Analogies Between Computer and Biological Viruses...

Epidemiological Theory

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Infectious Disease Processes

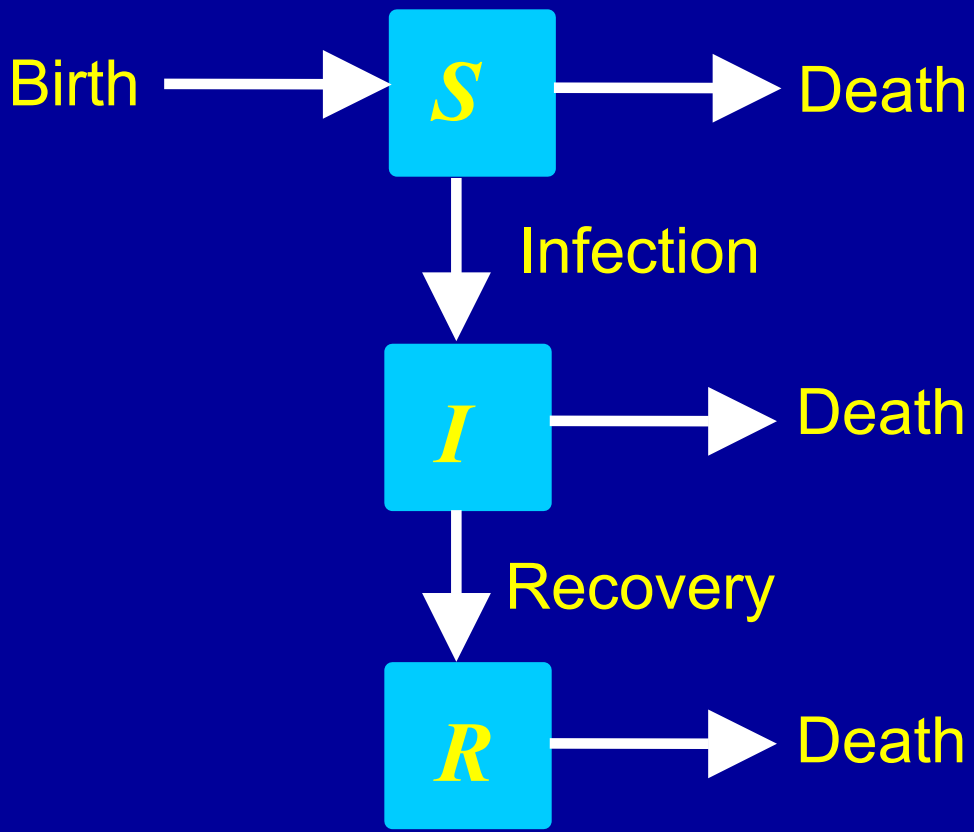
- Individuals are born susceptible to a disease
- Individuals become infected by meeting infectious individuals
- A latent period passes before an infected individual becomes infectious
- Individual is infectious for some time
- Individual may recover or may die from illness
- Recovered individuals may have lifelong immunity, or immunity might wane over time

Simple Compartmental Models

- Divide population according to their disease status (S,E,I or R)
- Label numbers in each class by *S*, *E*, *I* and *R*
- Depending on disease process, get SIR, SIS, SEIR, SEIRS, ... model

- I shall outline the standard SIR model, often used for describing childhood diseases, such as measles
- Further assumptions are needed...

