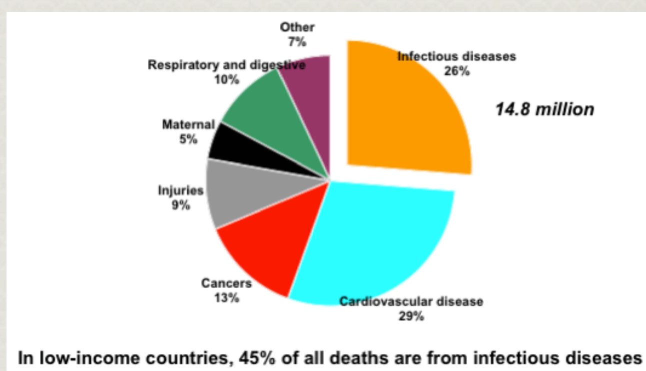
John Drake
Odum School of Ecology
University of Georgia

Global causes of mortality

Measles & pertussis account for ~300,000 and ~200,000 annual deaths



Infant mortality



Total mortality

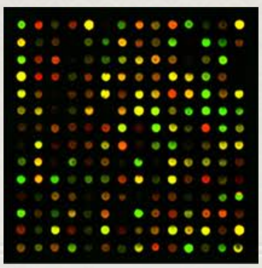
Multifaceted approach to understanding infectious diseases

Medicine

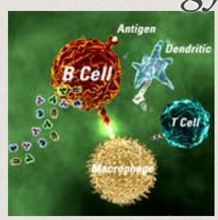
But these approaches don't address important questions at population level ...

