# **Epidemics with two levels of mixing**

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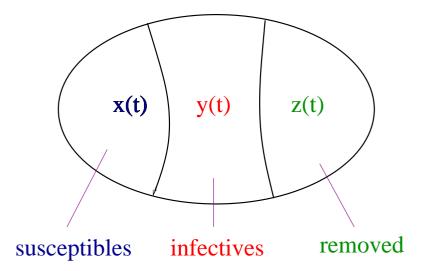
Joint work with Peter Neal (University of Manchester) and Owen Lyne (University of Kent)

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### **Outline of talk**

- Background on homogeneously mixing SIR (susceptible  $\rightarrow$  infective  $\rightarrow$  removed) epidemic models
- General two-level-mixing SIR epidemic model
  - Special cases
    - households model
    - overlapping groups model
    - great circle model
    - network model with casual contacts
  - Threshold behaviour and final outcome of global epidemic
    - general results
    - applications to special cases
    - numerical illustrations
- Vaccination in Households SIR model
- Concluding comments

# General deterministic epidemic



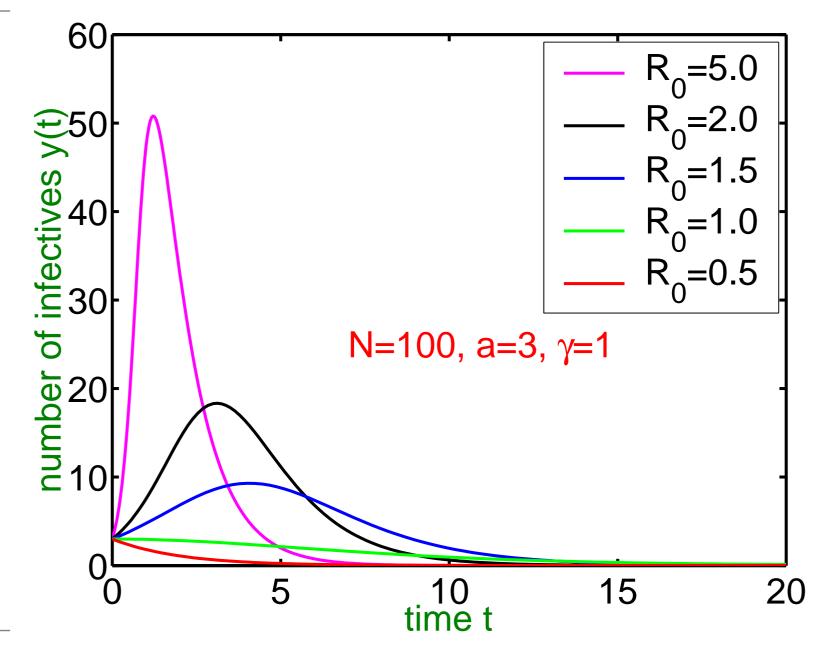
(x(0), y(0), z(0)) = (N, a, 0)  $\beta =$ infection rate  $\gamma =$ removal rate

SIR (susceptible → infective → removed)

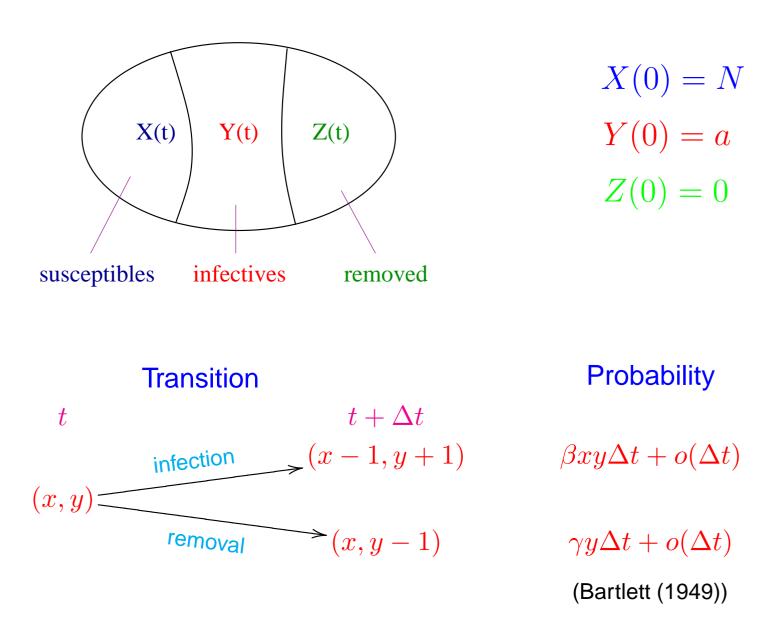
- $\frac{dy}{dt} > 0 \iff \beta xy \gamma y > 0 \iff x > \gamma/\beta$
- Epidemic takes off  $\iff N > \gamma/\beta \iff R_0 = N\beta/\gamma > 1$

(Kermack and McKendrick (1927))