The SIR Model for a Non-fatal Disease



- birth rate = death rate
  (NB: constant popn. size, N)
- perfect mixing (mass action)
- exponential duration of infectiousness, average $1/\gamma$

$$\dot{S} = \mu N - \beta SI - \mu S$$

$$\dot{I} = \beta SI - (\mu + \gamma)I$$

$$\dot{R} = \gamma I - \mu R$$

Behavior of the Model

- Depends on a single parameter combination
- Basic reproductive number, R_0
- Average number of secondary infections due to the introduction of a single infected individual into an entirely susceptible population

$$R_0 = \frac{\beta N}{\mu + \gamma}$$

- product of the average rate at which one infective gives rise to new cases in a totally susceptible population (numerator) and the average duration of infectiousness (corrected for mortality)

Behavior of the Model: Threshold Behavior

- Threshold phenomenon at $R_0=1$
- $R_0<1$: disease dies out (exponential decay)
- $R_0>1$: disease can invade and persist
  - # intuitively clear: R_0 gives the maximum replicative ability of the infection. Need each infected individual to be replaced by at least one other in order for disease not to die out.
  - # initial exponential growth, followed by approach to a stable steady state (the endemic equilibrium)
- Without births, would have a single epidemic wave
  - # classic result: size of epidemic wave in such case given by solution of $I_\infty = 1 - \exp(-R_0 I_\infty)$

Behavior of the Model: Threshold Behavior

- R_0 describes the replicative ability of the infection during the initial stage of infection

- More generally, replicative ability is written as R
- Mass action implies $R = R_0 \times S/N$

- At equilibrium, R = 1 and so S *=N / R_0
  - # notice that this provides a possible method to estimate R_0
- Also, average age at infection, A , = L /R_0

Threshold Behavior and Vaccination or Control

- Successful control corresponds to reducing R_0 below 1
  - A control measure might reduce β
  - Vaccination removes susceptibles from the system
- Easy to see that successful vaccination requires that a fraction p_c (or more) of population is vaccinated, with

$$p_c = 1 - 1 / R_0$$

- Vaccination increases the average age at first infection
  - Important consequences in certain cases. For example, the incidence of rubella, which can harm unborn children, might increase in women of child-bearing age

Dynamical Behavior

- Initial growth rate of epidemic, $r = \gamma (R_0 - 1)$
  - # Notice that this relates R_0 to more easily measurable epidemiological parameters
- For biologically realistic parameter values, endemic equilibrium is approached via damped oscillations