Microbiology

Genomics



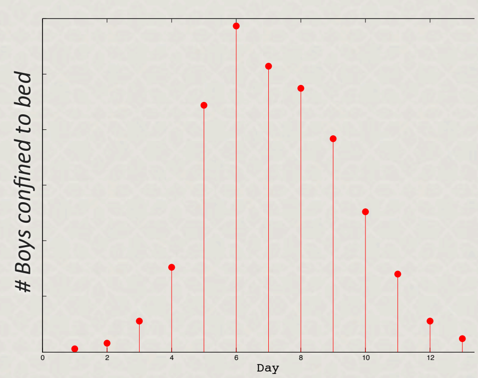
Immunology



Vaccines & Drugs

School outbreak

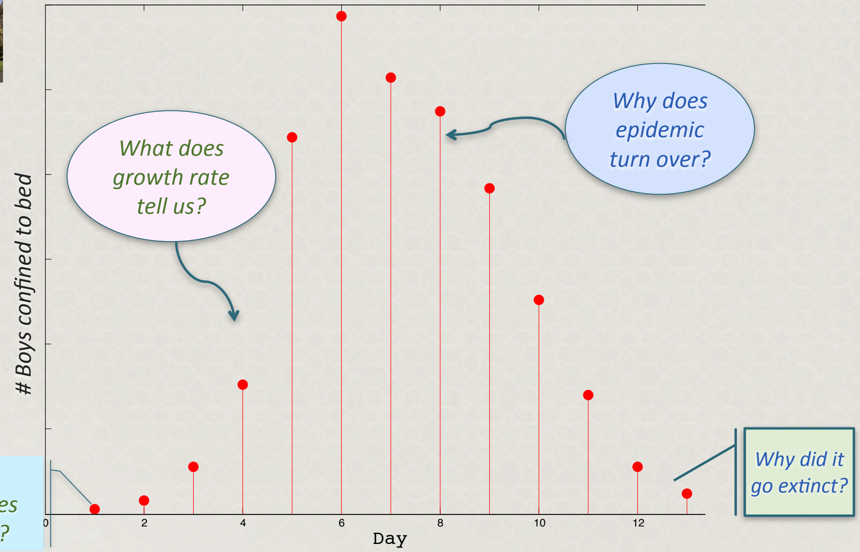
Boarding School, England
Jan 1978



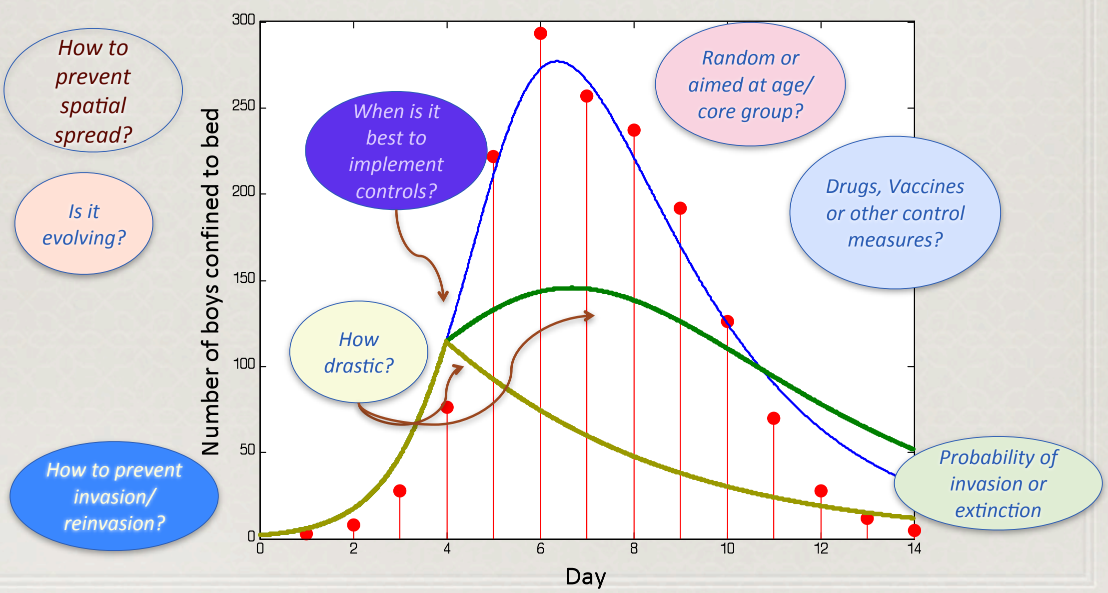
Raises numerous questions:

- *What is etiological agent?*
- *Is it novel?*
- *Is a vaccine available?*

Modeling questions I. Basics



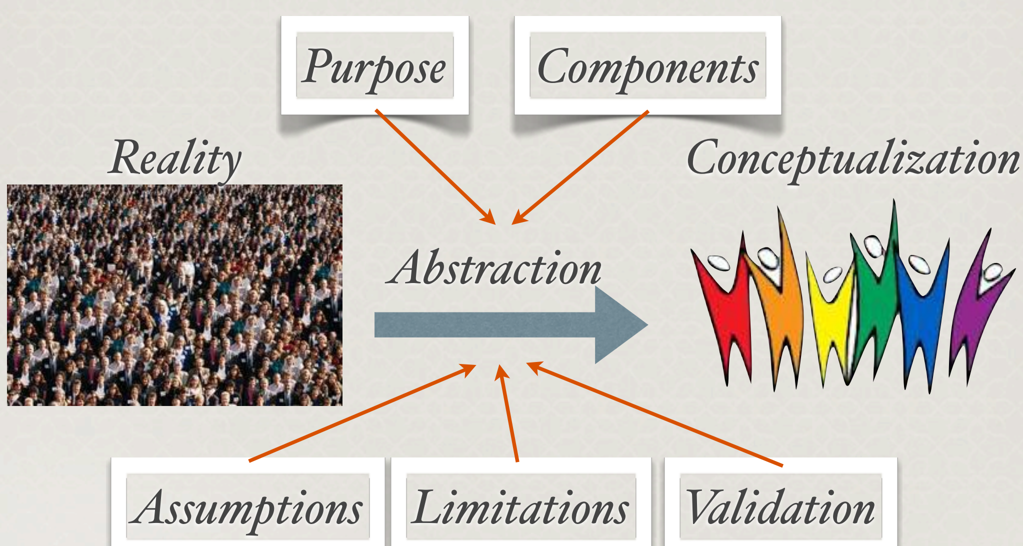
Modeling questions II. Control Implications



What is a model?