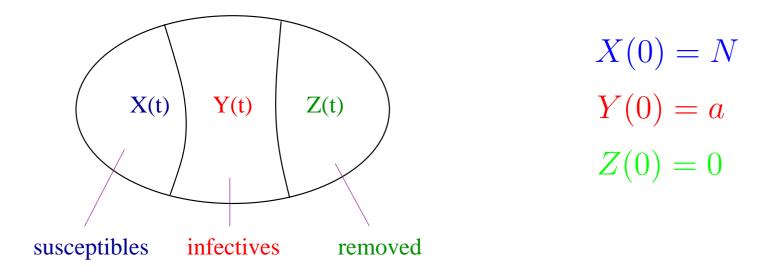
### **General deterministic epidemic**



### **General stochastic epidemic**



### **General stochastic epidemic**



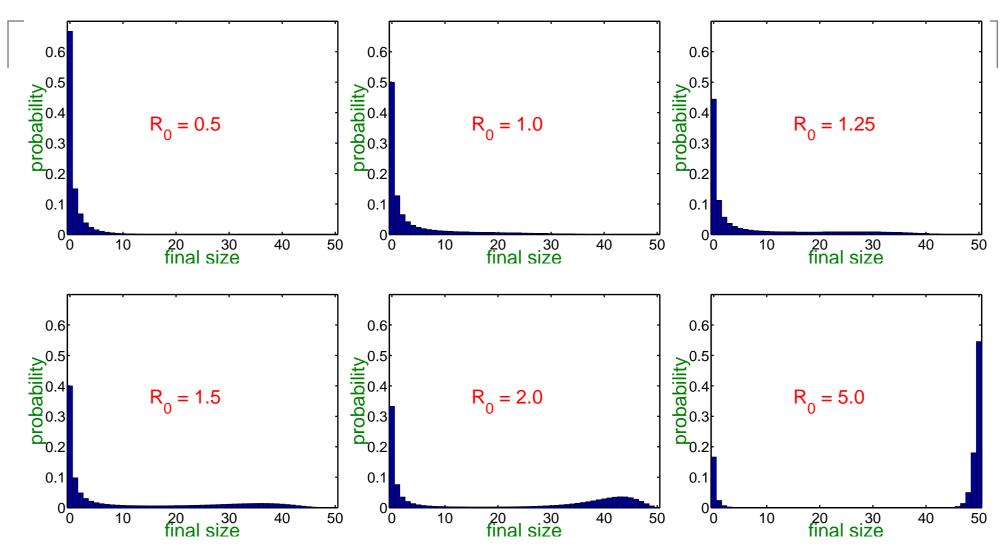
• Final size  $T = N - X(\infty)$  — number of susceptibles ultimately infected

• Let  $P_j = P(T = j) \ (j = 0, 1, ..., N)$ . Then

$$\sum_{j=0}^{i} \binom{N-j}{N-i} \left(1 + \left(1 - \frac{i}{N}R_0\right)\right)^{a+j} P_j = \binom{N}{i} \quad (i = 0, 1, \dots, N)$$

(Whittle (1955))

### **Final size**



Final size distribution for general stochastic epidemic with 1 initial infective and 50 initial susceptibles

### **Threshold behaviour**

- Consider epidemic with initially few infectives and many susceptibles
- If  $R_0 \leq 1$ , then
  - Only minor outbreaks occur
  - Size of outbreak distributed according to total progeny of approximating branching process, Z say, in which all contacts lead to an infection
- If  $R_0 > 1$ ,
  - P(major outbreak) = 1 P(Z goes extinct) > 0
  - Size of minor outbreak distributed according to total progeny of Z, conditional upon extinction
  - Size of major outbreak satisfies a central limit theorem with mean given by deterministic model

(von Bahr and Martin-Löf (1980))

# **Basic reproduction number** $R_0$

- R<sub>0</sub> = "the expected number of secondary cases produced by a typical infected individual during its entire infectious period, in a population consisting of susceptibles only" (Heesterbeek and Dietz (1996))
- Major outbreak can occur  $\iff R_0 > 1$
- If proportion *c* of susceptibles is vaccinated with a perfect vaccine,  $R_0$  is reduced to  $R_v = (1 c)R_0$ , so, if  $R_0 > 1$ ,

 $R_v \leq 1 \iff c \geq 1 - R_0^{-1}$  — critical vaccination coverage

(Smith (1964))

# Multitype general deterministic epidemic

*m* types of individual, labelled 1, 2, ..., *m*, reflecting e.g. age, vaccine status, geographical location.

$$\frac{dx_i}{dt} = -x_i \sum_{j=1}^m \beta_{ji} y_j,$$
$$\frac{dy_i}{dt} = x_i \sum_{j=1}^m \beta_{ji} y_j - \gamma_i y_i,$$
$$\frac{dz_i}{dt} = \gamma_i y_i \quad (i = 1, 2, \dots, m)$$

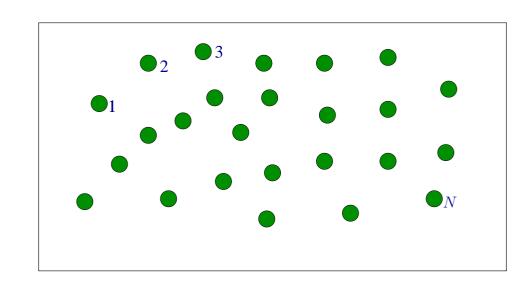
with  $(x_i(0), y_i(0), z_i(0)) = (N_i, a_i, 0)$ 

• Analogues of all previous results hold BUT threshold behaviour requires  $N_i \rightarrow \infty$  (i = 1, 2, ..., m), i.e. that the population is LOCALLY LARGE

## **Non-locally-large models**

- Spatial models
  - percolation
  - structure too rigid for human populations
- Network models
- Multi-level mixing models
  - metapopulation/households models
- Complex simulation models
  - more realistic but can be computationally expensive and difficult to interpret

# General two-level-mixing epidemic model

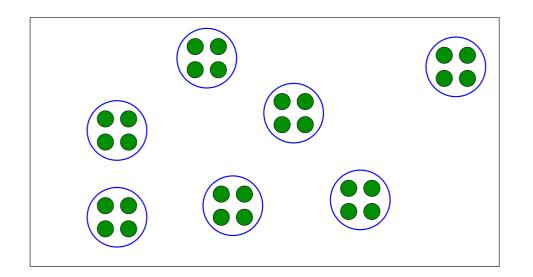


Population $\mathcal{N} = \{1, 2, \dots, N\}$ 

- **SIR** (susceptible  $\rightarrow$  infective  $\rightarrow$  removed)
- Infectious periods  $I_1, I_2, \ldots, I_N$  iid  $\sim I$  (arbitrary but specified)
- Infection rates (individual  $\rightarrow$  individual)
  - ightarrow local  $\lambda_{ij}^L$
  - global  $\lambda_G/N$
- Latent period



### **Households model**



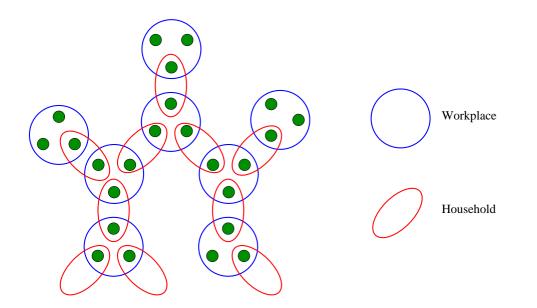
m households, each of size nN = mn

•  $\lambda_{ij}^L = \begin{cases} \lambda_L & \text{if } i \text{ and } j \text{ belong to same household} \\ 0 & \text{otherwise} \end{cases}$ 

Unequal-sized households.