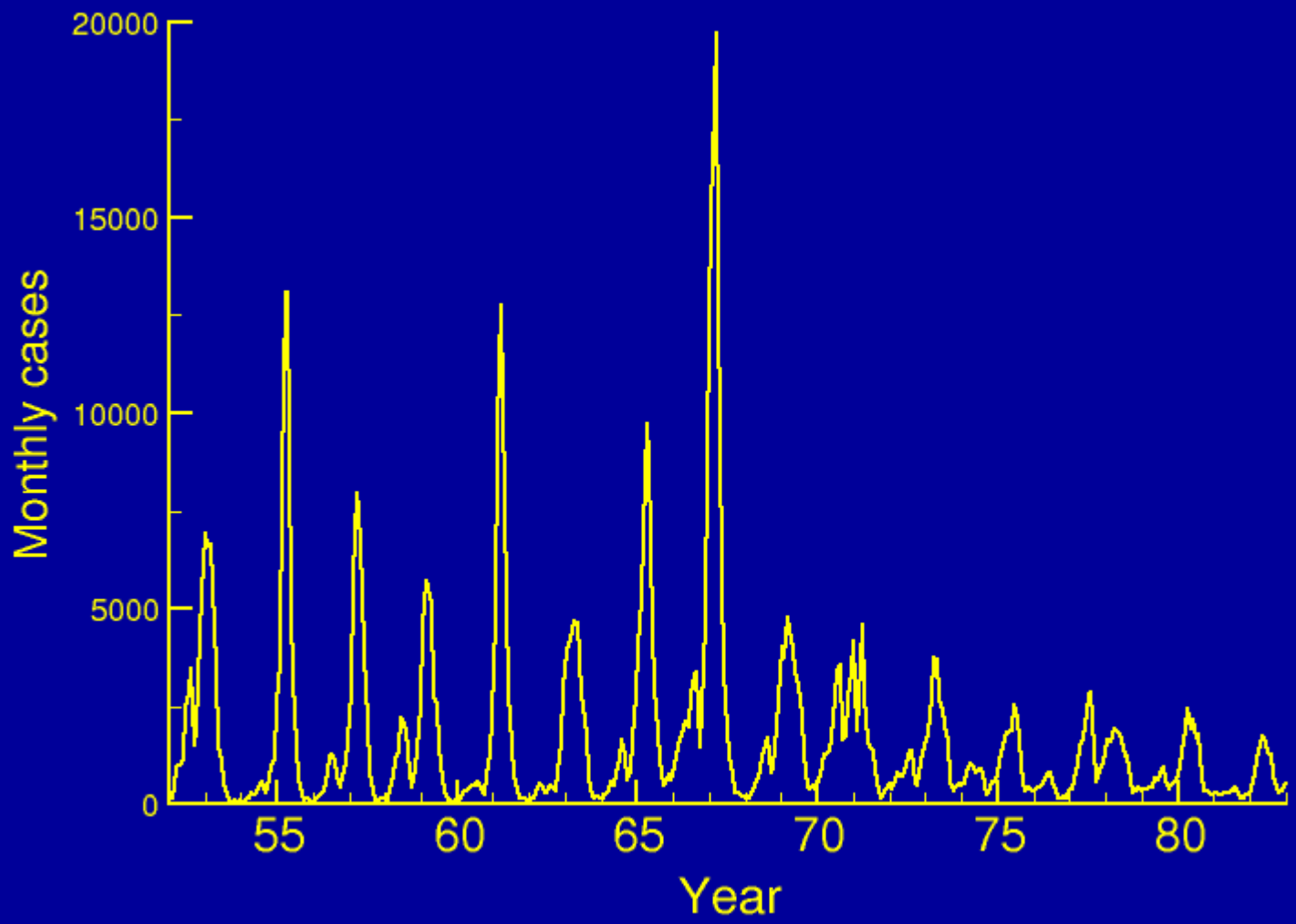
  period $\sim 2\pi (AD)^{1/2}$

  damping time $\sim 2A$

Beyond the Basic Model

- Epidemiological data often indicates limitations of basic models
  - # Experience with childhood diseases provides a nice illustration
- persistent oscillations in disease incidence
  - ♦ seasonal variations in transmission parameter
  - ♦ multi-strain structure
  - ♦ waning immunity
  - ♦ time delays
- stochastic effects
  - ♦ demographic stochasticity
  - ♦ environmental stochasticity
- evidence of heterogeneity in transmission (non mass-action)
  - ♦ age structure
  - ♦ spatial structure
  - ♦ genetic heterogeneity
  - ♦ behavioral heterogeneity

