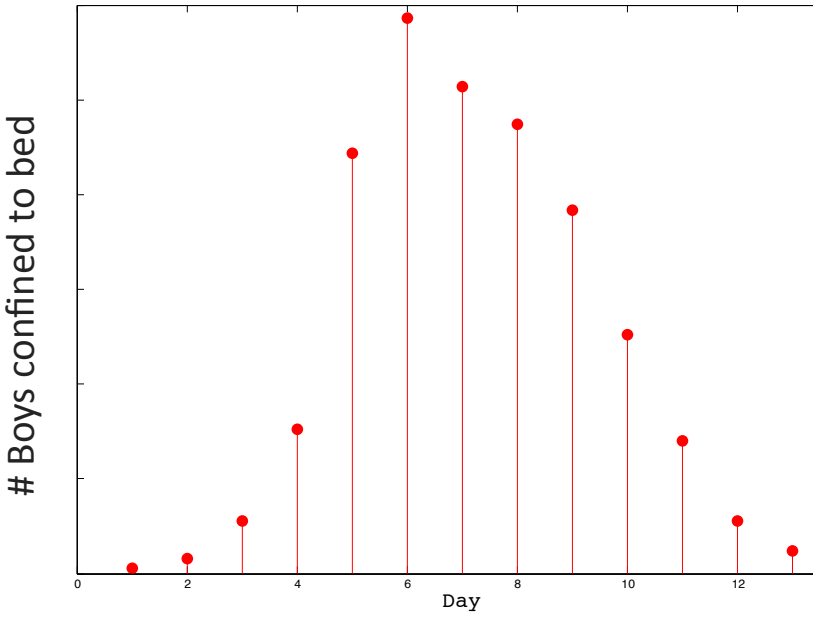
Modeling Infectious Diseases

- Pej Rohani & John Drake

- Odum School of Ecology
- University of Georgia

School outbreak

Boarding School, England
Jan 1978



Raises numerous questions:

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

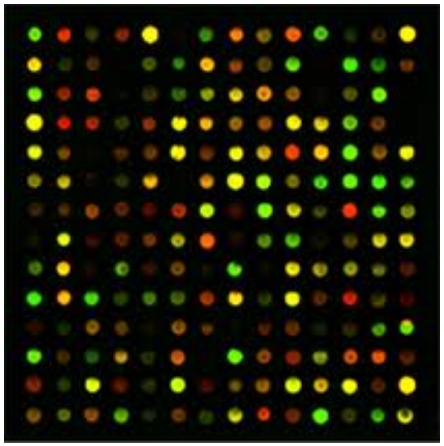
Multifaceted approach to understanding infectious diseases

Medicine

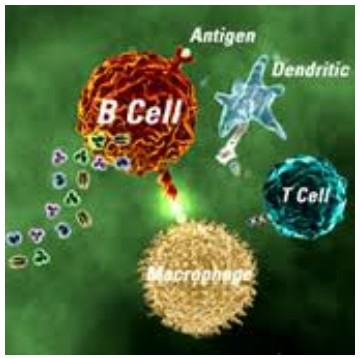
But these approaches don't address important questions at population level ...