(Bartoszyński (1972), Becker and Dietz (1995), Ball, Mollison and Scalia-Tomba (1997))

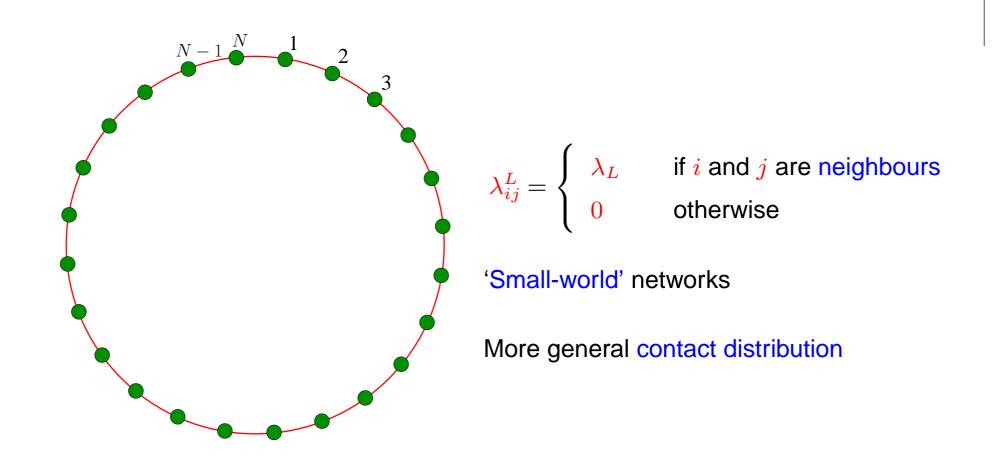
# **Overlapping groups model**



- $\square$   $m_{\alpha}$  households, each of size  $n_{\alpha}$ ,  $m_{\beta}$  workplaces, each of size  $n_{\beta}$ , so  $N = m_{\alpha}n_{\alpha} = m_{\beta}n_{\beta}$
- $\mathbf{I} \lambda_{ij}^{L} = \begin{cases} \lambda_{\alpha}^{L} & \text{if } i \text{ and } j \text{ belong to same household} \\ \lambda_{\beta}^{L} & \text{if } i \text{ and } j \text{ belong to same workplace} \\ 0 & \text{otherwise} \end{cases}$ otherwise

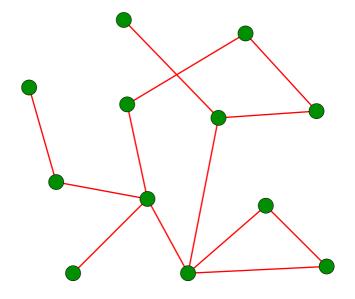
(Ball and Neal (2002), cf. Andersson (1997))

### **Great circle model**



(Ball, Mollison and Scalia-Tomba (1997), Ball and Neal (2002, 2003))

### **Networks with casual contacts**

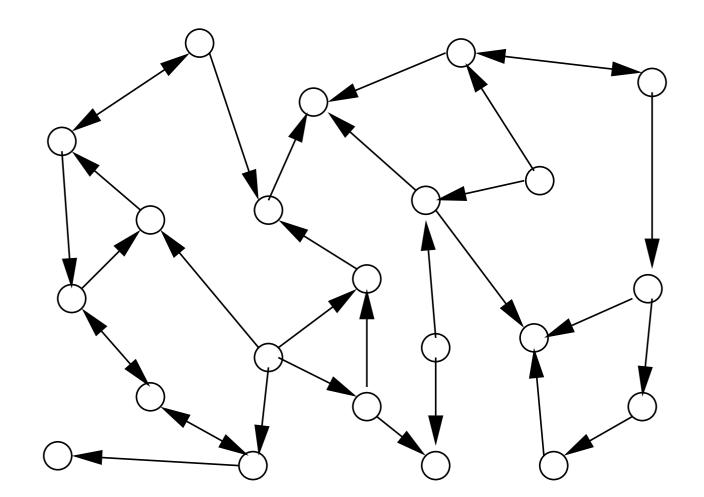


• 'independent' random graph of possible local contacts with specified degree distribution  $p_k = P(D = k)$  (k = 0, 1, ...)

$$\ \, \bullet \ \, \lambda_{ij}^L = \left\{ \begin{array}{ll} \lambda_L & \text{ if } i \text{ and } j \text{ are neighbours} \\ 0 & \text{ otherwise} \end{array} \right.$$

(Diekmann et al. (1998), Ball and Neal (2002), (2008), Kiss et al. (2006); Newman (2002))

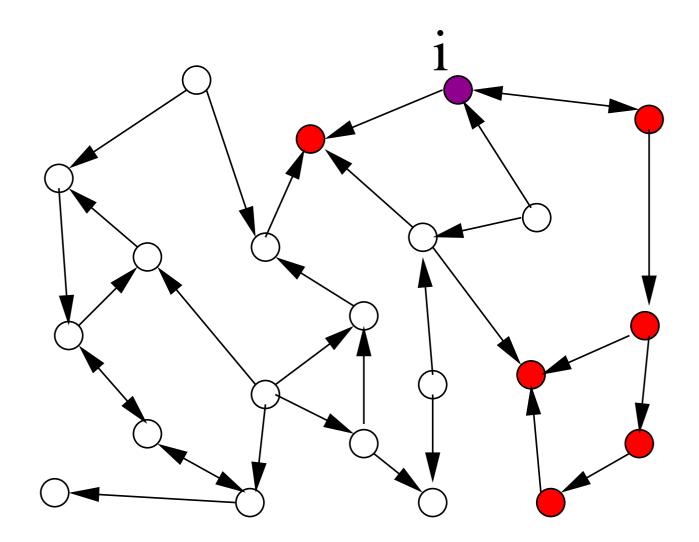
# **Directed graph of potential local contacts**



 $i \rightarrow j$  if and only if *i*, if infected, contacts *j* locally.