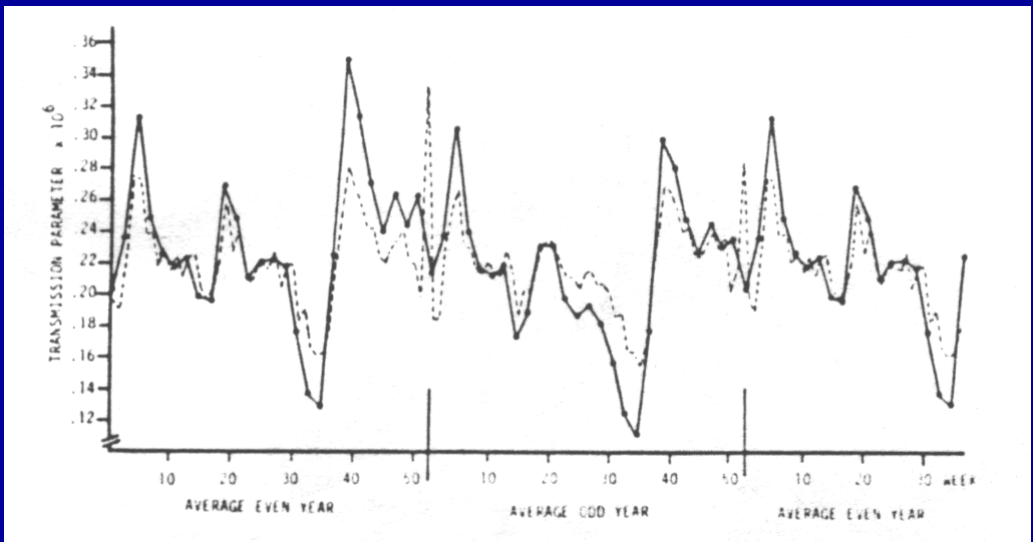
UK Monthly Measles Incidence



Seasonality and Multi-Annual Epidemics

- Schools are centers for disease transmission
- Higher rates of disease transmission during school terms
- Seasonal variations in contact rate 'pump' the natural predator-prey oscillations of the system, leading to multi-annual recurrent epidemics

Transmission parameter, estimated from E&W data set



Dynamics of Seasonally Forced Model

- Within the model, multi-annual oscillations can be maintained by allowing the transmission parameter to vary seasonally
- Various functional forms for $\beta(t)$
  - Sinusoidal forcing term (simplest)
  - Term-time step function (more realistic)
- As seasonality strengthens, there is a series of period doubling bifurcations
  - annual, biennial, four-yearly, ..., chaos
  - other cycles also generated in saddle-node bifurcations
  - multiple attractors
  - intermittency, saddles/repellors

Time Delays

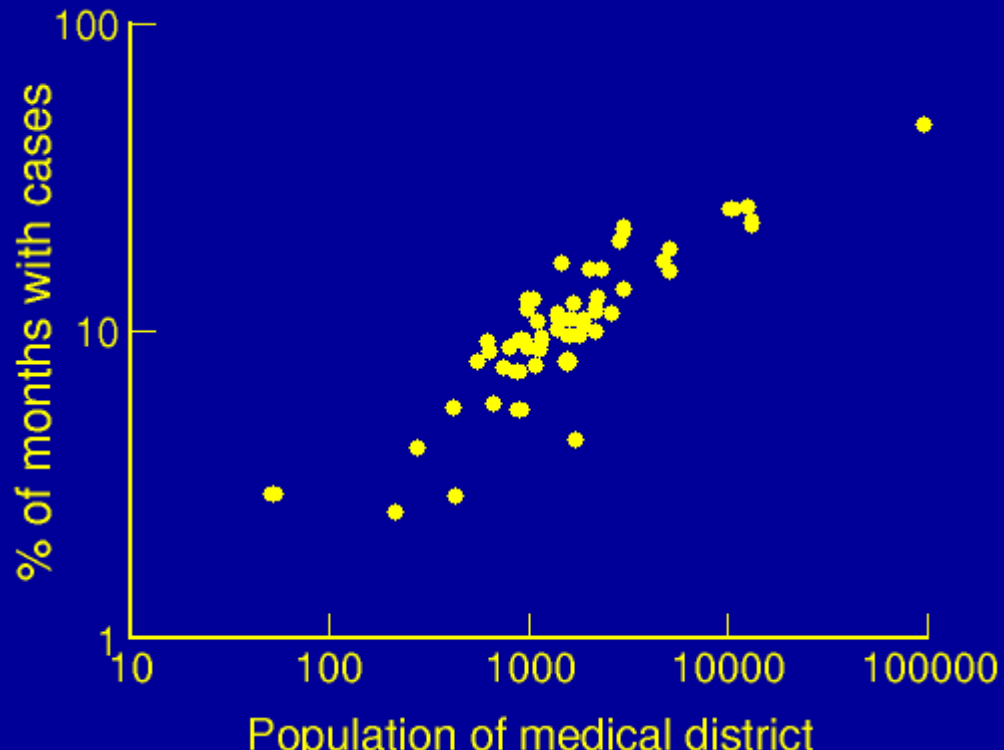
- Latent periods
- Non-exponential distributions of infectious periods
- Alters relationship between r and R_0 in an important way
  - # neglecting latent period, or assuming it is exponentially distributed, can lead to serious underestimates of R_0
- Destabilization of model
  - # complex dynamics realized with weaker seasonality
  - # can lead to sustained oscillations