Microbiology

Genomics

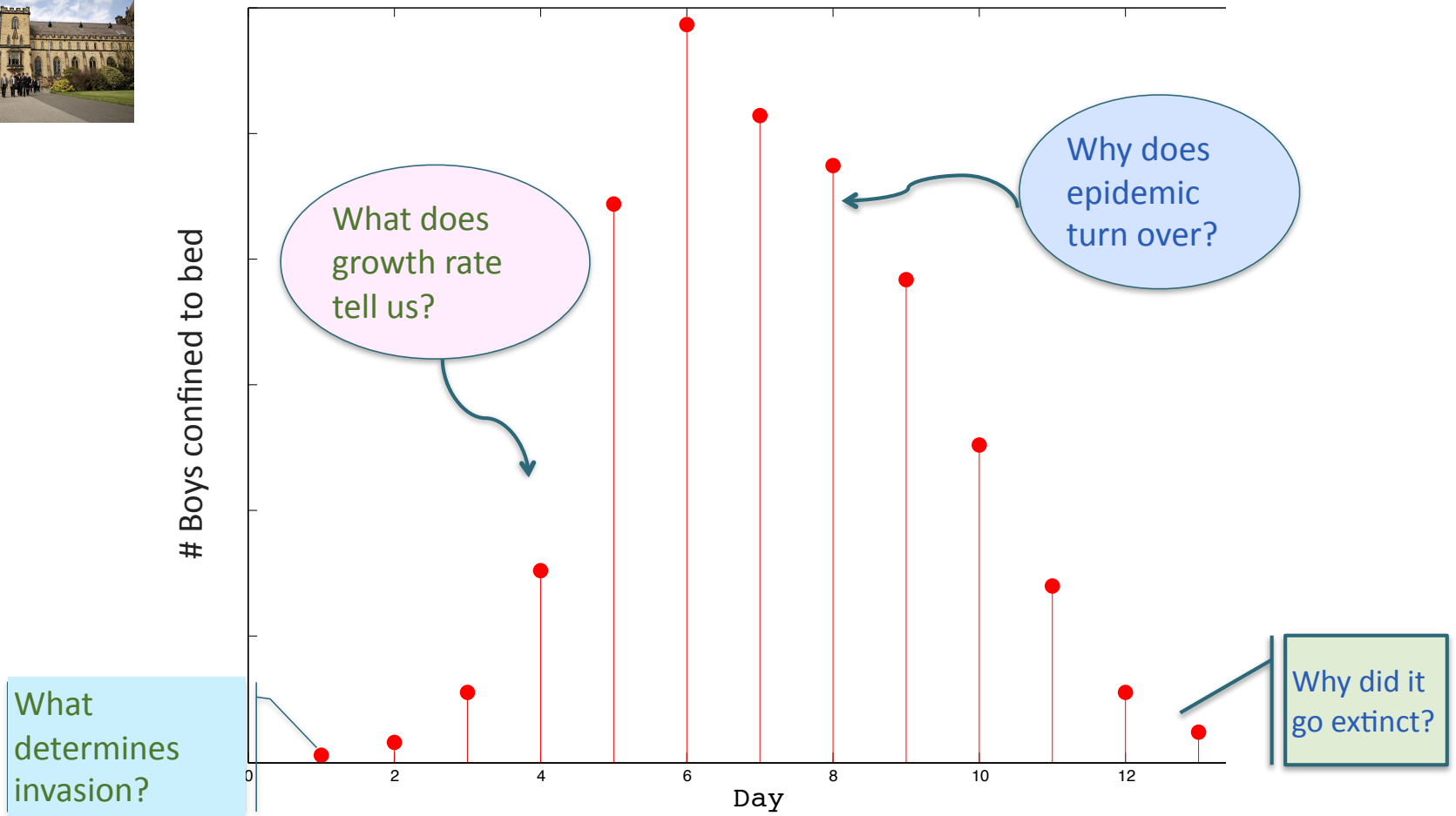


Immunology

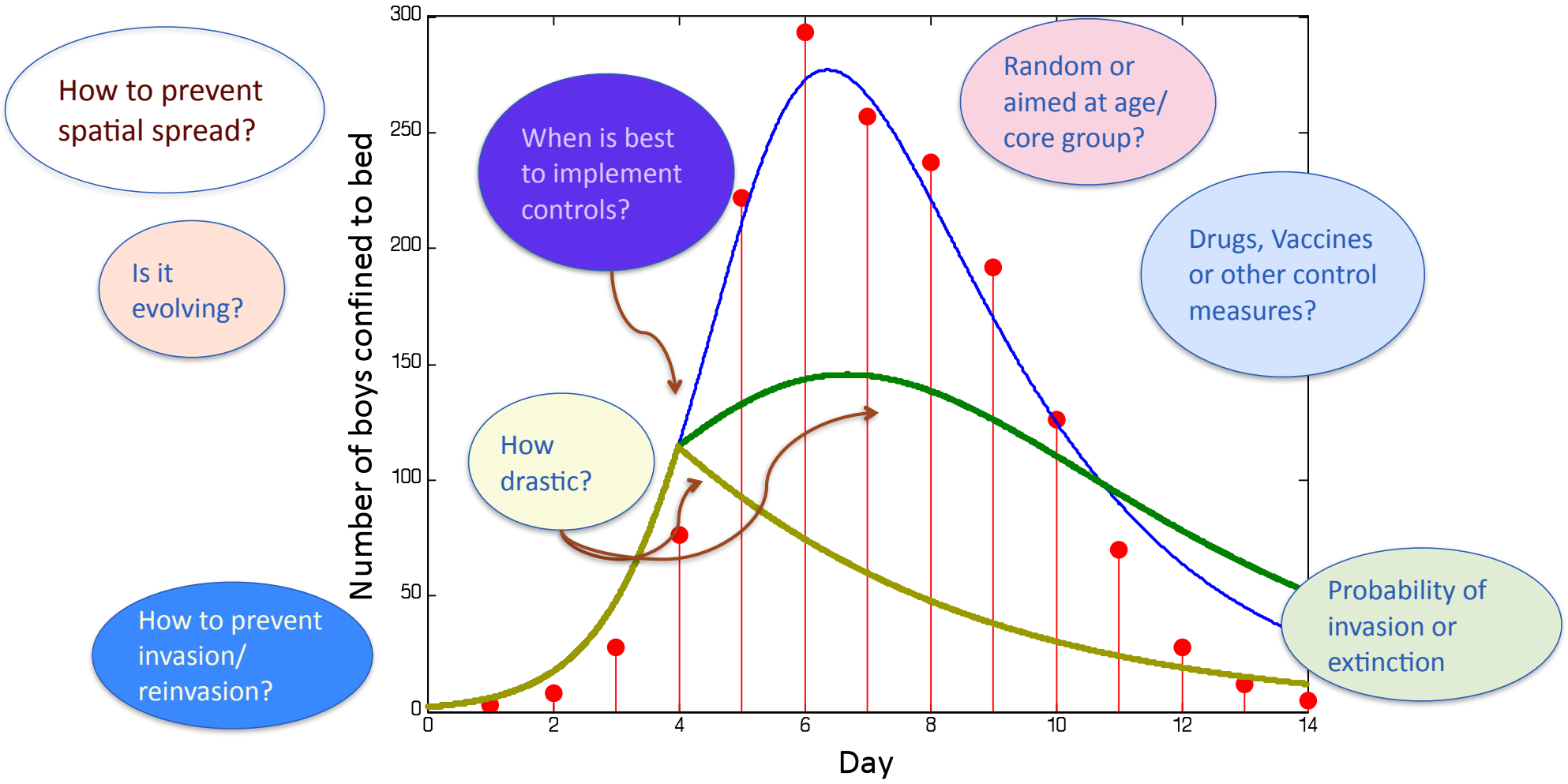


Vaccines & Drugs

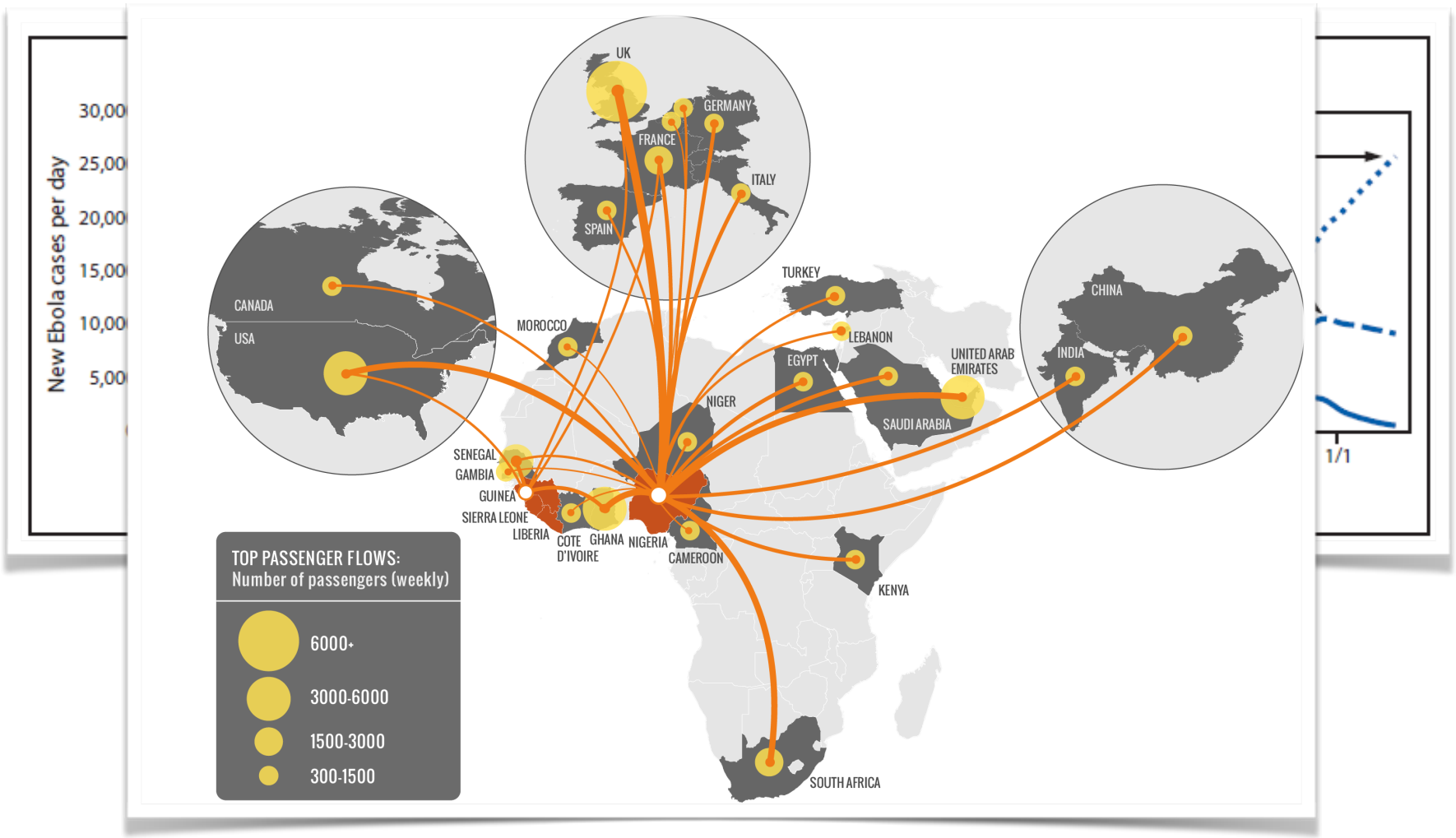
Modeling questions I. Basics



Modeling questions II. Control Implications



Emerging pathogens

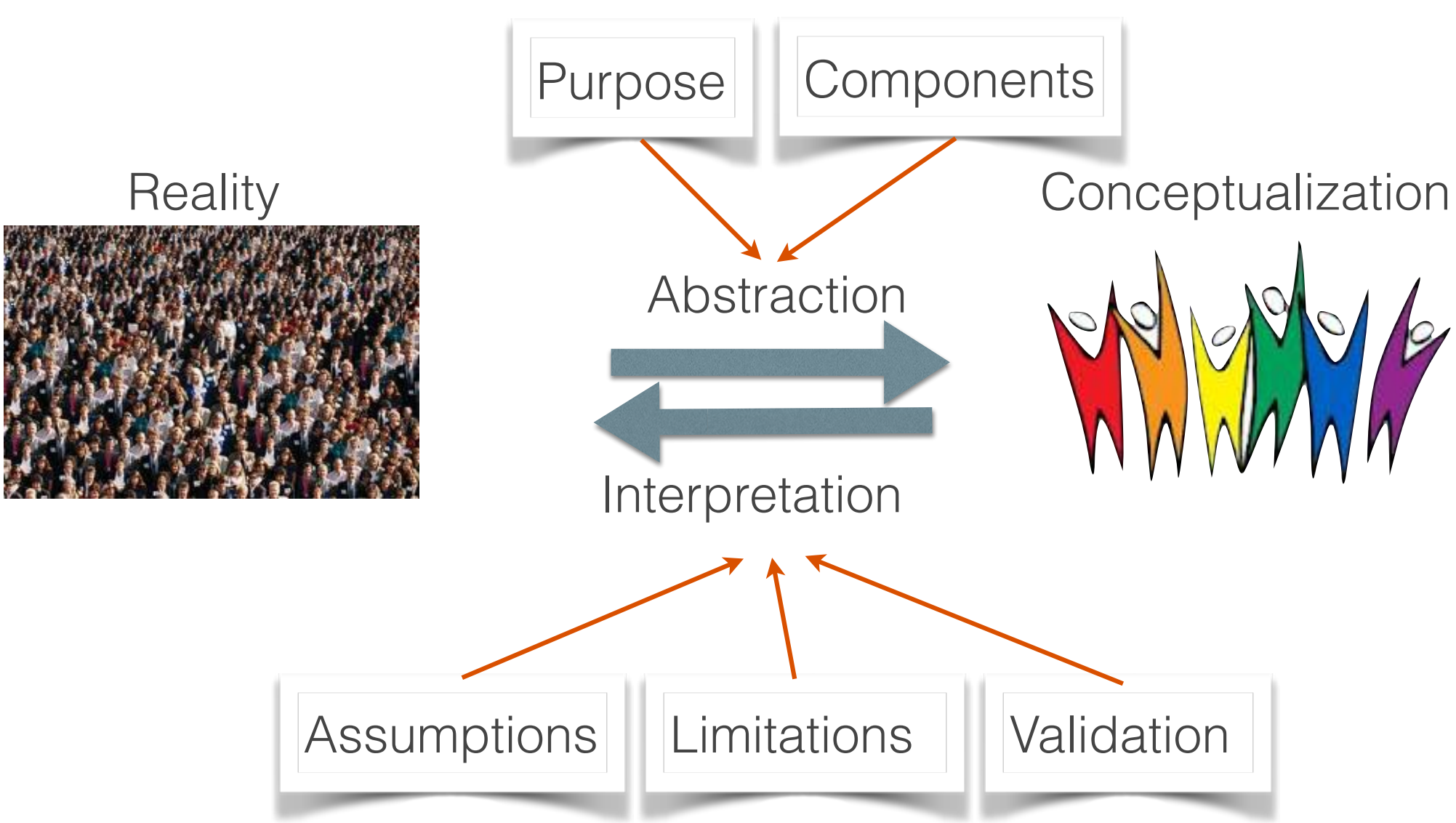


What is a model?