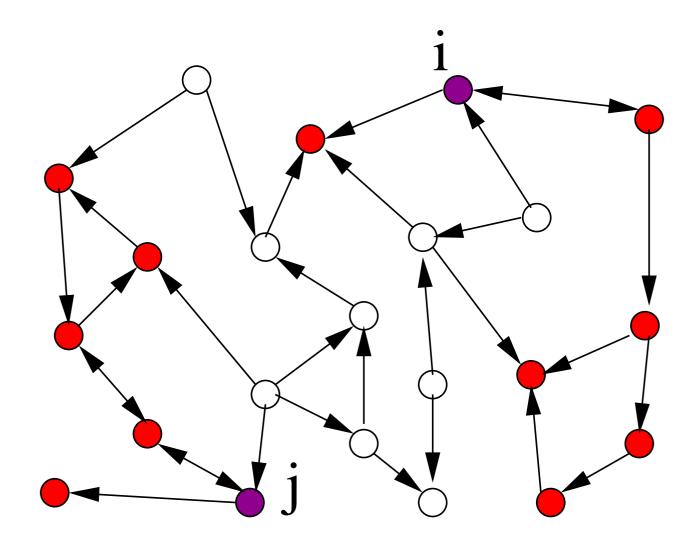
Given infectious periods  $I_1, I_2, \ldots, I_N$ ,  $P(i \rightarrow j) = 1 - e^{-\lambda_L I_i}$ independently for distinct (i, j).

# Local infectious clump $\mathcal{C}_i^N$



 $C_i^N = \{j \in \mathcal{N} : i \rightsquigarrow j\}$ , where  $i \rightsquigarrow j$  if and only if there exists a \_chain of directed arcs from i to j, and  $C_i^N = |C_i^N|$ .

### Local infectious clumps

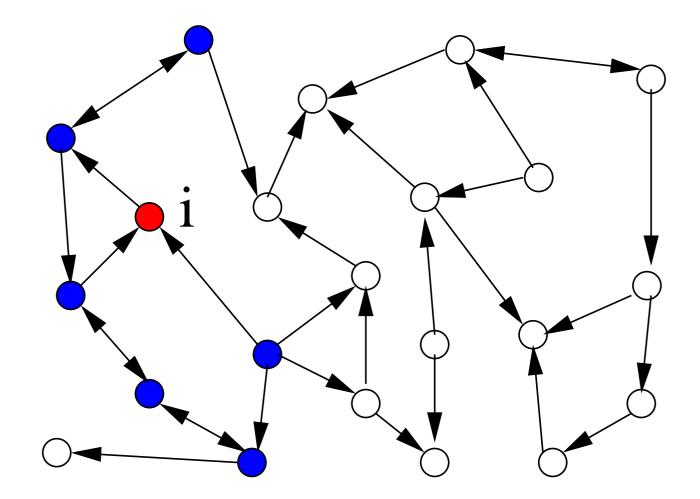


 $C_i^N = \{j \in \mathcal{N} : i \rightsquigarrow j\}$ , where  $i \rightsquigarrow j$  if and only if there exists a \_chain of directed arcs from i to j, and  $C_i^N = |C_i^N|$ .

# **Threshold parameter** $R_*$

- As  $N \to \infty$ , process of infected clumps tends to a branching process having offspring random variable  $R \sim \text{Poisson}(\lambda_G A)$ , where  $A = \sum_{j \in \mathcal{C}} I_j$
- Global epidemic occurs if and only if this branching process does not go extinct
- $R_* = E[R] = \lambda_G E[A] = \lambda_G E\left[\sum_{j \in \mathcal{N}} I_j \mathbb{1}_{\{j \in \mathcal{C}\}}\right] = \lambda_G \sum_{j=1}^N E[I_j] P(j \in \mathcal{C}) = \lambda_G \mu_I E[C]$
- $P(\text{global epidemic}) > 0 \iff R_* > 1$

# Local susceptibility set $\mathcal{S}_i^N$



 $\mathcal{S}_i^N = \{j \in \mathcal{N} : j \rightsquigarrow i\} \text{ and } S_i^N = |\mathcal{S}_i^N|.$ 

# **Final outcome of global epidemic**

Suppose N is large and there are few initial infectives. Let z be the expected proportion of the population who are infected by the epidemic. Then

 $\pi = P(\text{typical susceptible avoids global infection}) = \exp\left(-\frac{\lambda_{\text{G}}}{N}Nz\mu_{\text{I}}\right) = \exp(-\lambda_{\text{G}}z\mu_{\text{I}})$ 

and

1 - z = P(typical susceptible avoids infection by epidemic)

= P(typical local susceptibility set avoids global infection)

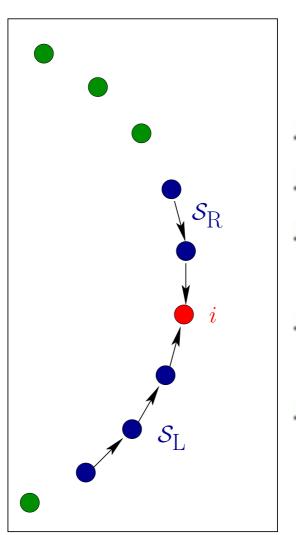
$$= \sum_{k=1}^{\infty} P(S=k)\pi^{k} = f_{S}(\pi) = f_{S}(e^{-\lambda_{G} z \mu_{I}})$$
(1)

- $R_* = \lambda_G \mu_I \mathbf{E}[C] = \lambda_G \mu_I \mathbf{E}[S]$ 
  - $R_* \leq 1$  z = 0 is the only solution of (1) in [0, 1]

 $R_* > 1$  unique second solution  $\hat{z} \in (0, 1)$ , giving mean 'size' of global epidemic

Fully rigorous proof and central limit theorem for final size of global epidemic is available using Scalia-Tomba (1985) embedding technique

