Stochastic epidemic modelling and analysis: current perspective and future challenges

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Outline of presentation

- Orientation (FGB)
- Emerging epidemics – early stages of an outbreak (FGB)
- Established epidemics – beyond the initial phase (TB)
- Open problems (TB)

When are stochastic models needed?

When numbers are small

- Start of an outbreak
- End of an epidemic
  - time to extinction
  - fade out
- Small populations/subgroups*
- Smaller units within populations, e.g. households and workplaces
- Estimation, e.g. confidence intervals

* Not considered in talk.

Model types

- Focus on (simple) stochastic models for which some fully-rigorous analytic progress is possible.
- Complex agent-based simulation models
  - invaluable tool for informing public health policy, owing to their far greater realism
  - probably also miss some features
  - require numerous parameters to be estimated
  - more difficult to interpret and perform sensitivity analyses on.
- Deterministic models are appropriate when all numbers are large and are usually easier to analyse than stochastic models.
- Different modelling approaches complement each other.

Early stages of an outbreak

KEY QUESTIONS

- Is a major outbreak possible? (R_0)
- If so,
  - What is the probability of a major outbreak?
  - How fast will it spread? (exponential growth rate)
- Estimation in an emerging outbreak.
- Control measures, e.g. vaccination strategies.

All of these questions can be addressed using branching processes.

General branching process

- In a general Crump–Mode–Jagers branching process individuals have independent and identically distributed (iid) life histories $\mathcal{H} = (I, \xi)$, where I denotes a typical individual's age at death and ξ is a point process of ages at which she reproduces. [Note that $\xi((I, \infty)) = 0$.]
- Thus if an individual with life history $\mathcal{H} = (I, \xi)$ is born at time b and $0 < \tau_1 \leq \tau_2 \leq \cdots \leq I$ denote the points of ξ then she has one child at each of times $b + \tau_1, b + \tau_2, \cdots$.
- The life histories are pieced together in the obvious fashion to form the population process.
- Such a process approximates the process of infectives in the early stages of an epidemic in a large, closed homogeneously mixing population, where I denotes the sum of an infective's latent and infectious periods and ξ gives the infectious ages at which that infective creates new infectives.

General branching process

- In an epidemic setting, equate extinction/survival of the branching process with a minor/major outbreak.
- Let $R = \xi((0,\infty))$ be the number of offspring of a typical individual and $R_0 = \mathrm{E}[R]$. Suppose there are a initial individuals.
  - $\mathrm{P}(\text{extinction}) < 1 \iff R_0 > 1$.
  - $\mathrm{P}(\text{extinction}) = q^a$, where q is given by the smallest solution of $f(s) = s$ in $[0,1]$ and $f(s) = \mathrm{E}[s^R]$ is the PGF of R.
- Extends to multitype processes. E.g. if there are J types of individuals, labelled $1, 2, \cdots, J$, then R_0 is the maximal eigenvalue of the mean offspring matrix $M = [m_{ij}]$, where m_{ij} is the mean number of type-j individuals spawned by a type-i individual.

General branching process

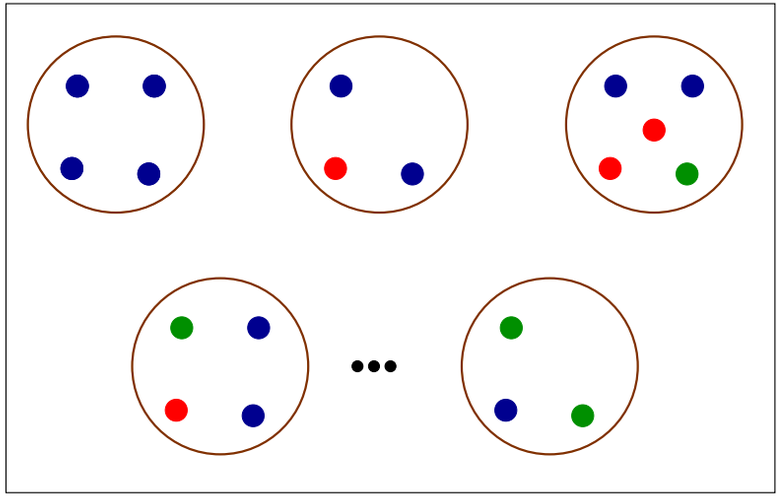
Let $Z(t)$ be the number of individuals alive at time t. Suppose that $R_0 > 1$ and there exists a Malthusian parameter $r > 0$ given by

$$\int_0^\infty \mathrm{e}^{-rt}\mu(\mathrm{d}t) = 1,$$

where $\mu(t) = \mathrm{E}[\xi((0,t])]$.