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

- Developing a mechanistic model is different from statistical analyses of data

Abstraction



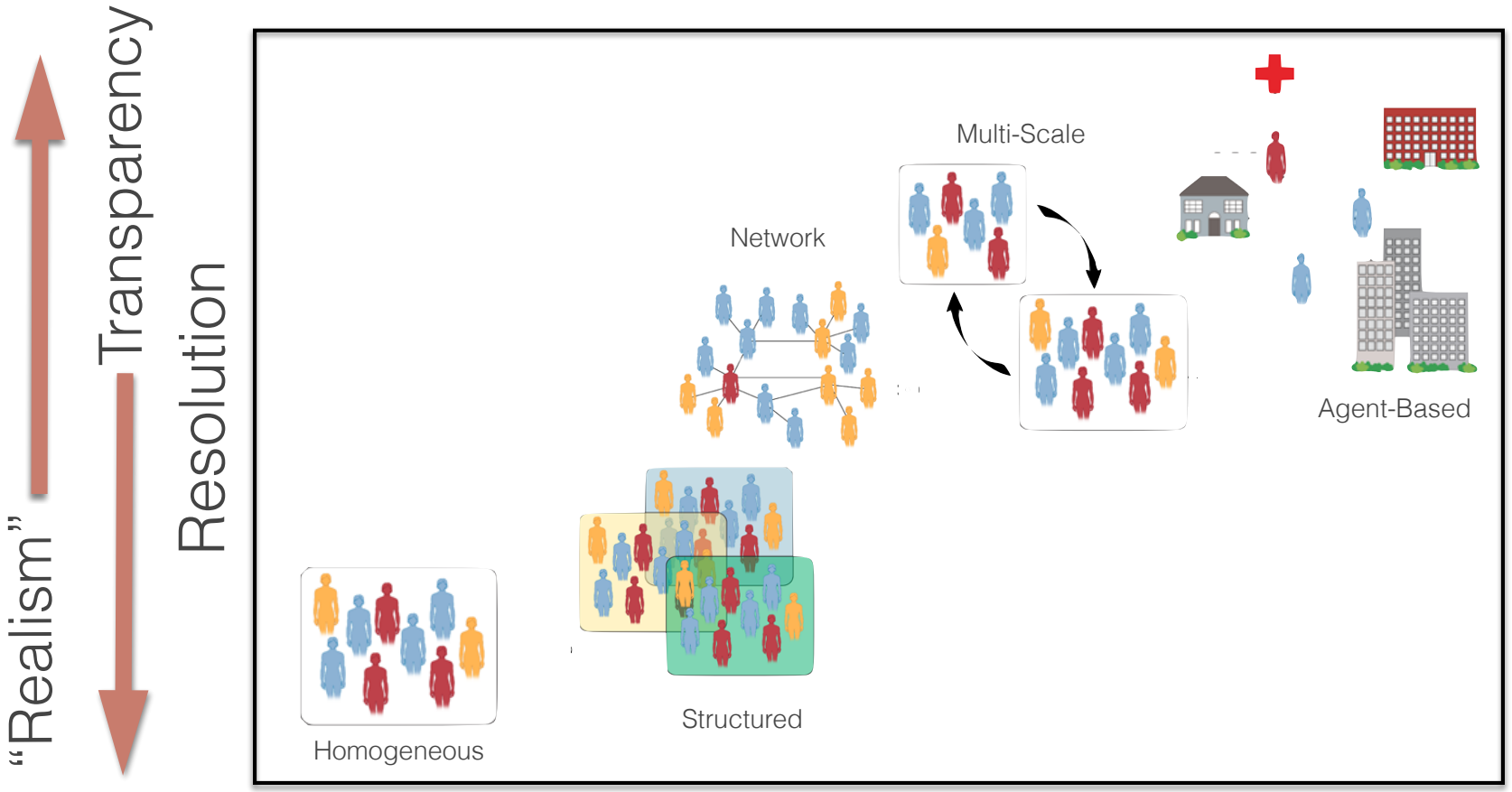
What's a 'Good' Model?

- 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



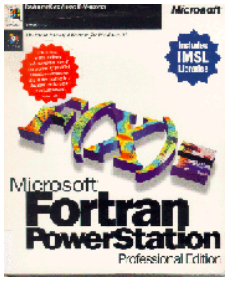
Solution tools

‘How’ do you Model?

Analytical Models

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

Problem-based Models

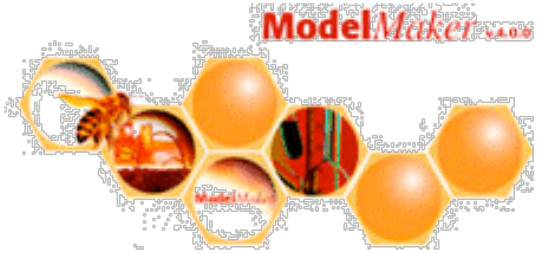


The MathWorks

Construct most “appropriate” model and use whatever combination of methods for analysis and prediction

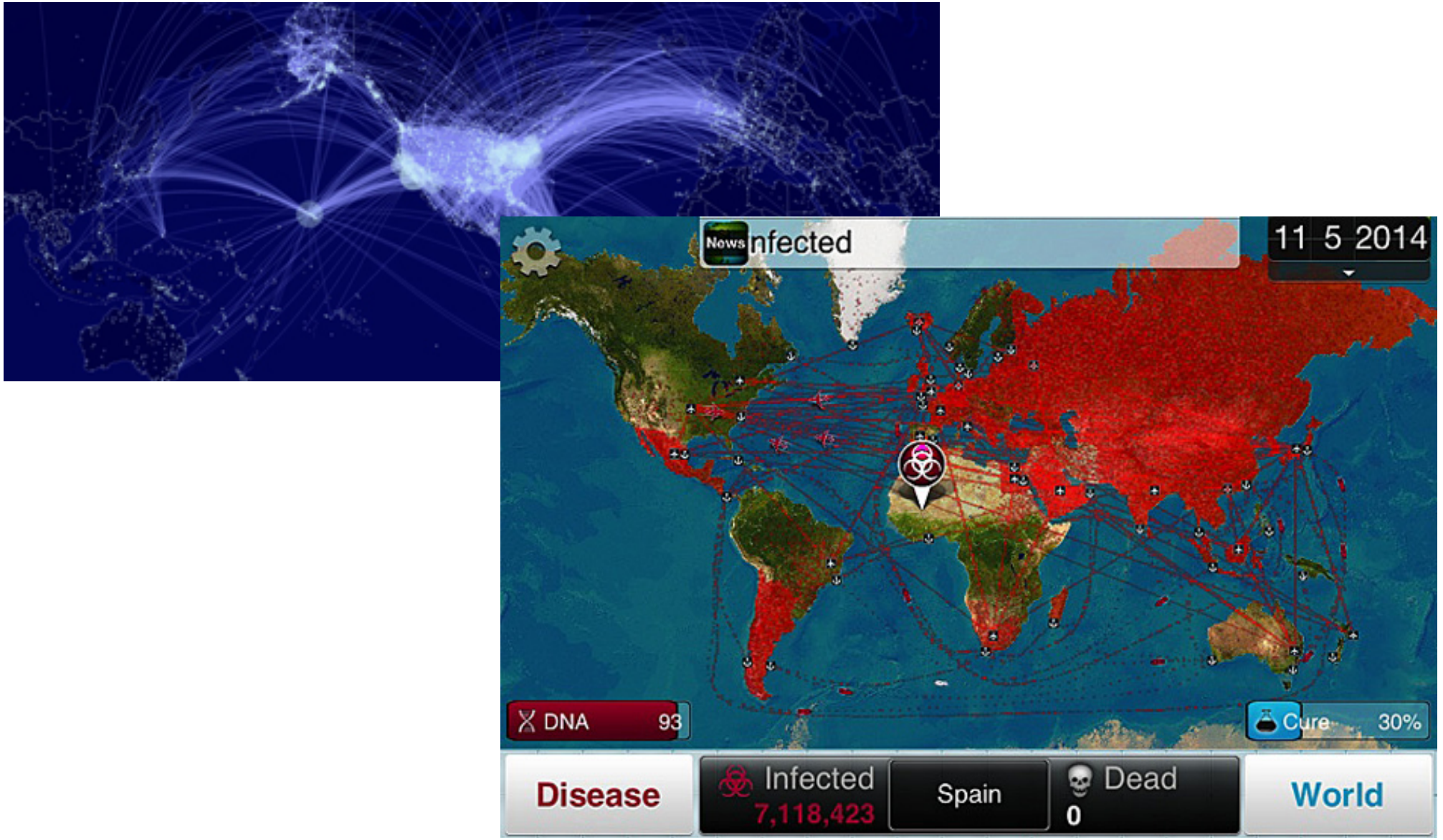
Ready-Made Software

ModelMaker



www.modelkinetix.com/modelmaker/modelmaker.html

Global simulators



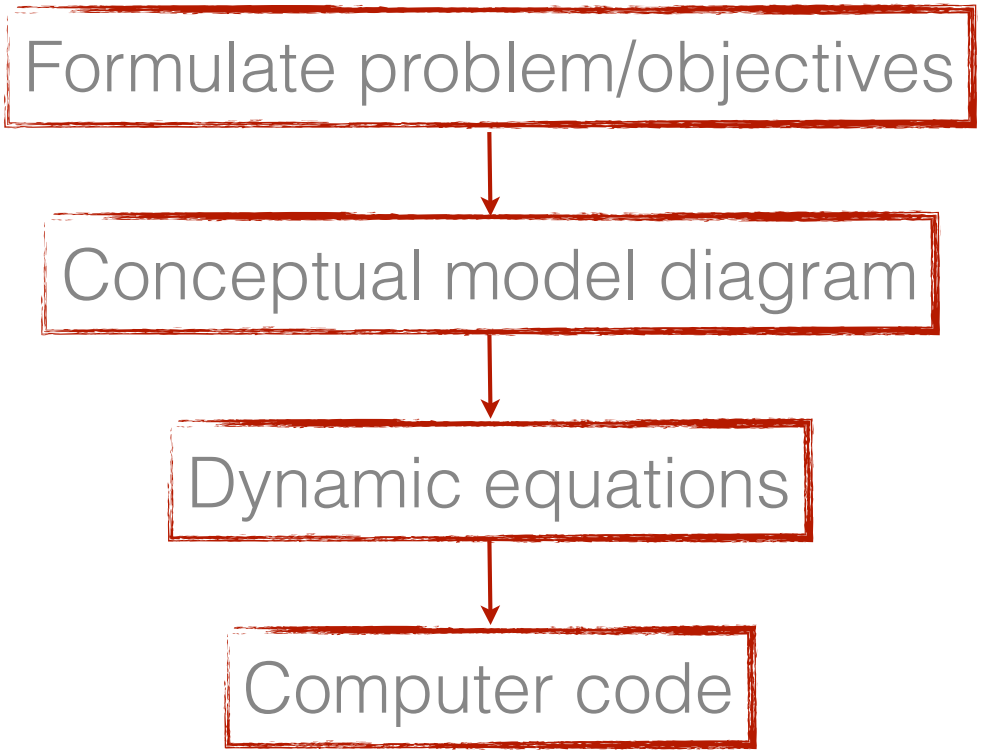
Resource Materials

- Keeling & Rohani (2008)
- Vynnycky & White (2010)
- Anderson & May (1991)
- Otto & Day (2007)
- Diekmann et al. (2012)

Modelling Infectious Diseases

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

Steps in Developing a Model



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 within affected population?
   - *Antibody titre* of everyone in population (school)?
   - *Concentration* of virus on fomite surfaces?