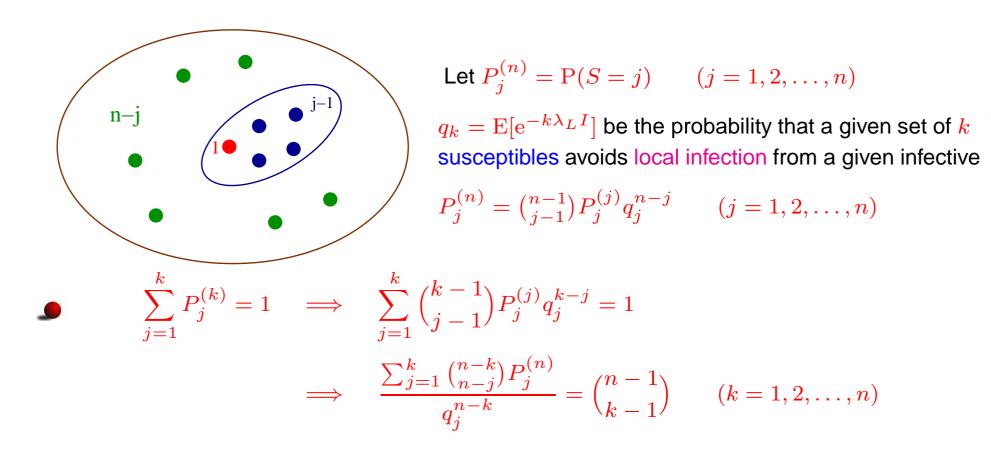
### **Great circle model**



- $p_L = P(i \text{ infects } i + 1 \text{ locally}) = 1 E[e^{-\lambda_L I}]$
- $P(S_L = k) = P(S_R = k) = (1 p_L)p_L^k$ (k = 0, 1, ...)
- $S_L$  and  $S_L$  are independent, so  $P(S = k) = (1 - p_L)^2 p^{k-1} \ (k = 1, 2, ...)$
- $\bullet \quad \mathbf{E}[S] = 2p_L^{-1} 1$

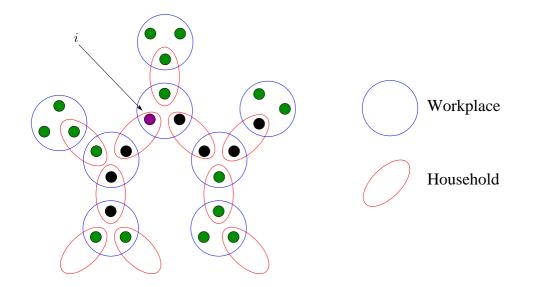
### **Households model**

Consider household of n individuals, labelled 1, 2, ..., n, and let S be the local susceptibility set of individual 1.



Triangular system of linear equations for P(S = j) (j = 1, 2, ..., n)

# **Overlapping groups model**



Construct local susceptibility set S of typical individual i via a two-type branching process in which individuals beget only the opposite type and the offspring of a type α (β) individual are the individuals in its workplace (household) susceptibility set.

If  $\mu_{\alpha}(\mu_{\beta})$  is the mean size of a household (workplace) susceptiblity set, then

$$\mathbf{E}[S] = \begin{cases} \frac{\mu_{\alpha}\mu_{\beta}}{\mu_{\alpha} + \mu_{\beta} - \mu_{\alpha}\mu_{\beta}} & \text{if } (\mu_{\alpha} - 1)(\mu_{\beta} - 1) < \\ \infty & \text{otherwise} \end{cases}$$

1

# **NETWORK** — Configuration model

- Population  $\mathcal{N} = \{1, 2, \ldots, N\}$
- D = degree of typical individual

 $p_k = P(D = k)$  (k = 0, 1, ...) specified  $\mu_D = E[D]$ 

- $D_1, D_2, \dots, D_N$  iid copies of D, conditioned on  $S_N = D_1 + D_2 + \dots + D_N$  being even
- Attach D<sub>i</sub> half-edges to individual i (i = 1, 2, ..., N)
- Pair up the S<sub>N</sub> half-edges uniformly at random to form the network
  IMPERFECTIONS sparse if  $\sigma_D^2 = var(D) < \infty$

(Bollobás (2001))

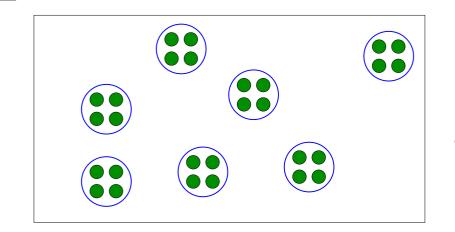
### **Networks with casual contacts**

• Let  $\tilde{D}$  = degree of typical neighbour of typical individual in the network and  $\mu_{\tilde{D}} = E[\tilde{D}]$ . Then  $P(\tilde{D} = k) = kp_k/\mu_D$  (k = 1, 2, ...) and  $\mu_{\tilde{D}} = \frac{\operatorname{var}(D) + \mu_D^2}{\mu_D}$ .

Size of typical local susceptibility set  $S^N \xrightarrow{a.s.} S$  as  $N \to \infty$ , where *S* is the total size of a branching process having offspring law  $\operatorname{Bin}(D, p_L)$  for the initial individual and  $\operatorname{Bin}(\tilde{D} - 1, p_L)$  for all subsequent individuals

$$\mathbf{E}[S] = \begin{cases} 1 + \frac{\mu_{\mathrm{D}} p_{\mathrm{L}}}{1 - (\mu_{\tilde{\mathrm{D}}} - 1)p_{\mathrm{L}}} & \text{if } (\mu_{\tilde{\mathrm{D}}} - 1)p_{\mathrm{L}} < 1\\ \infty & \text{otherwise} \end{cases}$$

# **'Deterministic' households model**



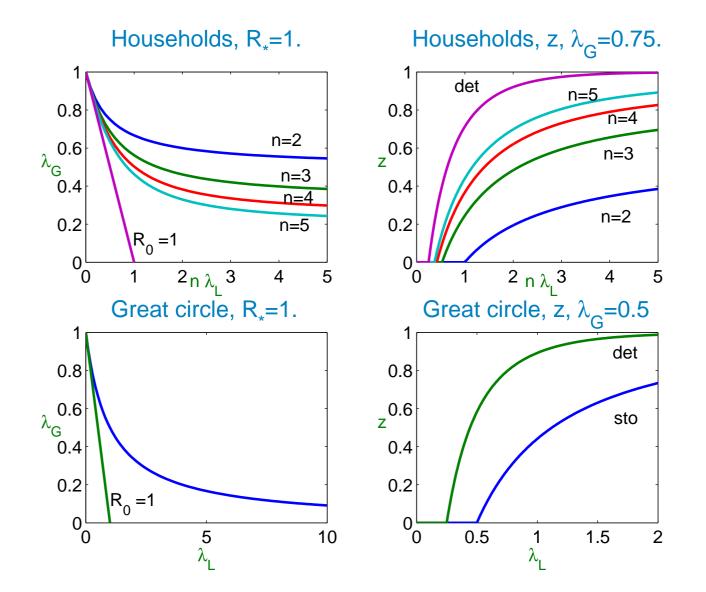
m households of size n, labelled  $1, 2, \ldots, m$ .