- $\mathrm{e}^{-rt}Z(t) \xrightarrow{\text{a.s.}} W$, where $W \geq 0$ is a random variable that equals 0 if and only if the process goes extinct.
- r is the real time growth rate for the corresponding epidemic model.

Households SIR epidemic model



m_n households of size n $(n = 1, 2, \dots)$

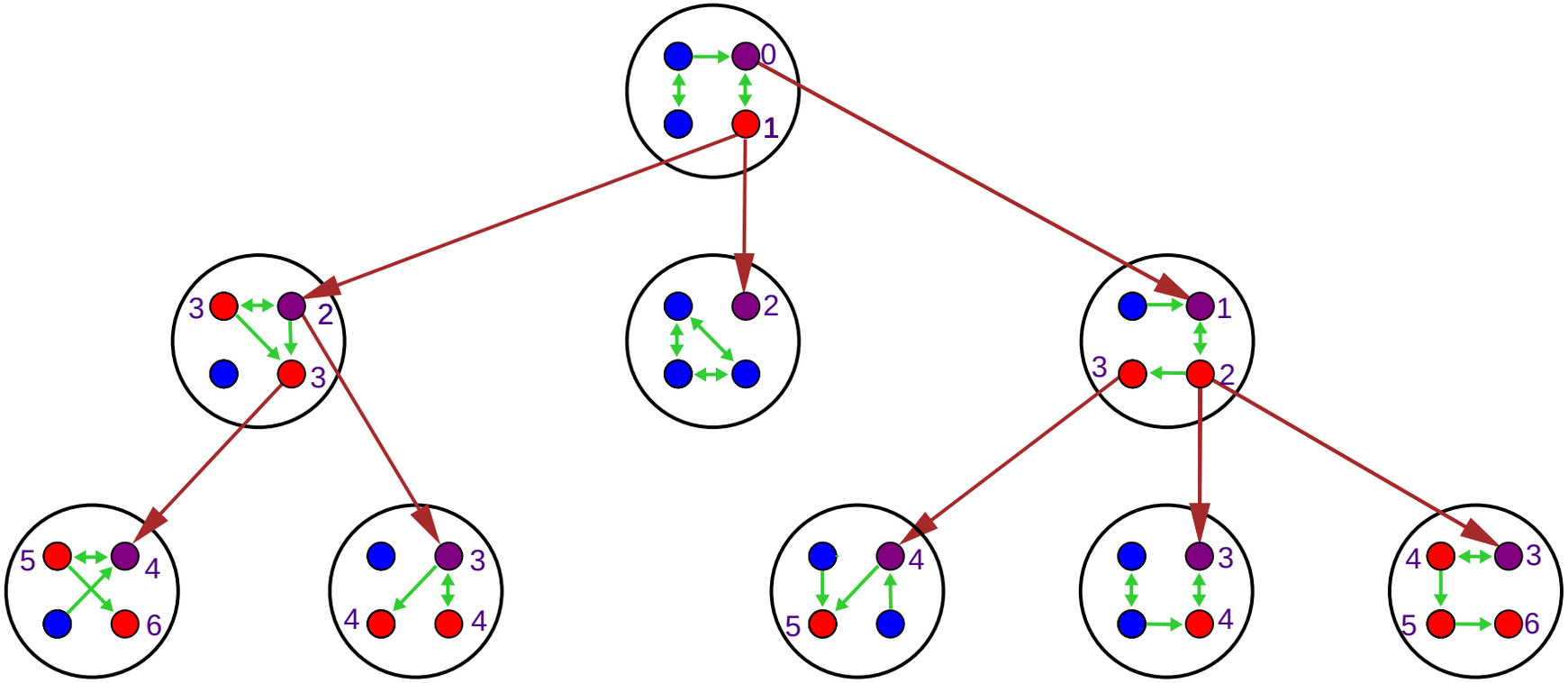
total no. of households $m = \sum_{n=1}^{\infty} m_n$

total no. of individuals $N = \sum_{n=1}^{\infty} n m_n < \infty$

- Let μ_G be the expected number of global contacts made by a typical infective.
- Let μ_H be the (household-size-biased) mean final size (including the initial infective) of a typical single-household epidemic.