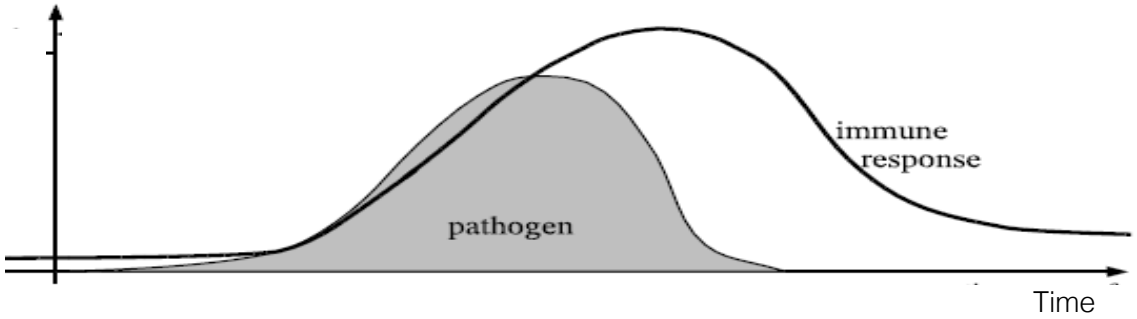
Categorising individuals

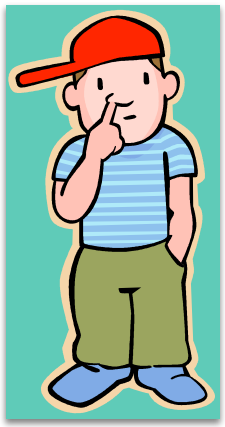
Healthy → Incubating → Diseased

Clinical status

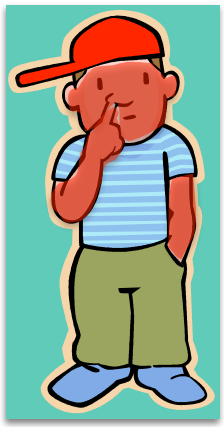
Susceptible → Exposed/latent → Infectious → Recovered/Immune

Infection status



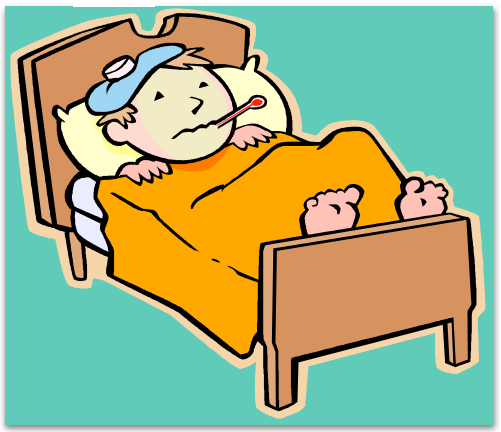


Incubating



Infectious, latent

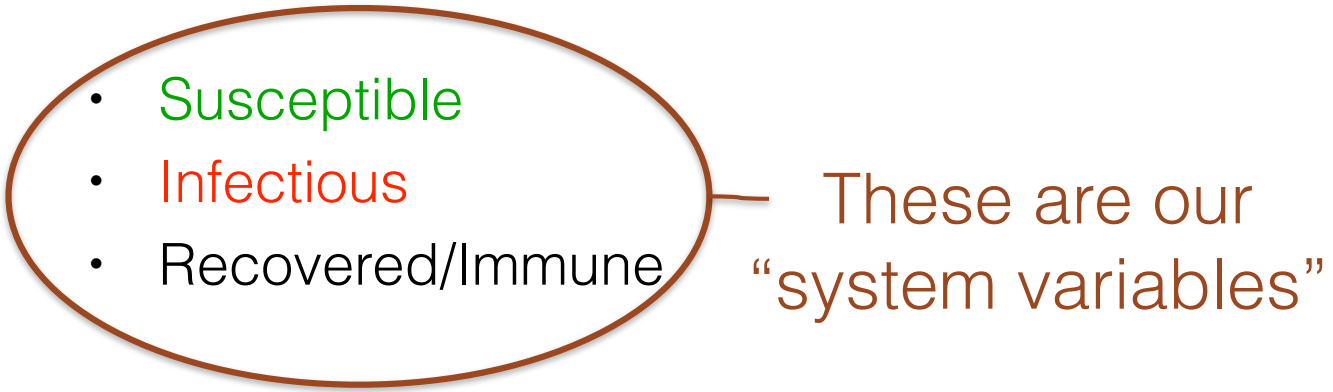
Infectious, symptomatic



Infectious, quarantined

The simplest models

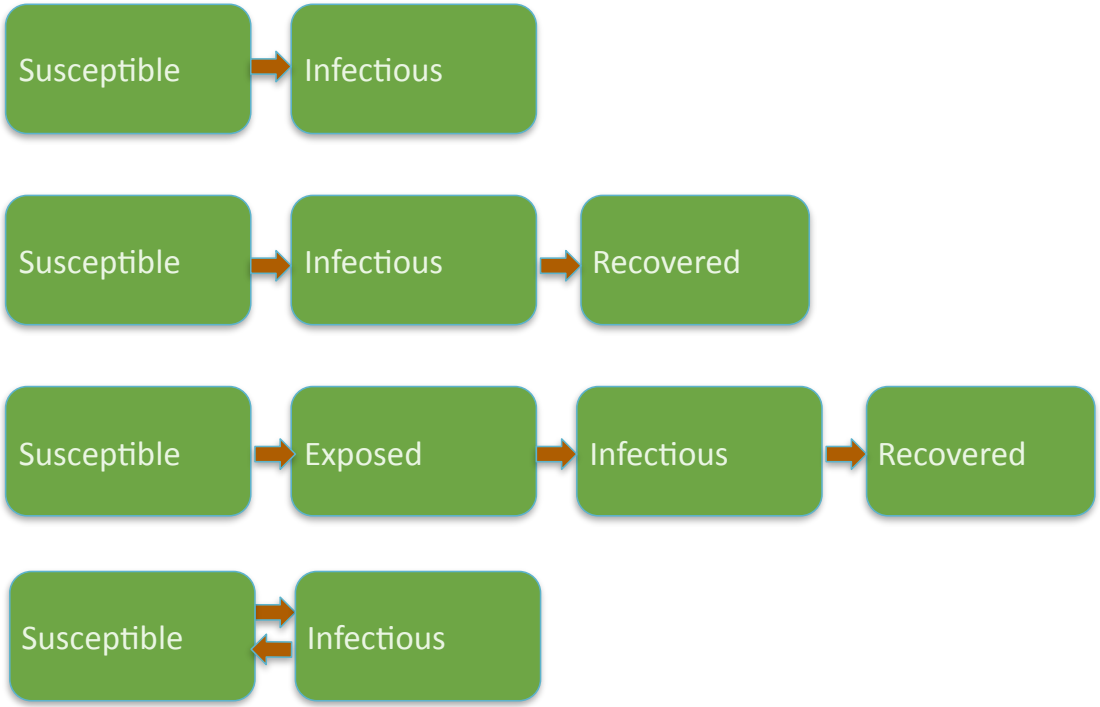
- Pragmatic choice: categorise individuals in population according to their infection status, eg:



The simplest models

2. **What model structure?**

   -- Determined by pathogen biology



SI – signifies fatal infection

SIR – recovery after infection

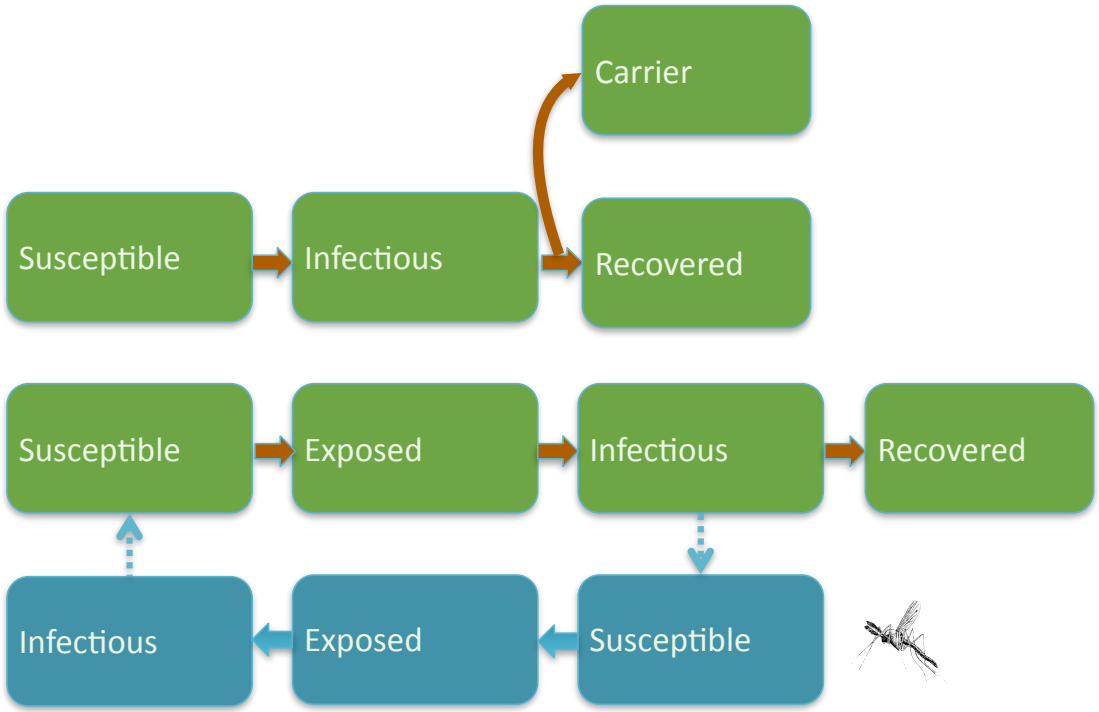
SEIR – latency

SIS – no immunity elicited

The simplest models

2. **What model structure?**

   -- Determined by pathogen biology



SIR – with carriers

Vectored transmission

The simplest models

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

The simplest models

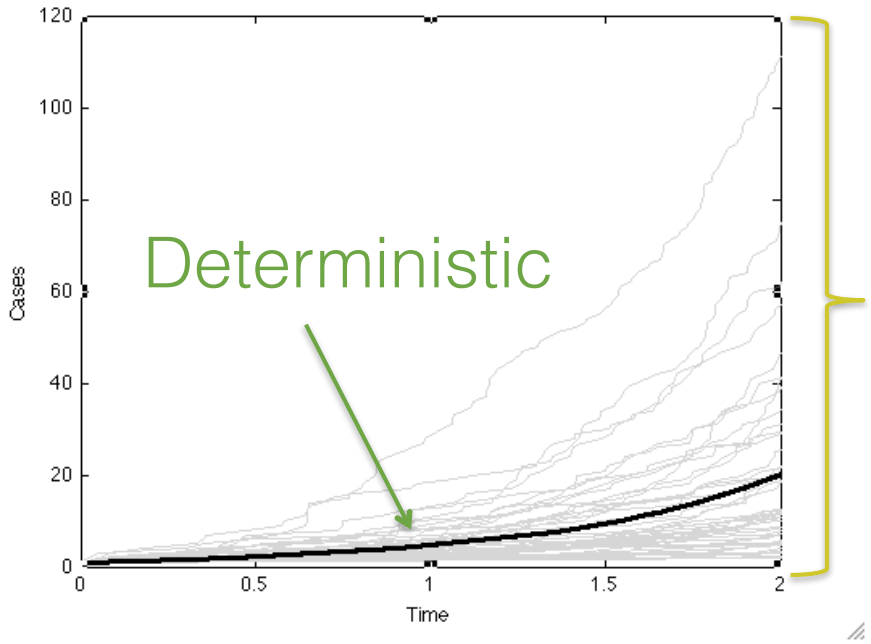
- Flow between classes/compartments determined by details of host population structure and pathogen biology

- Host population size
- Contact rates
- Pathogen infectivity

These are our "parameters"

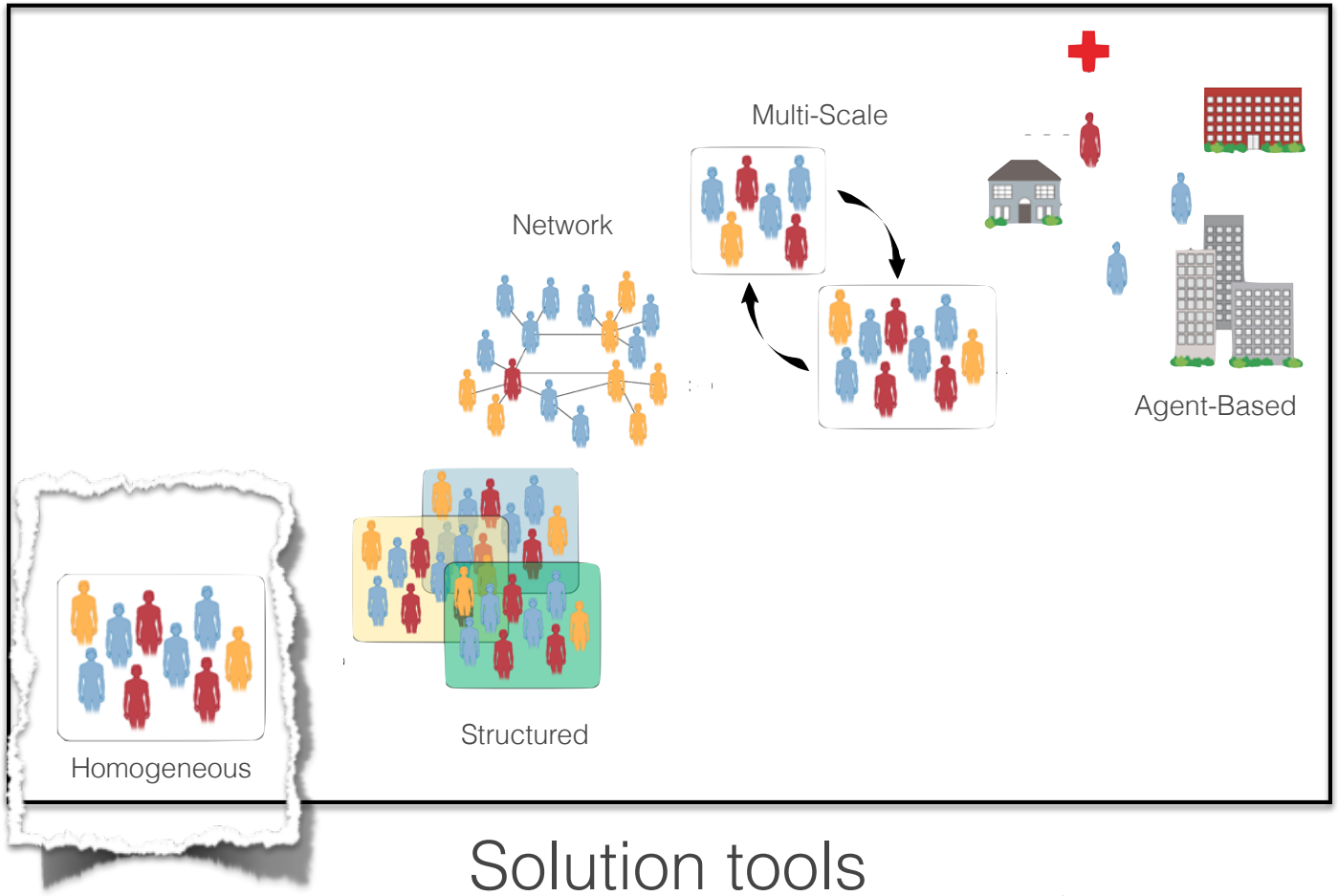
The simplest models

- **Deterministic or Stochastic?**



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

Realism Vs Transparency



Solution tools

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

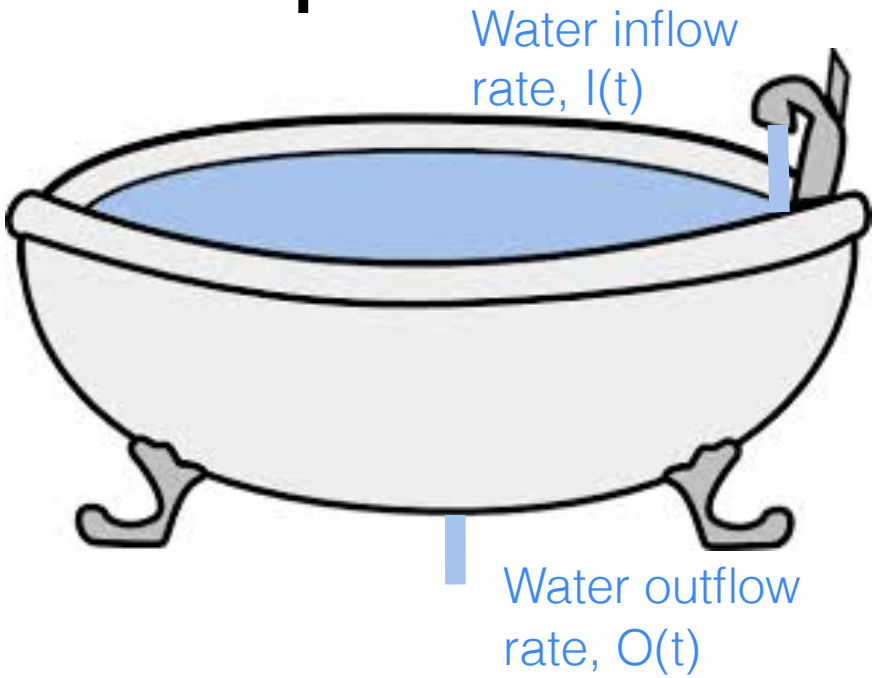
Very important!

- 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!

3. Model equations

Bath tub example

- Let W(t) be amount of water in bathtub (ml)
- Need a dynamic equation that tells us how W(t) will change through time

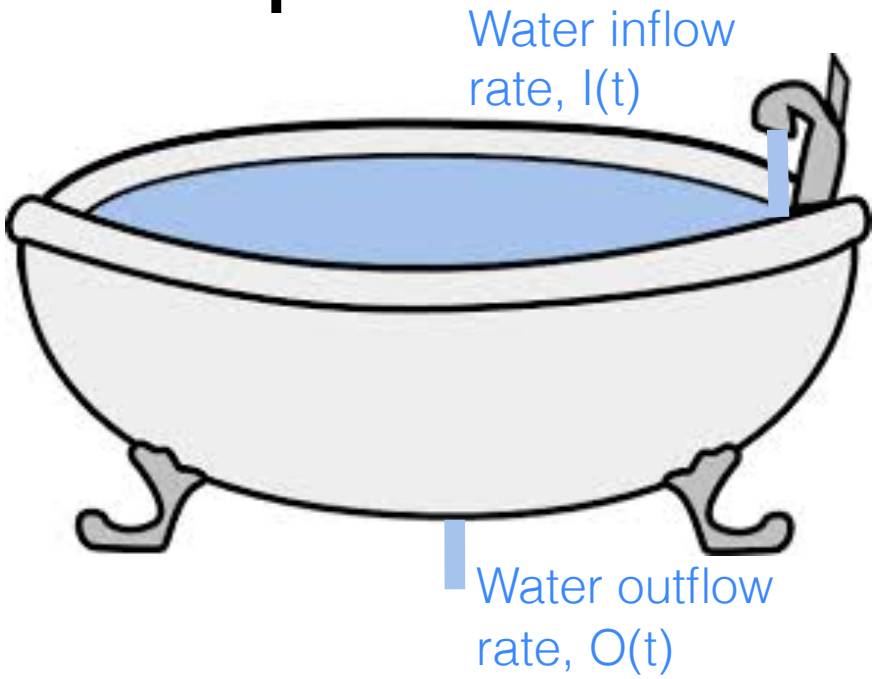


* Consider a small time interval, δt
* Then,

$$W(t+\delta t) = W(t) + \text{Inflow rate} \times \text{elapsed time} - \text{Outflow rate} \times \text{elapsed time}$$