Let  $x_i(t)$  and  $y_i(t)$  be the number of susceptibles and infectives in household *i* at time *t*.

$$\frac{dx_i}{dt} = -(\lambda_L y_i + N^{-1} \lambda_G \sum_{j=1}^m y_j) x_i,$$
$$\frac{dy_i}{dt} = (\lambda_L y_i + N^{-1} \lambda_G \sum_{j=1}^m y_j) x_i - \gamma y_i \quad (i = 1, 2, \dots, m),$$

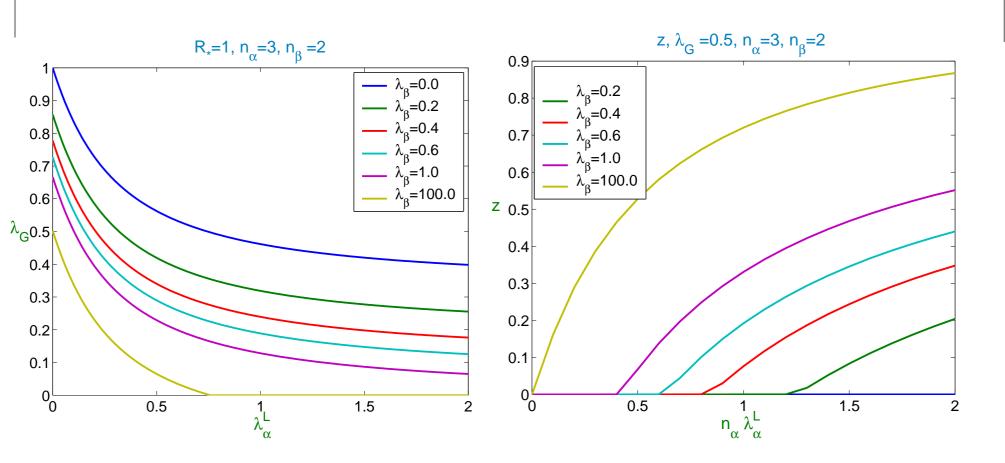
- **Basic Reproduction number**  $R_0 = (\lambda_G + n\lambda_L)/\gamma$
- Proportion of susceptibles ultimately infected,  $\hat{z}_{det}$  given by largest root in [0, 1] of  $1 z = \exp(-R_0 z)$

# Households and great circle models



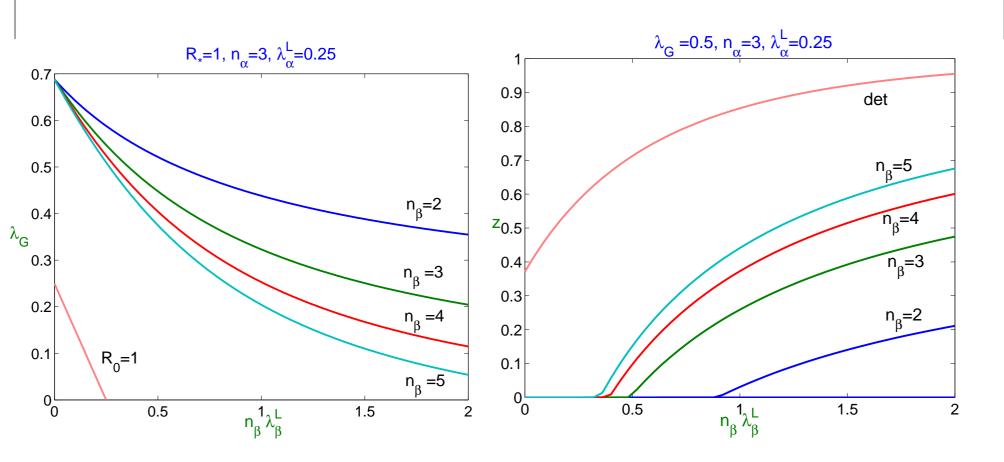
Critical values of  $(\lambda_{\rm L}, \lambda_{\rm G})$  so that  $R_* = 1$  and final outcome  $\hat{z}$  when  $I \sim \text{Exp}(1)$ .

# **Overlapping groups model, varying** $\lambda_{\beta}^{L}$



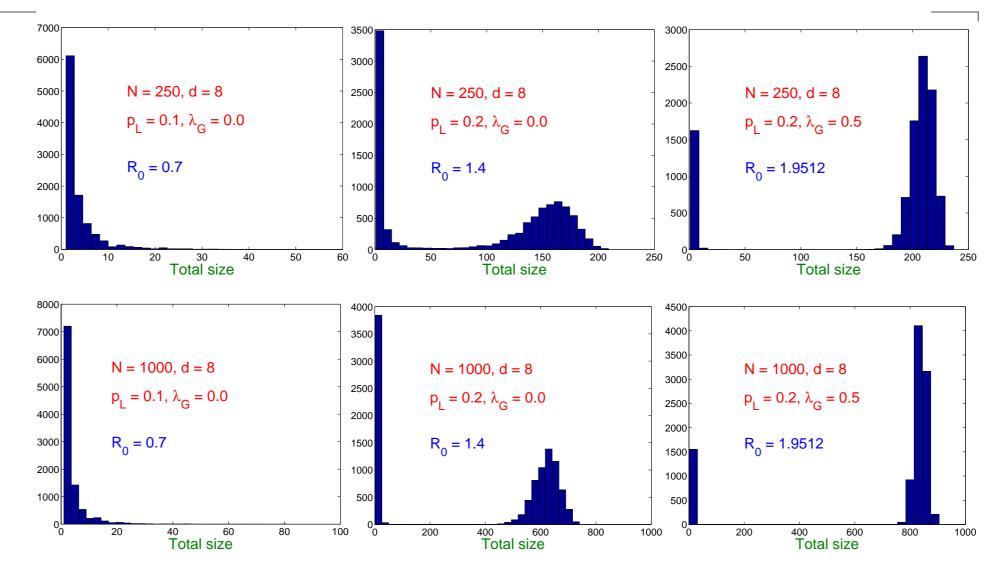
Critical values of  $(\lambda_{\alpha}^{L}, \lambda_{G})$  so that  $R_{*} = 1$  and final outcome  $\hat{z}$  when  $I \sim \text{Exp}(1)$ 