- *Different types of models:*
  - *A **mathematical/computational model** is an abstract model that uses mathematical language to describe the behaviour of a system*
  - *A **Statistical model** attempts to describe relationships between observed quantities and independent variables*
- *Developing a model is different from statistical analyses of data*

Abstraction



What's a 'Good' Model?

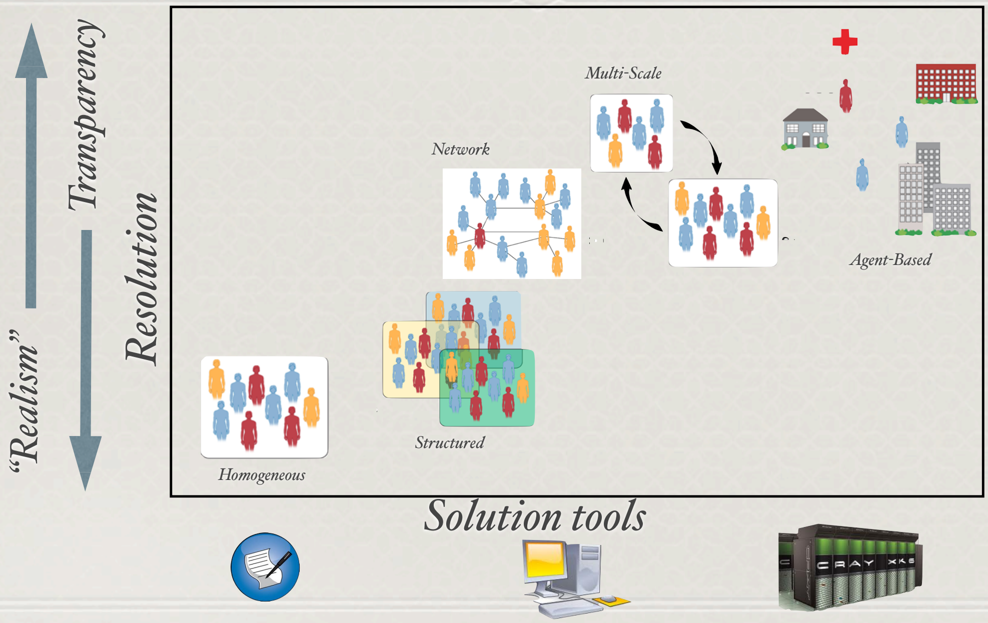
- Choice of model depends crucially on focal question and available data (hammer & chisel or pneumatic drill?)

- Use model principally for
  - understanding nature
  - making predictions

Judging a Model...

- Three fundamental features of models, often opposing forces:
  - ***Accuracy***
    - *Capture observed patterns (qualitative or quantitative?) and make predictions*
    - *Increases with model complexity*
  - ***Transparency***
    - *Ability to understand model components*
    - *Decreases with model complexity*
  - ***Flexibility***
    - *How easily can model be adapted to new scenarios?*
    - *Decreases with model complexity*

Realism Vs Transparency

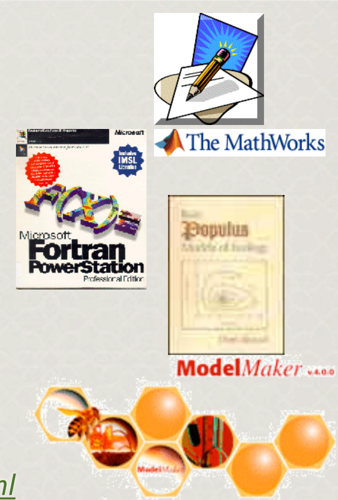


'How' do you Model?

Analytical Models
Concentrate on problems that can be expressed and analysed fully using analytical approaches.

Problem-based Models
Construct most "appropriate" model and use whatever combination of methods for analysis and prediction.