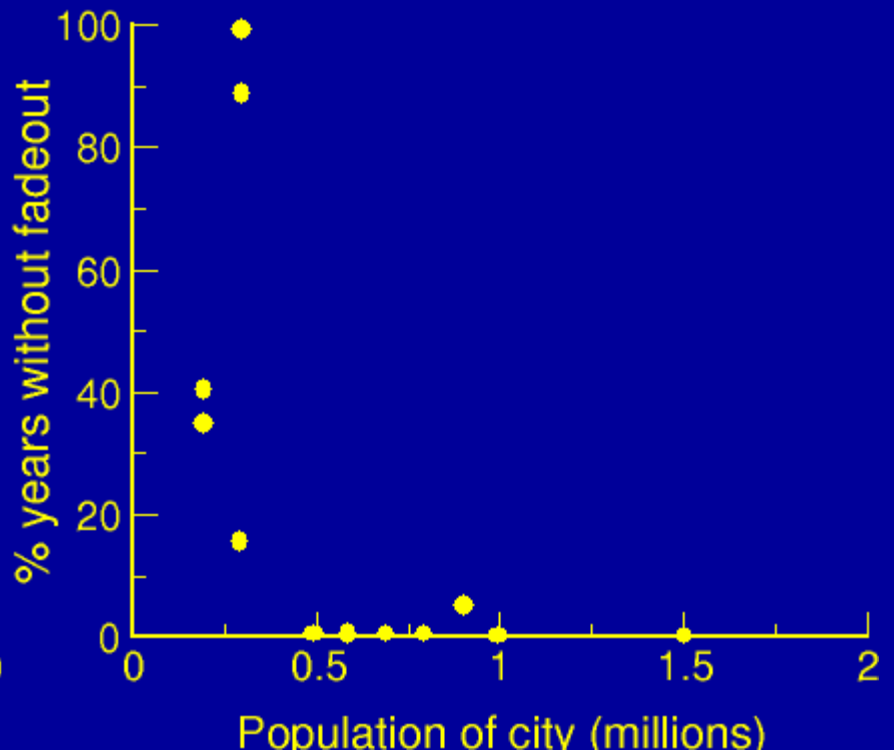
Persistence Patterns

- With increasing seasonality, amplitude of oscillations increases and the numbers of infectives fall to low levels between epidemics
  - Also seen in the incidence records
- There is the possibility of the number of cases falling to zero between epidemics— endemic fadeout
  - Studied by Bartlett in late 50s/early 60s
  - Further outbreaks only possible with the reintroduction of disease from elsewhere
- Disease can rebound from extremely low levels in deterministic models
- Model should account for demographic stochasticity (random effects due to finite size of population)
  - Opens up the possibility of interactions between stochasticity and nonlinear dynamics

Persistence Patterns

- Effects of demographic stochasticty scale as $1/\sqrt{N}$
- Critical community size (CCS): minimum size of (isolated) population needed to maintain disease
  - # On the order of 250 000 people





Reconciling Dynamics and Persistence

- It's easy to get a model to exhibit temporal patterns similar to those seen in incidence records
- It's easy to get a model to exhibit persistence patterns similar to those seen in incidence records

- But... a model which exhibits both remains elusive

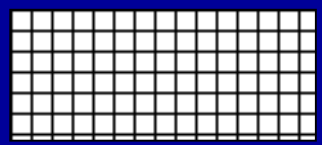
- Heterogeneity in disease transmission is believed to be the answer
  - Age structure (eg Schenzle & Dietz or Grenfell & Bolker)
    Spatial structure (Bolker & Grenfell, Lloyd & May, Keeling)

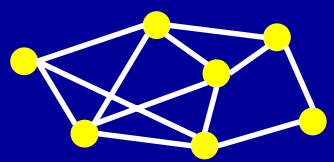
Heterogeneities in Transmission: Age Structure