# **Overlapping groups model, varying** $n_\beta$



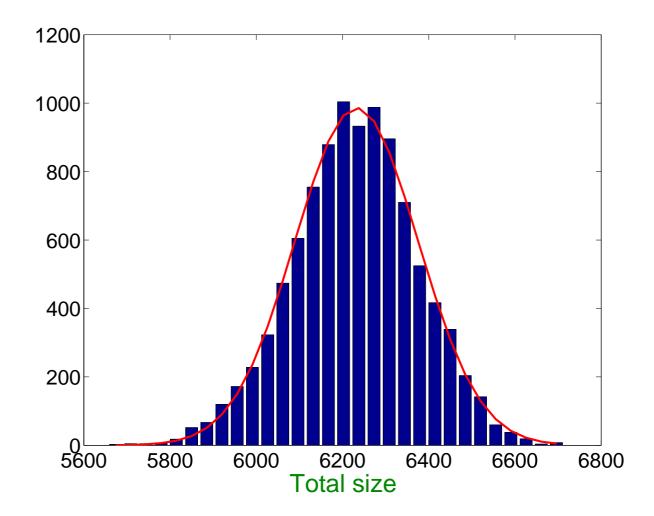
Critical values of  $(\lambda_{\beta}^{L}, \lambda_{G})$  so that  $R_{*} = 1$  and final outcome  $\hat{z}$  when  $I \sim \text{Exp}(1)$ 

### **Networks with casual contacts**



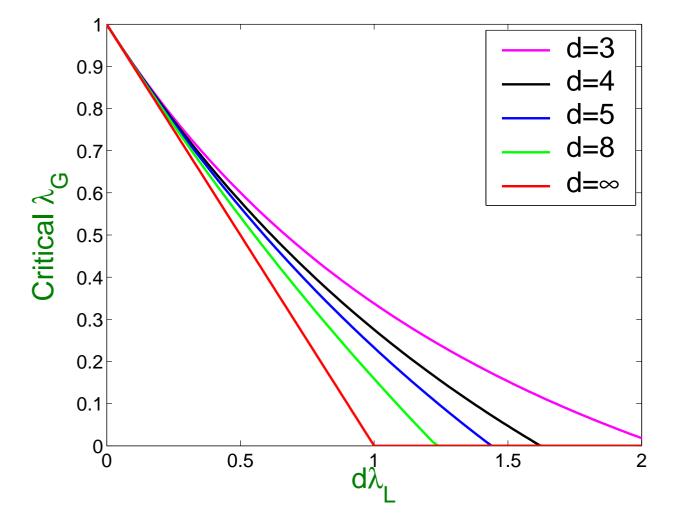
Histograms of size of 10,000 simulated epidemics per parameter combination, for a constant-degree network with  $D \equiv d, I \equiv 1$  and other parameters as shown.

### **Illustration of CLT**



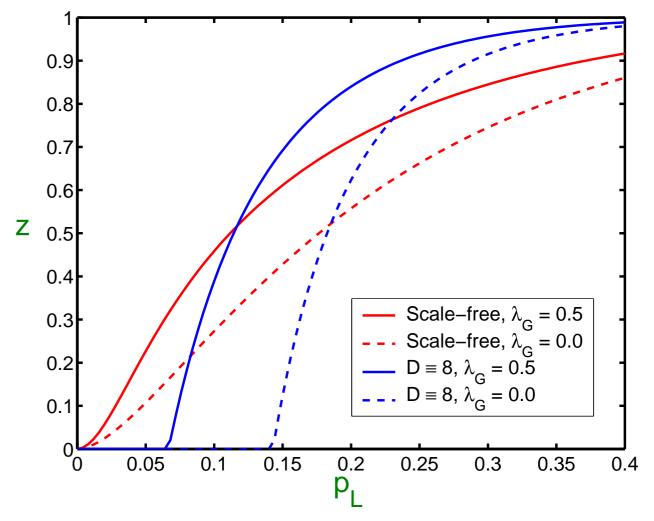
Histogram of size of 10,000 simulated global epidemics in a population of size N = 10,000 when  $D \equiv 8, \lambda_{\rm G} = 0$  and  $p_{\rm L} = 0.2$  ( $I \equiv 1$  and  $\lambda_{\rm L} = -\log 0.8$ ), with asymptotic normal approximation superimposed.

### **Networks with casual contacts**



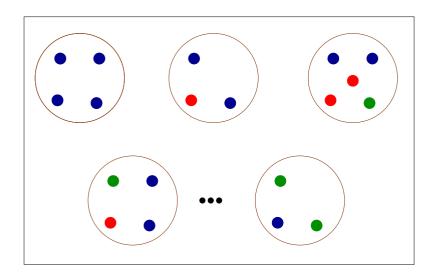
Critical values of  $(\lambda_{\rm L}, \lambda_{\rm G})$  so that  $R_* = 1$  when  $I \equiv 1$ . [Expected number of potentially infectious contacts made by an infective is  $\lambda_{\rm G} + d\lambda_{\rm L}$ .]

### **Networks with casual contacts**



Asymptotic proportion of population infected by global epidemic,  $\hat{z}$ , for constant-degree and scale-free (P(D = k)  $\propto k^{-2.466956}$  (k = 3, 4, ...)) \_ networks with  $\mu_{\rm D} = 8$  when  $I \equiv 1$ .