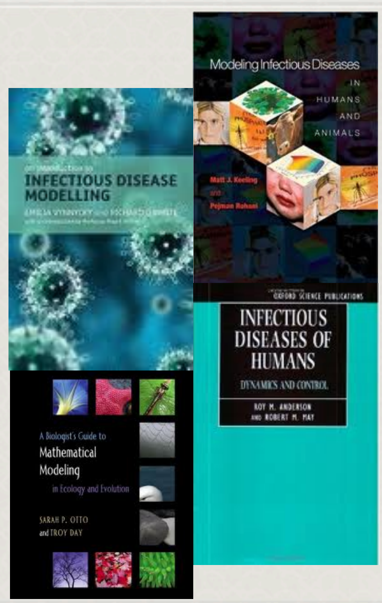
Ready-Made Software
ModelMaker
www.modelkinetix.com/modelmaker/modelmaker.html



Global simulators

Resource Materials

- *Keeling & Rohani (2008)*
- *Vynnycky & White (2010)*
- *Anderson & May (1991)*
- *Otto & Day (2007)*



Mathematical Modelling of Infectious Diseases

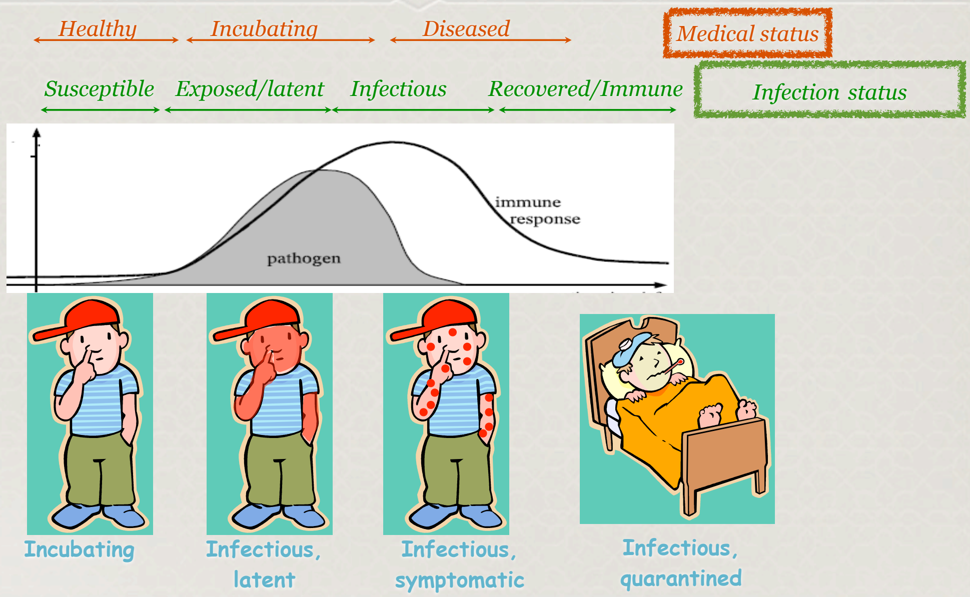
- Objective 1: Setting up simple models
  - Different transmission modes
    - Basic Reproduction Ratio (R_0), Simple Epidemics, Invasion threshold & extinction
  - Stability analysis
- Objective 2: Control
  - Infection management
- Objective 3: Statistical estimation
  - R_o and other parameters
- Objective 4: Heterogeneities
  - Risk structure
  - Realistic pathogenesis
  - Seasonality
  - Age-structured transmission effects
- Objective 5: Sensitivity
  - Stochastic implementation
  - Parameter uncertainty

The simplest models

- *Let's develop a model for Boarding School influenza outbreak*
- *Some **important** choices need to be made at outset*

1. ***What do we want to keep track of?***
   - *Amount of virus in population?*
   - *Antibody titre of everyone in population (school)?*
   - *Cities in which infected people have been found?*