Bath tub example

$$W(t+\delta t) = W(t) + I \times \delta t - O \times \delta t$$



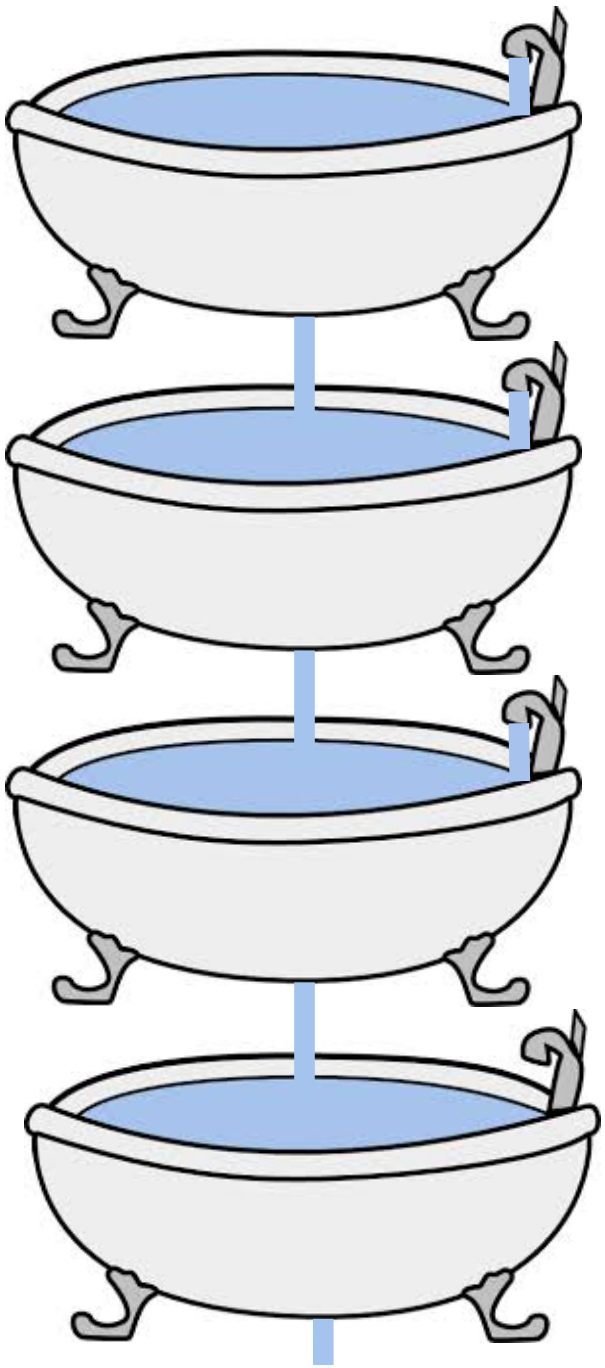
* Rearrange

$$\frac{W(t+\delta t) - W(t)}{\delta t} = I - O$$

* Left hand side is a difference quotient for derivative of W with respect to time

* Let δt → 0

$$\frac{dW}{dt} = I - O$$



Many Linked bath tubs
= compartment models

Model equations

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

$X_{t+\delta t} = X_t$ – Transmission

$Y_{t+\delta t} = Y_t$ + Transmission

- Transmission rate per susceptible $\propto$ Contacts x P(Infectious) x P(Transmission)

$$= \kappa \times \delta t \times \frac{Y_t}{N} \times \nu$$

$$= \kappa\nu \frac{Y_t}{N}$$

$$= \beta \frac{Y_t}{N}$$

$\beta = \nu\kappa$

Model equations

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

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

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

- Recovery assumed at constant rate, γ

Basic questions?

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

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

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

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

$\beta = \nu\kappa$

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 $\gamma e^{-\gamma t}$

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

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

An ODE model

- Consider 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

$$\frac{dX}{} \qquad Y$$

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

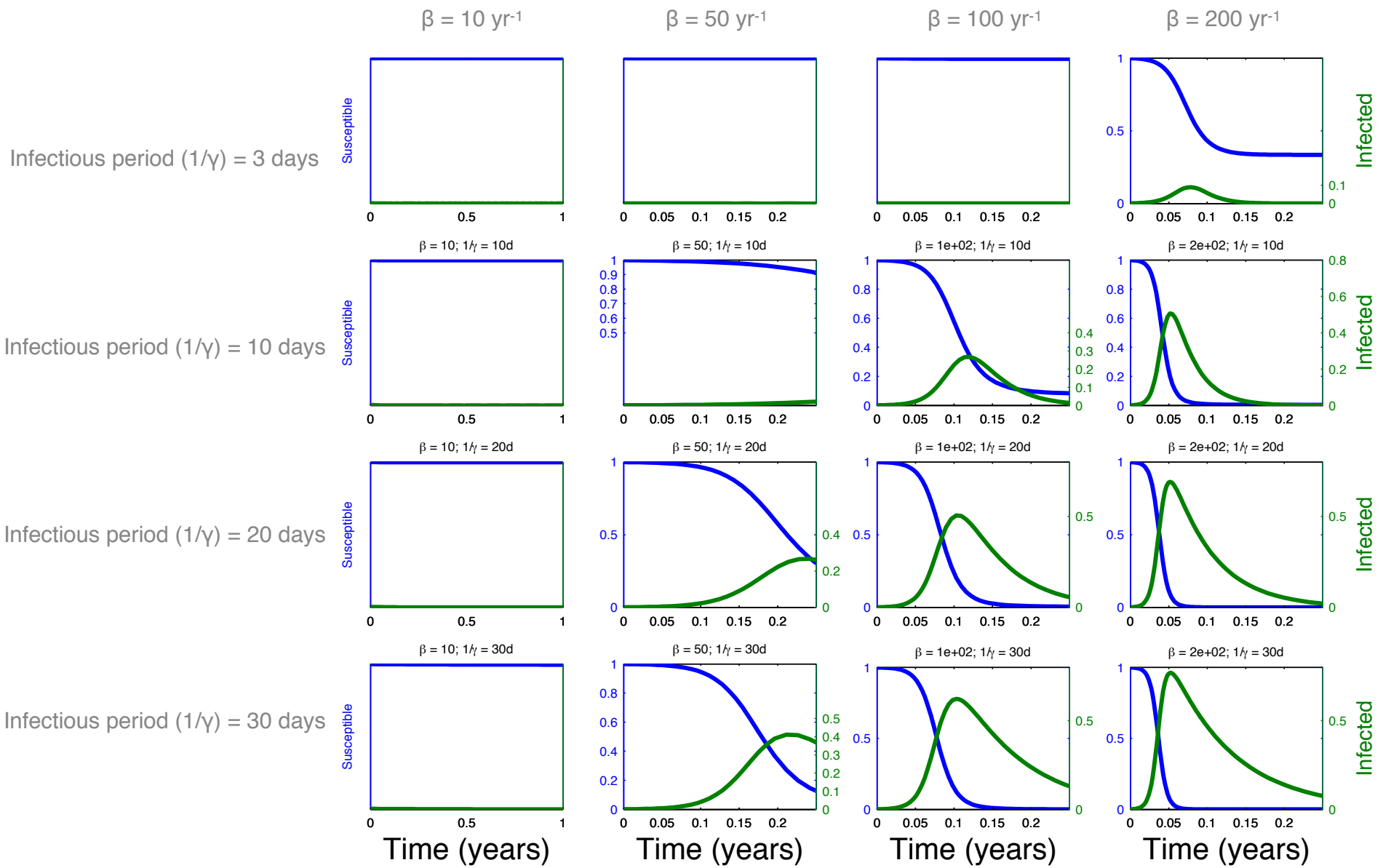
$$\frac{dX}{dt} = -\beta X \frac{Y}{N}$$

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

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

- 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?