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

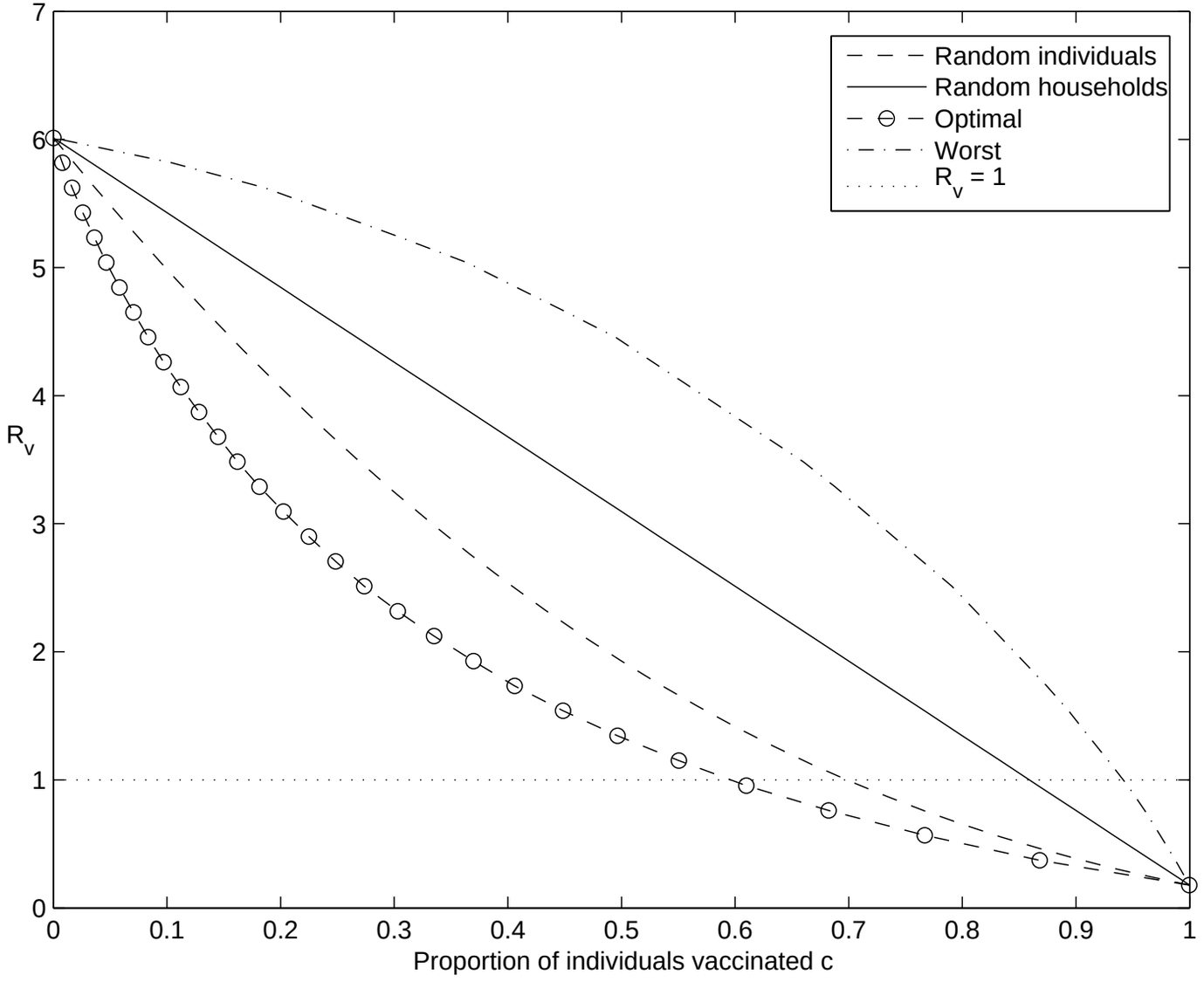
Households model



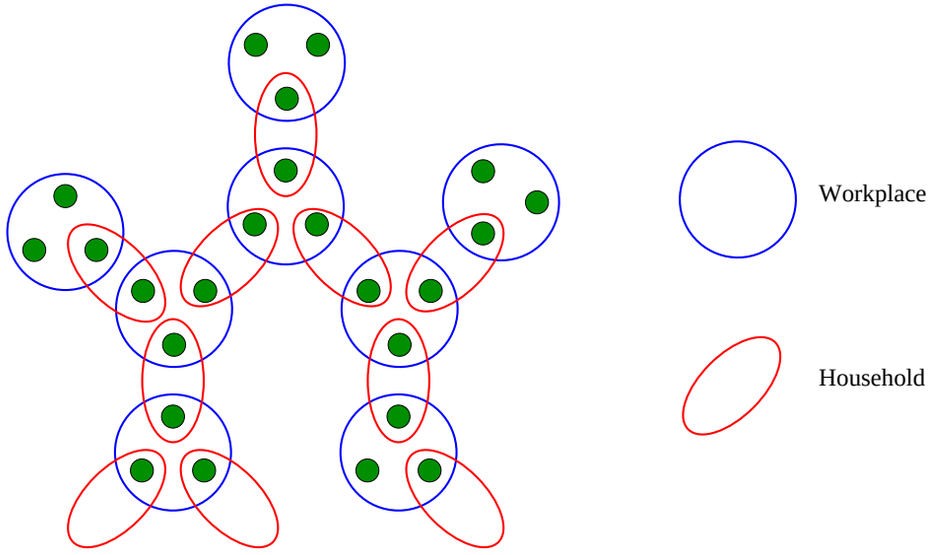
Branching process of infected households

Threshold parameter $R_* = \mu_G \mu_H$

Comparison of vaccination strategies



Households-workplaces model



- Three types of infectious contacts: global, within-household and within-workplace.
- Let μ_H (μ_W) be the household (workplace)-size-biased mean final size (including the initial infective) of typical single-household (single-workplace) epidemic.