Categorising individuals



The simplest models

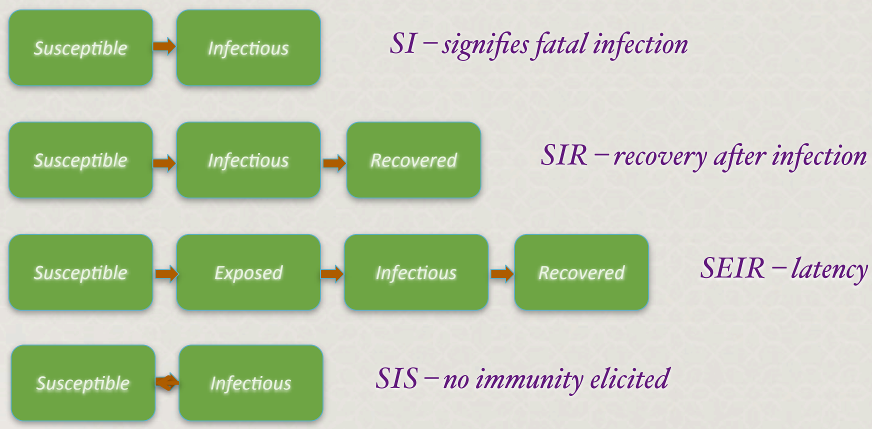
- Pragmatic choice: categorise individuals in population according to their infection status, eg:
  - Susceptible
  - Infectious
  - Recovered/Immune

These are our "system variables"

The simplest models

2. **What model structure?**

-- Determined by pathogen biology



The simplest models

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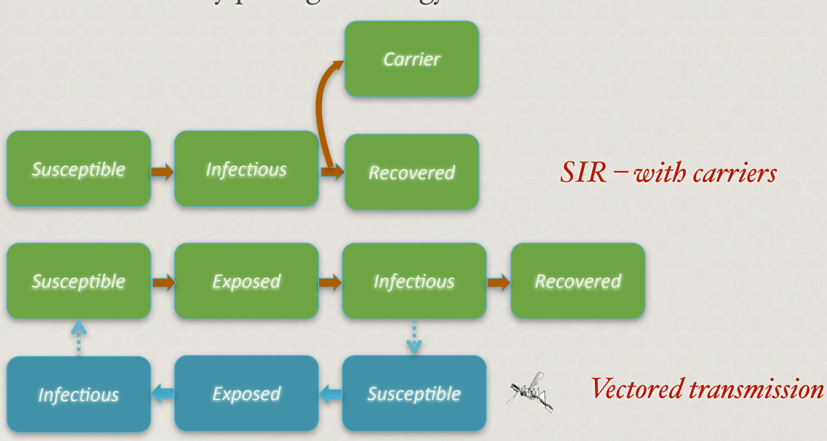


The simplest models

- **What model structure?**
- Depends on what do we know about the pathogen (eg, influenza)
  - It's directly transmitted (aerosol)
  - An acute infection
  - Lifelong immunity (to that strain)

The simplest models

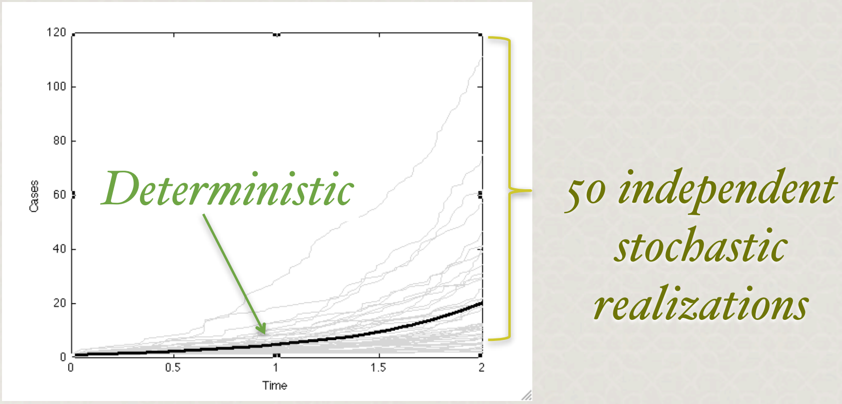
- *Flow between classes/compartments determined by details of host population structure and pathogen biology*

- *Host population size*
- *Contact rates*
- *Pathogen infectivity*

These are our "parameters"