# Households SIR epidemic model



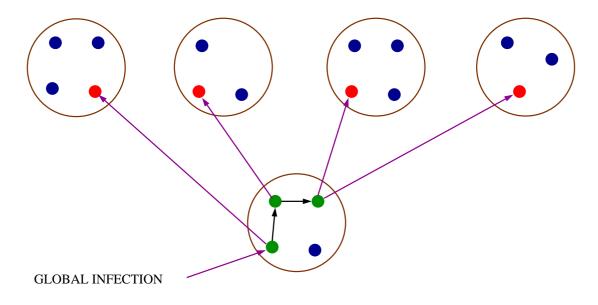
 $m_n$  households of size n (n = 1, 2, ...)total no. of households  $m = \sum_{n=1}^{\infty} m_n$ total no. of individuals  $N = \sum_{n=1}^{\infty} nm_n < \infty$ 

- **SIR** (susceptible  $\rightarrow$  infective  $\rightarrow$  removed)
- Infectious period  $\sim T_I$ , having an arbitrary but specified distribution
- Infection rates (individual  $\rightarrow$  individual)
  - (i) local (within-household)  $\lambda_L$
  - (ii) global (between-household)  $\lambda_G/N$

#### Latent period

(Bartoszyński (1972), Becker and Dietz (1995), Ball, Mollison and Scalia-Tomba (1997))

# **Threshold parameter** $R_*$



 $R_* =$  mean number of global contacts emanating from a typical single-household epidemic

$$R_* = \sum_{n=1}^{\infty} \tilde{\alpha}_n \mu_n(\lambda_L) \lambda_G \mathbf{E}[T_I],$$

where

 $\tilde{\alpha}_n = \frac{nm_n}{N}$  = P(randomly chosen person lives in a household of size *n*)

 $\mu_n(\lambda_L)$  = mean size of single (size-*n*) household epidemic with 1 initial infective

P(global epidemic) > 0 \iff R\_\* > 1

(Ball, Mollison and Scalia-Tomba (1997), Becker and Dietz (1995))

### Vaccination

• For n = 1, 2, ... and v = 0, 1, ..., n, let

 $x_{nv}$  = proportion of size-*n* households that have *v* members vaccinated

- $\mu_{nv}$  = mean number of global contacts emanating from a single-household epidemic in a household in state (n, v), initiated by an individual chosen uniformly at randomly being contacted globally
- Post-vaccination

$$R_v = \sum_{n=1}^{\infty} \tilde{\alpha}_n \sum_{v=0}^n x_{nv} \mu_{nv}$$

Vaccination coverage

$$c = \sum_{n=1}^{\infty} \tilde{\alpha}_n \sum_{v=0}^n \frac{v}{n} x_{nv}$$

Determination of optimal vaccination scheme (e.g. to reduce  $R_v$  to 1 with minimum vaccination coverage) is a linear programming problem, whose solution can be constructed explicitly.

(Becker and Starczak (1997), Ball and Lyne (2002, 2006))

# **Calculation of** $\mu_{nv}$

- $x_{nv}$  = proportion of size-*n* households that have *v* members vaccinated
- $\mu_{nv}$  = mean number of global contacts emanating from a single-household epidemic in a household in state (n, v), initiated by an individual chosen uniformly at randomly being contacted globally
- $\mu_{nv}$  depends on model for vaccine action.
- For an all-or-nothing model, in which vaccinees are rendered immune independently with probability  $\epsilon$ , otherwise the vaccine has no effect

$$\mu_{nv} = \sum_{k=0}^{v} \underbrace{\binom{v}{k} \epsilon^{k} (1-\epsilon)^{v-k}}_{(1)} \underbrace{\frac{n-k}{n}}_{(2)} \underbrace{\frac{\mu_{n-k}(\lambda_L)}{n}}_{(3)} \lambda_G \mathbf{E}[T_I]$$

- (1) P(k vaccinations are successful)
- (2) P(globally contacted individual is susceptible)
- (3) Mean size of single-household epidemic

# Variola Minor, Sao Paulo, 1956

- Data comprise final numbers infected in each of 338 households. Household size varied from 1 to 12 (mean = 4.56)
- Each individual labelled vaccinated or unvaccinated

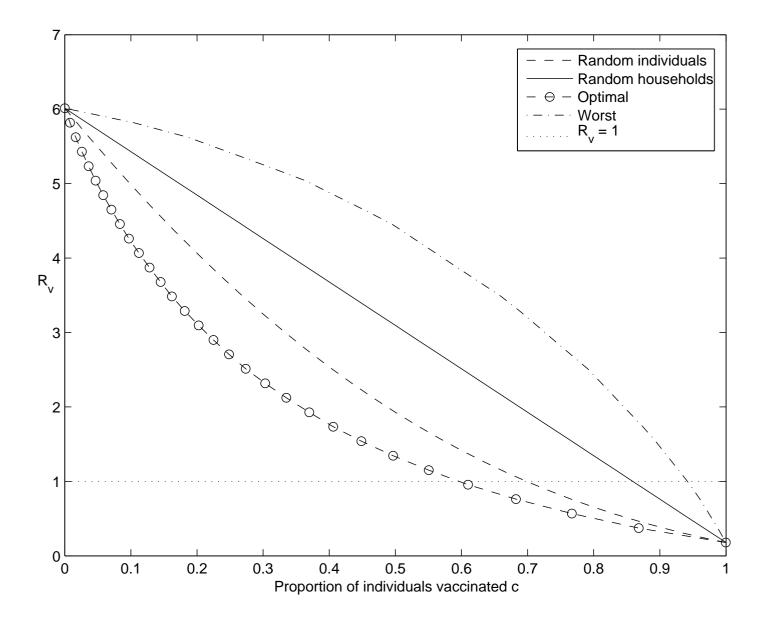
 773 unvaccinated
 —
 425 infected (58%)

 809 vaccinated
 —
 85 infected (11%)

• Fit households SIR model with non-random vaccine response, assuming infectious period  $T_I \equiv 1$ , using pseudolikelihood method of Ball and Lyne (2010) to obtain the estimates

 $\hat{\lambda}_L = 0.3821, \hat{\lambda}_G = 1.4159, \hat{a} = 0.1182, \hat{b} = 0.8712$ 

# **Comparison of vaccination strategies**



# **Concluding comments**

- General framework for determining threshold behaviour and final outcome of stochastic SIR epidemics with two levels of mixing.
- Local (e.g. household) structure matters!
  - Significant impact on threshold and final outcome.
  - Consequent impact on performance of vaccination schemes.
- Explicit calculation is possible only in a few special cases need to find other local structures which are both practically relevant and mathematically tractable.
- Can relax symmetries and/or consider multitype epidemics.
- Non-SIR models
  - SIS households and great circle
  - SIR households with demography? FADE OUT

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