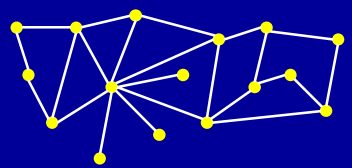
- Basic model predicts that fraction of individuals of age a that are susceptible to infection ~ exp (–λa)
- Contradicted by serological data
- Heterogeneity arises because of increased transmission between school-age children
  - Pre-school children represent a pool of susceptibles which is shielded, to some degree, from the strongest levels of transmission
- Tends to stabilize dynamics?
- Tends to enhance persistence of disease

Heterogeneities in Transmission: Spatial Structure

- Epidemics in different regions not perfectly synchronized
  - # Local spreading from large population center into surrounding areas
- Various modeling frameworks
- Reaction-diffusion models
  - # space is modeled continuously
    look for wave-like solutions
- Metapopulation models
  - # collection of 'patches'
    e.g. weakly coupled cities
- Network models
  - # explicitly model individuals and their connections
    e.g. STDs or computer viruses

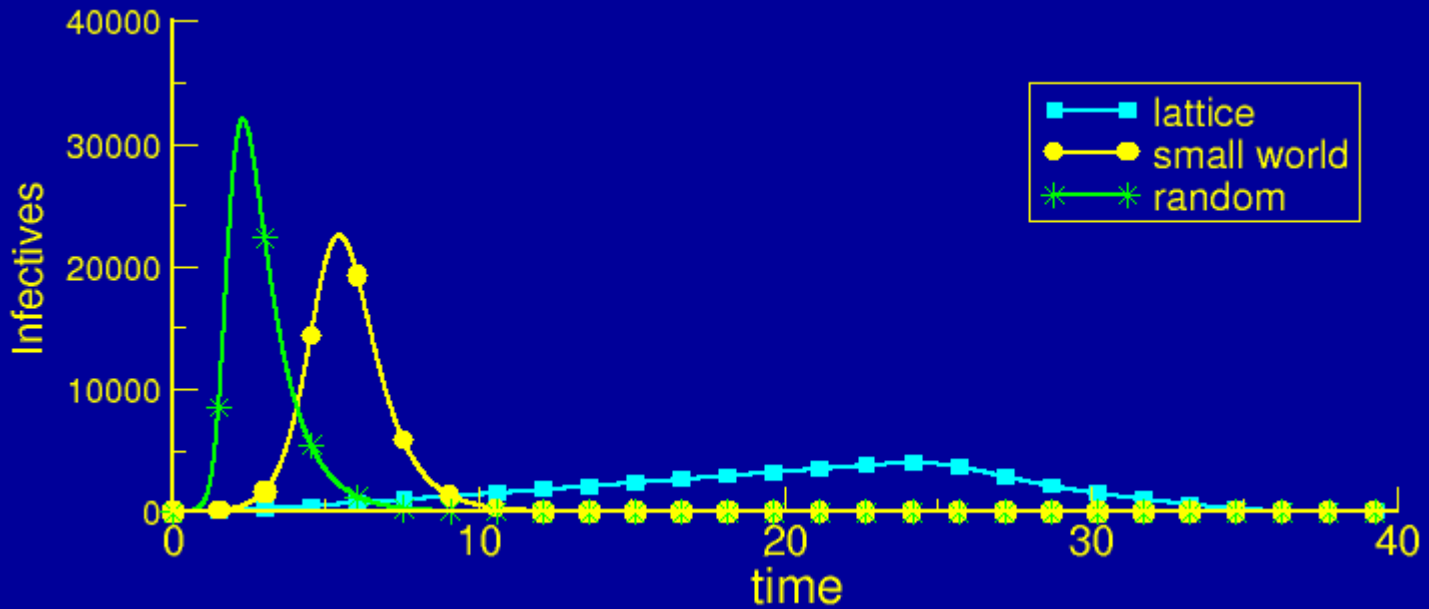






Implications of Spatial Heterogeneity

- Local spatial structure tends to slow epidemic spread
  - # Disease must pass through many intermediates to get from A to B
  - # Clique structure – many shared neighbors – reduces infection opportunities
  - # c.f. mass-action where infection is immediately seen by everyone
- 'Small world' effects rapidly overcome local spatial structure
  - # Surprising result that only a small number of long-range contacts are needed to recover well-mixed situation (Watts & Strogatz)