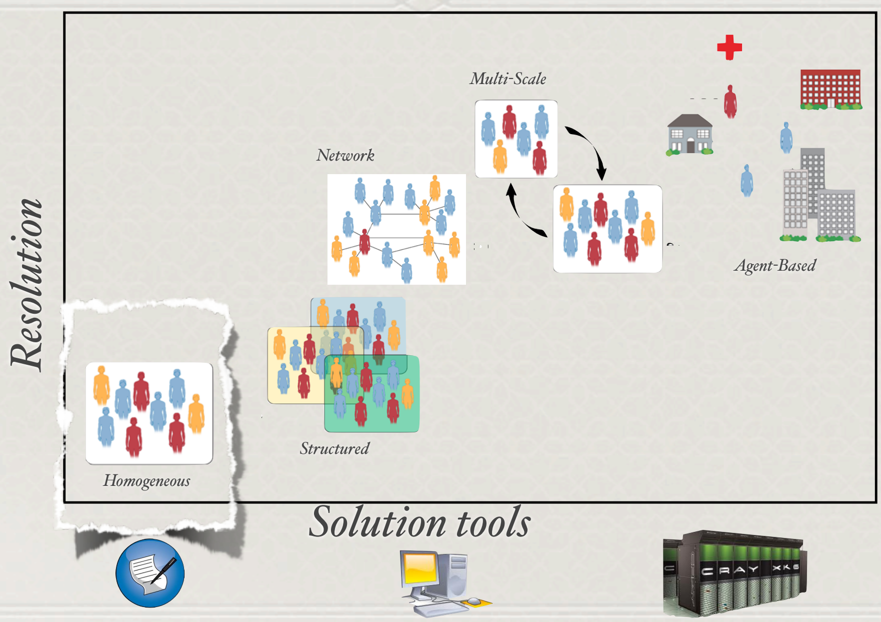
The simplest models

3. **Deterministic or stochastic?**



On average, stochastic simulations identical to deterministic predictions, though individual realizations may be quite different

Realism Vs Transparency



The simplest models

- We've settled on a deterministic SIR model – now what?
- How do we write down some equations to describe spread of 'flu in this population?
- Assign each system variable a unique Roman letter, eg:
  - Susceptible, S (proportion) or X (number)
  - Infectious, I (proportion) or Y (number)
  - Recovered/Immune, R (proportion) or Z (number)
- Assign parameters a unique (typically Greek) letter, eg:
  - Contact rate, κ
  - Pathogen infectivity, ν

Very important!

- NOTHING SPECIAL ABOUT MY CHOICE OF NOTATION – USE OF PARTICULAR LETTERS HIGHLY IDIOSYNCRATIC
- OTHER AUTHORS MAY USE DIFFERENT LETTERS TO DENOTE SAME VARIABLES OR PARAMETERS.
- YOU CANNOT AUTOMATICALLY ASSUME THAT β IN TWO DIFFERENT PAPERS MEANS THE SAME THING!

Model equations

- If we knew X_t and Y_t, could we predict $X_{t+\delta t}$ and $Y_{t+\delta t}$, where δt is some (very short) time later?

$$X_{t+\delta t} = X_t - (\nu\kappa\ \delta t)\ X_t\ Y_t/N$$

$$Y_{t+\delta t} = Y_t + (\nu\kappa\ \delta t)\ X_t\ Y_t/N - (\gamma\ \delta t)\ Y_t$$

- And

$$Z_{t+\delta t} = Z_t + (\gamma\ \delta t)\ Y_t$$

ν is probability of transmission given contact
κ is contact rate

Basic questions?

$\boxed{\beta=\nu\kappa}$

$$X_{t+\delta t} = X_t - (\beta\ \delta t)\ X_t\ Y_t/N$$

$$Y_{t+\delta t} = Y_t + (\beta\ \delta t)\ X_t\ Y_t/N - (\gamma\ \delta t)\ Y_t$$

$$Z_{t+\delta t} = Z_t + (\gamma\ \delta t)\ Y_t$$

- Average infectious period given by $1/\gamma$ [why?]