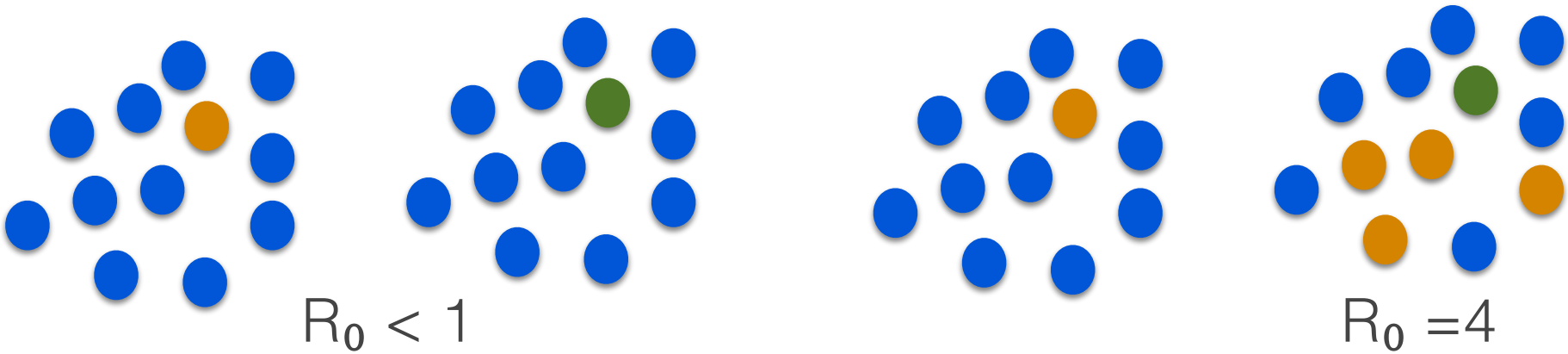
The Invasion Threshold

- 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_0

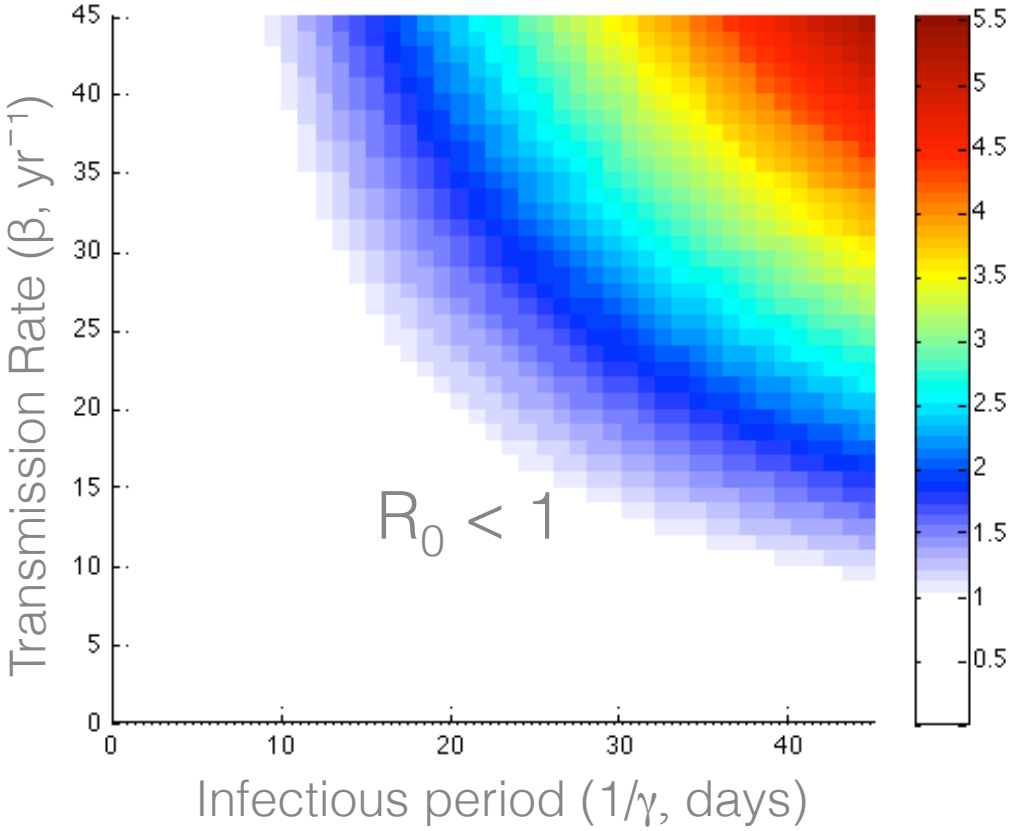
- Ratio β/γ gives number of cases before infected individual recovers
- Universally referred to as R_0 or **Basic Reproductive Ratio**
- Definition: Number of secondary cases generated by a typical infected in an entirely susceptible population



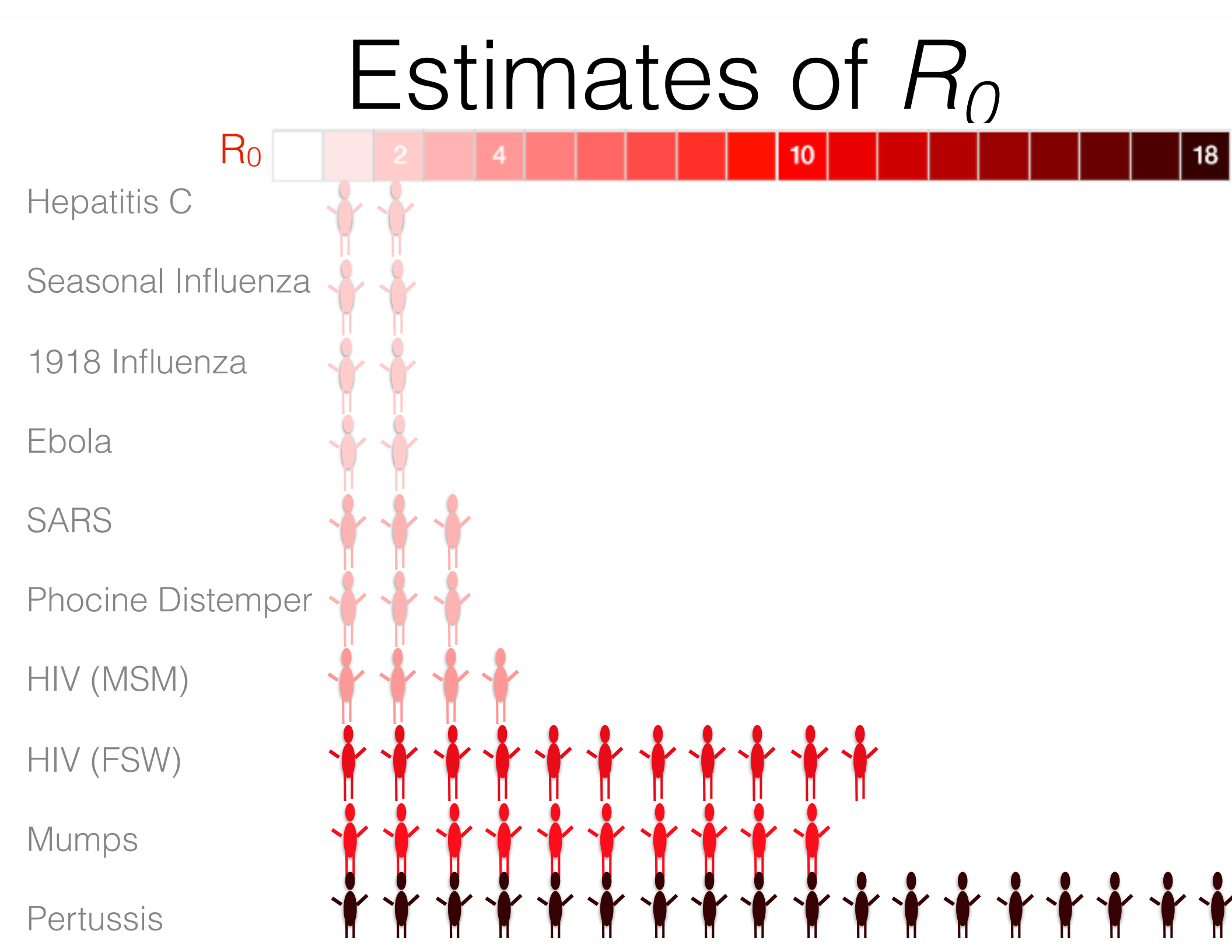
No invasion

Successful invasion

R_0 and Model parameters



Estimates of R_0



The death of an epidemic

- SIR equations, let's divide equation for dX/dt by dZ/dt:
  $dX/dZ = - (\beta X Y/N)/(\gamma Y)$
  $= - R_0 X/N$

- Integrate with respect to Z
  - $X(t) = X(0)\, e^{-Z(t)\, R_0/N}$

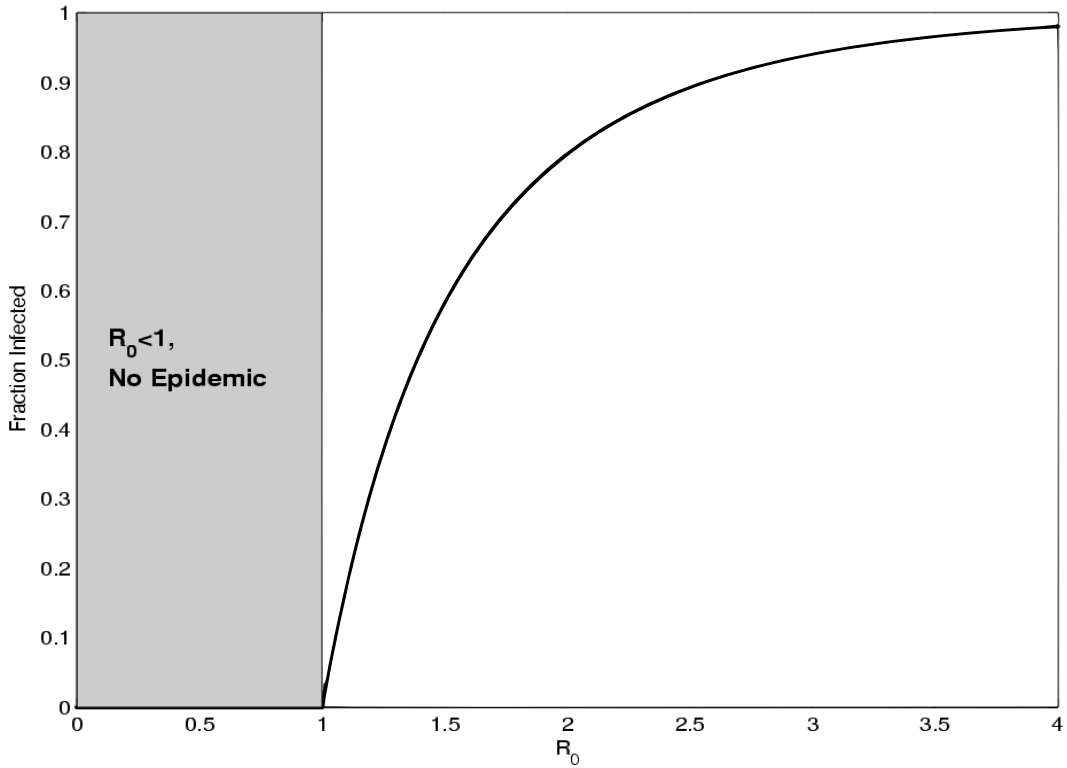
- When epidemic is over, by definition, we have $X(\infty)$, $Y(\infty)$ $(=0)$, and $Z(\infty)$