Behavioral and Genetic Heterogeneity

- Behavioral differences between individuals may lead to their disease exposure, or transmission potential, being quite different
  - # High risk groups
  - # Superspreaders
- Thinking about transmission potential, characterize differences by a distribution of activities. Label this distribution by k
- Extend compartmental model by activity class
- R_0 gains an extra contribution depending on the variance of the activity distribution, over and above the contribution from the mean activity

$$R_0 = \rho_0 \left(1 + \mathrm{CV}^2\right)$$
$$= \beta D \langle k \rangle \left(1 + \mathrm{CV}^2\right)$$

Behavioral and Genetic Heterogeneity

- Consider SIR model with no births (single epidemic)
- Expression for size involves solving k simultaneous nonlinear equations
- Assume that transmission parameter, β_{kl} factorizes as $\beta_{kl} = g_k h_l$
- Then, fraction ever infected in the k th group is

$$I_k = 1 - \exp(-g_k \alpha)$$

where

$$\alpha = \sum_k h_k \overline{N}_k \left(1 - \exp\{-g_k \alpha\}\right) / \gamma$$

- Can then insert an appropriate description of transmission
  - # e.g. average no. of partners per unit time proportional to k , and assume `random mixing' (k of partner does not depend on your k, just the relative frequencies in the population)
  - # corresponds to $\beta_{ij} = i\, j \beta \Big/ \sum_i i N_i$

Behavioral and Genetic Heterogeneity

- Heterogeneity leads to lower equilibrium level of infection (or smaller total no. of cases)
- Infection tends to be concentrated in high risk groups (core groups) who are responsible for a disproportionate number of cases

- Warns against naive use of 'averages'

- Important implications for control or vaccination policies
- Homogeneous vaccination strategy is far from optimal
- Vaccination should target high-risk groups
  - Anderson & May: 'bang bang' strategy is optimal
  - vaccinate everyone whose activity is greater than k_c

Why Study Childhood Diseases?

- For epidemiologists:
  - These diseases cause significant mortality in third world...
  - They still persist in developed countries...
  - Despite the availability of (in many cases) cheap, effective vaccines
  - Data covers the introduction of mass vaccination
  - Therefore lessons learnt inform design of future vacc. programs
- For ecologists:
  - Such disease systems can be viewed as predator-prey systems
  - Many of the issues underlying their behavior are exactly those of interest in similar ecological contexts (e.g. impacts of seasonality, stochasticity and spatial structure on dynamics and persistence)

Why Study Childhood Diseases?

- For those interested in nonlinear dynamics:
  - # Incidence records exhibit periodic or more complex behavior
    In many situations, it's clear that the dynamics reflect
    the interaction between nonlinearity and stochasticity
- For modelers:
  - # Excellent data is available:
    can ask detailed questions about spatial and temporal dynamics
    and can test and improve models
  - # The biological system is fairly simple

Summary and Conclusions

- R_0 is a central concept of mathematical epidemiology, and its estimation is often a main aim
- Epidemiological data highlights inadequacies of simplest models
- Importance of seasonality, stochasticity and heterogeneity
- Childhood diseases have been of particular interest, for many reasons, but not least of all because of the availability of comparatively good data sets

- Good introduction: Diekmann & Heesterbeek 'Mathematical Epidemiology of Infectious Diseases' (Wiley)
- Classic, comprehensive: Anderson & May 'Infectious Diseases of Humans' (Oxford)