Mean life time calculation

Consider recovery of a single infectious individual $I(t) = e^{-\gamma t}$

$$1 = \int_o^\infty c e^{-\gamma t} dt \quad = \frac{c}{\gamma}$$

Hence, probability density function is $\gamma e^{-\gamma t}$

$$\tau = \int_0^\infty t\gamma e^{-\gamma t} dt \ = \frac{1}{\gamma}$$

For a random variable x, with probability density function f(x), the mean is given by $\int_0^\infty x f(x) dx$

An ODE model

- Consider the equation describing Susceptible dynamics

  $X_{t+\delta t} = X_t - (\beta\ \delta t)\ X_t\ Y_t/N$

- Re-write as

  $X_{t+\delta t} - X_t = -(\beta\ \delta t)\ X_t\ \ Y_t/N$

  $(X_{t+\delta t} - X_t)/\ \delta t = \beta\ X_t\ Y_t/N$

By fundamental theorem of calculus, as $\delta t \rightarrow 0$,

$dX/dt = -\ \beta\ X\ Y/N$

An ODE SIR model

$$\frac{dX}{dt} = -\beta X \frac{Y}{N}$$

$$\frac{dY}{dt} = \beta X \frac{Y}{N} - \gamma Y$$

$$\frac{dZ}{dt} = \gamma Y$$

- By definition, X+Y+Z = N
- These equations describe rates of change in state variables
- Parameters β, γ represent instantaneous rates

An ODE SIR model

In my lectures (as in K&R 2008), variables X, Y & Z refer to the <u>numbers</u> of individuals in each class. Variables S, I, & R refer to the <u>proportions</u> of the population in each class

- These equations describe rates of change in state variables
- Parameters β, γ represent instantaneous rates

An ODE SIR model

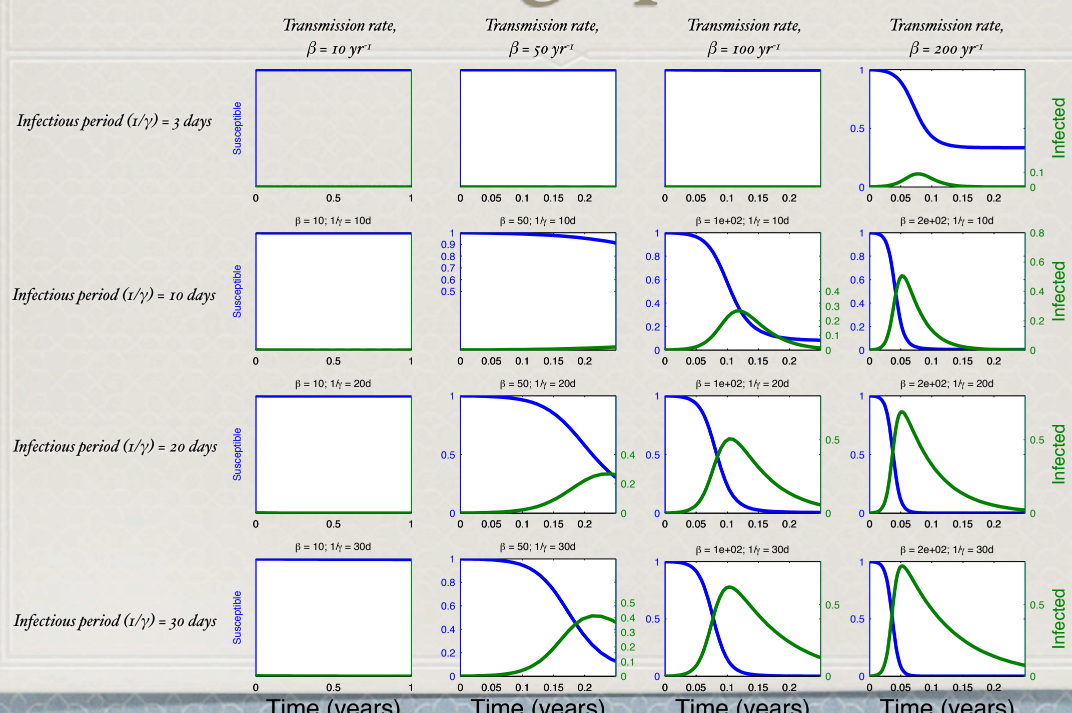
$$\frac{dX}{dt} = -\beta X \frac{Y}{N}$$

$$\frac{dY}{dt} = \beta X \frac{Y}{N} - \gamma Y$$

$$\frac{dZ}{dt} = \gamma Y$$

- Important to notice: transmission rate is assumed to depend on frequency of infecteds in population (Y/N). Hence, this is frequency-dependent transmission