- $X(\infty) = N - Z(\infty) = X(0)\, e^{-Z(\infty)\, R_0/N}$

The death of an epidemic

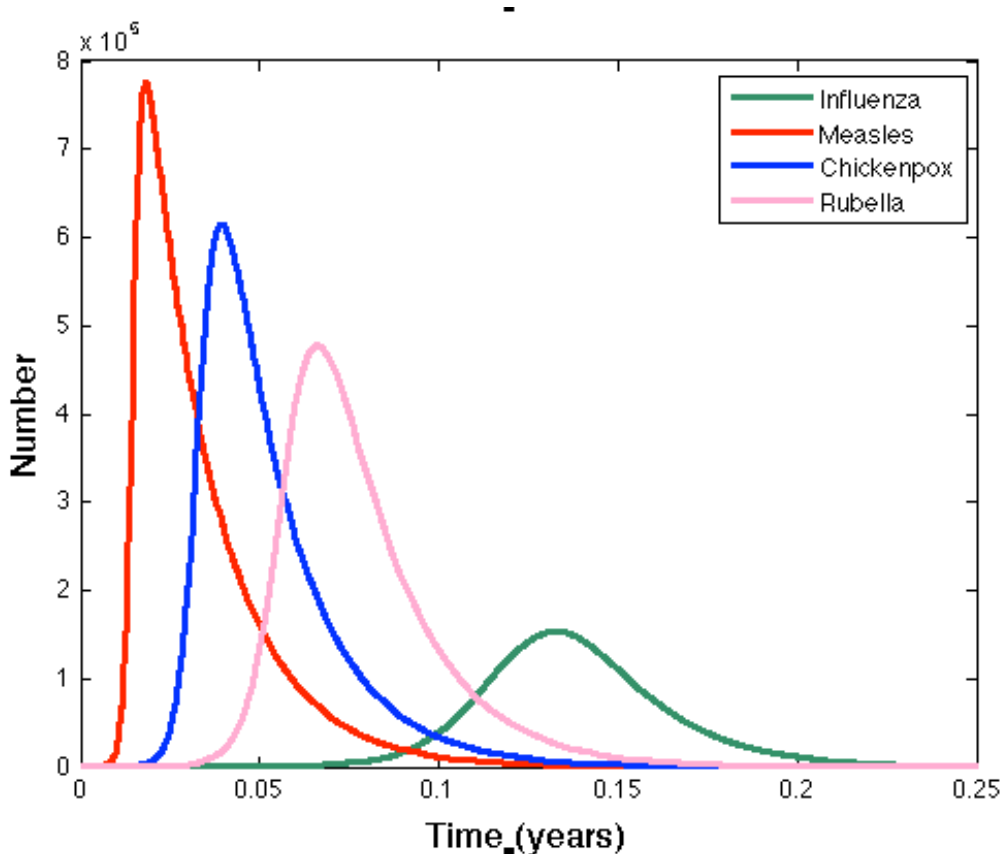
- So, $N - Z(\infty) - X(0)\, e^{-Z(\infty) R_0/N} = 0$
- Solve this numerically ('transcendental' equation)

Epidemic dies out because there are too few infectives, not because of too few susceptibles



Kermack & McKendrick (1927)

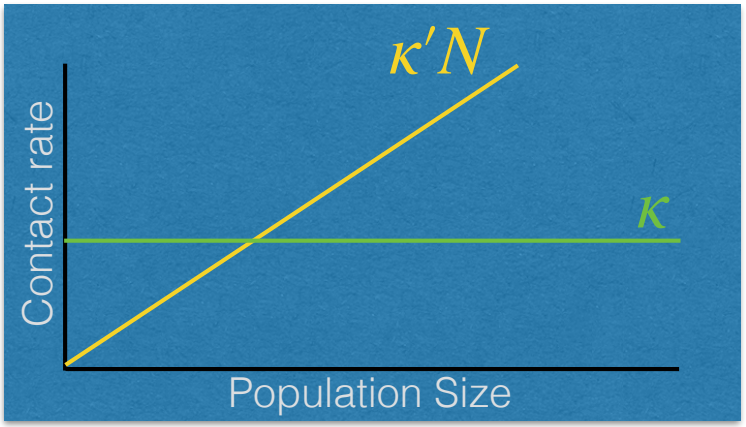
Simple Epidemics



	β	1/γ	R_0
"Measles"	886 /yr	0.019 yr	17
"Influenza"	180 /yr	0.011 yr	2
"Chickenpox"	315 /yr	0.022 yr	7
"Rubella"	200 /yr	0.025 yr	5

Frequency- or Density-Dependent Transmission?

- Assumed contact rate, κ, constant: 'mixing' is independent of population size: frequency-dependent transmission. Reasonable?
- If we assume contact rate to be κ'N (increases with 'crowding'), then transmission rate is
  - $dX/dt = -\beta XY$
- Called density-dependent transmission



Does it Matter?

- Again, pathogen invasion if $dY/dt > 0$
- If initially everyone susceptible ($X=N$),

  $$\beta NY - \gamma Y > 0 \Rightarrow Y(\beta N - \gamma) > 0$$

- In this case, we define $R_0 = \beta N/\gamma$, so need $R_0 > 1$

- Hence, for any particular β and γ, there's now a threshold population density required for invasion

Incorporating virulence

- Assume infectious individuals die at rate α

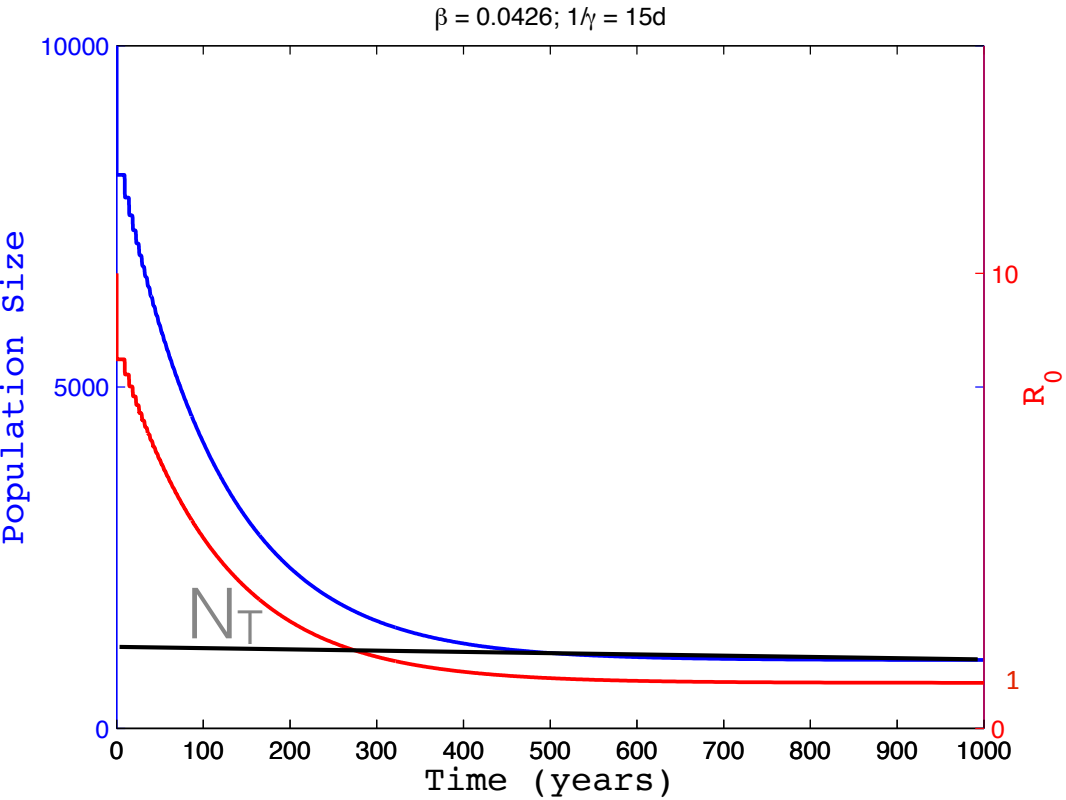
$$\frac{dY}{dt} = \ldots - \gamma Y - \alpha Y$$

Transmission & R_0

Density Dependent

β=0.0426, γ=24, α=18, μ=0.02

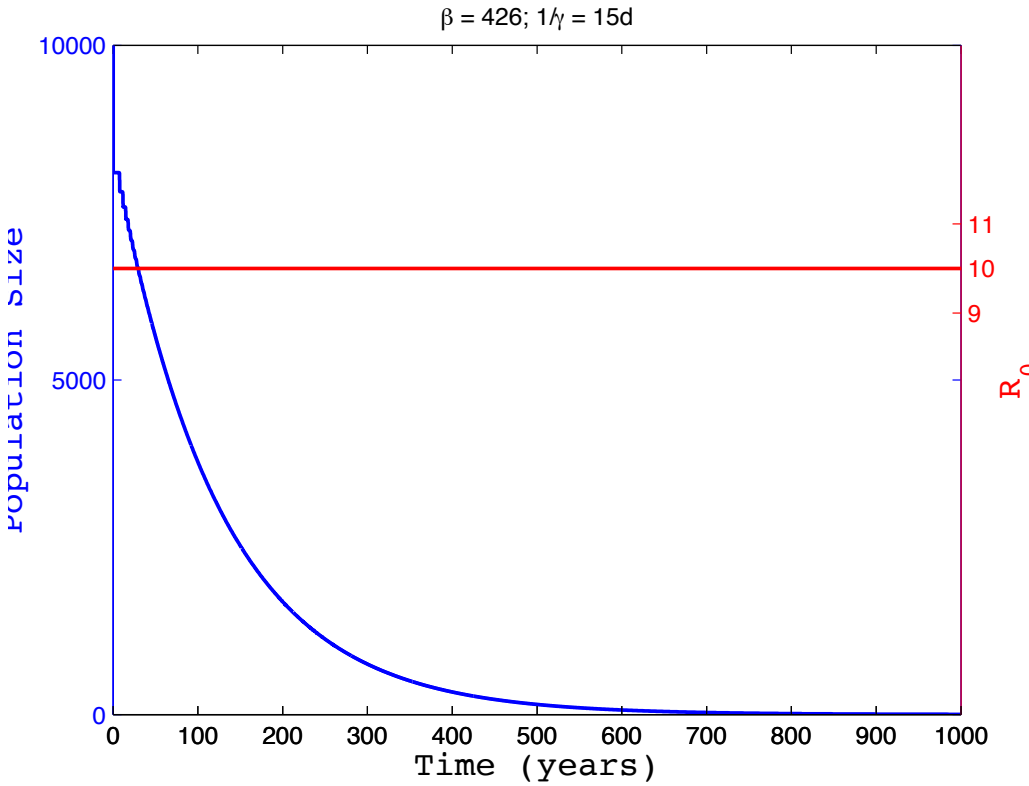
N_T = 1000



Frequency Dependent

β=426, γ=24, α=18, μ=0.02

No invasion threshold



FD transmission → pathogen can wipe out host

What should we do?

- If population size doesn't change, FD & DD equivalent ($\beta_{FD} = N \times \beta_{DD}$)
- Otherwise:
  - Frequency-dependence generally more appropriate in large populations with heterogenous mixing, STDs, vector-borne pathogens
  - Density-dependence representative of wildlife & livestock diseases (especially with smaller population sizes)