Simulating epidemics



Model dynamics

- *As parameters are varied, model predicts different outcomes*
- *Can we anticipate trajectories without resorting to numerical integration?*
- *Question: under what conditions will an infectious disease invade a system?*

The Invasion Threshold

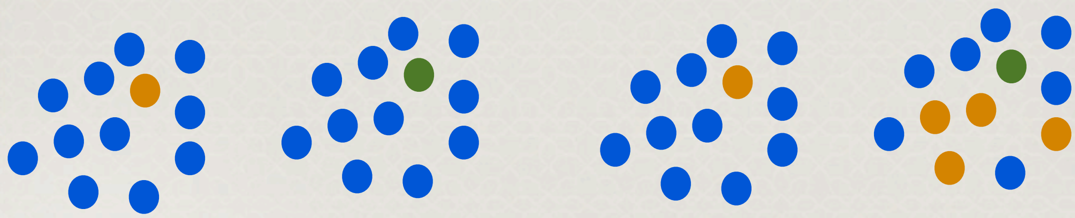
- When can an infectious disease invade a population?
- Initial conditions: $X(0) = N$, $Y(0) = 1$, $Z(0) = 0$
- Invasion only if $dY/dt > 0$
- ie, $\beta XY/N - \gamma Y > 0 \quad \Rightarrow Y(\beta X/N - \gamma) > 0$
  - If and only if $X/N > \gamma/\beta$
  - Since $X=N$, requires $1 > \gamma/\beta$
  - Or $\beta/\gamma > 1$

Kermack & McKendrick (1927)

Basic Reproductive Ratio, R_o

- Ratio β/γ gives number of cases before infected individual recovers
- Universally referred to as R_o or **Basic Reproductive Ratio**

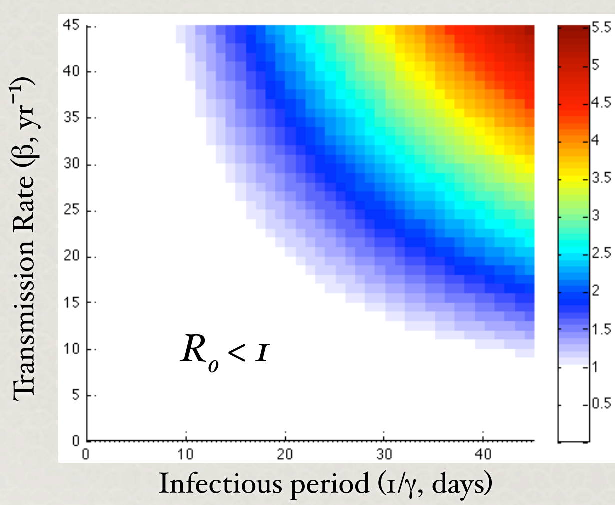
- Definition: Number of secondary cases generated by a typical infected in an entirely susceptible population



$R_0 < 1$
No invasion

$R_0 = 4$
Successful invasion

R_o and Model parameters



Estimates of R_0

Pathogen	Host	Estimated R_0
FIV	domestic cats	1.1-1.5
Rabies	dogs (Kenya)	2.4
Phocine Distemper	Harbour seals	2-3
Tuberculosis	Cattle	2.5
Seasonal Influenza	Humans	3-4
Foot-and-Mouth Disease	Livestock	3.5-4.5
Smallpox	Humans	3.5-6
Rubella	Humans	6-7
Chickenpox	Humans	10-12
Measles	Humans	16-18
Whooping Cough	Humans	16-18
HIV (MSM)	Humans	4
HIV (sex workers)	Humans	11
SARS	Humans	3
Pandemic Influenza (1918)	Humans	1.5-3
Pandemic Influenza (2009)	Humans	1.2-1.5
Polio	Humans	8-10

Keeling & Rohani (2008)