(Ball and Neal (2002), Pellis et al. (2009), (2011), (2012), cf. Andersson (1997))

Households-workplaces model

- Approximate early stages of an epidemic by a three-type branching process, with types being
  - double-primary – infected by a global contact
  - household-primary – infected through a workplace
  - workplace-primary – infected through a household

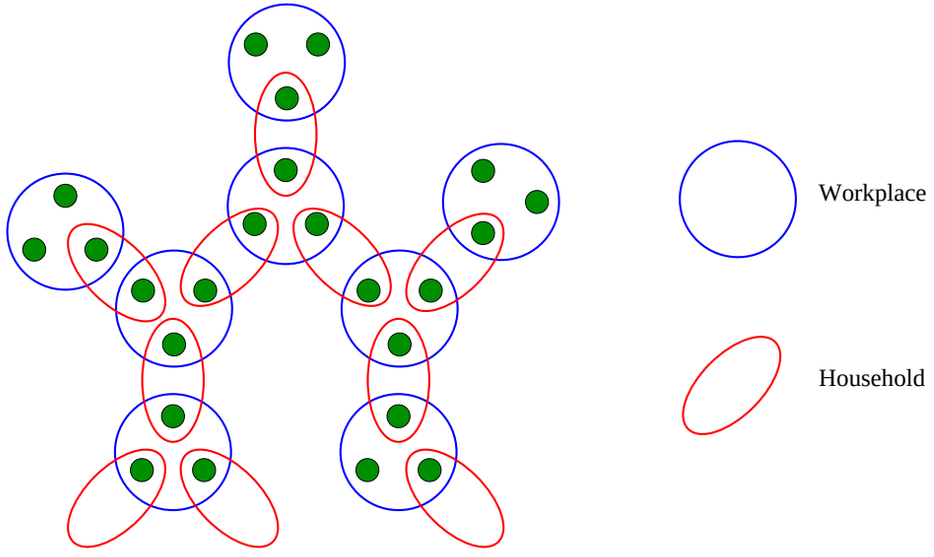
  in which all secondary cases in a single-household (or -workplace) epidemic are attributed to the initial case in that household (workplace).
- The mean offspring matrix of this branching process is

$$M = \begin{bmatrix} \mu_G & \mu_W - 1 & \mu_H - 1 \\ \mu_G & 0 & \mu_H - 1 \\ \mu_G & \mu_W - 1 & 0 \end{bmatrix}.$$

- Threshold parameter R_I given by maximal eigenvalue of M.

Households-workplaces model

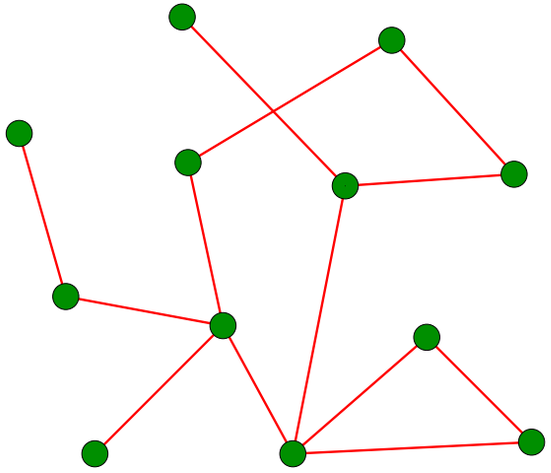
- Impact of second mixing group is significant (e.g. model is supercritical without global infection if $(\mu_H - 1)(\mu_W - 1) \geq 1$) BUT analysis makes unrealistic assumptions about how households and workplaces interact, in that they locally form a tree.



Households-workplaces model

- Impact of second mixing group is significant (e.g. model is supercritical without global infection if $(\mu_H - 1)(\mu_W - 1) \geq 1$) BUT analysis makes unrealistic assumptions about how households and workplaces interact, in that they locally form a tree.
- Similar unrealistic assumptions are made in mathematically tractable models of random networks with clustering, such as random intersection graphs.
- Challenge is to develop more realistic models that are still susceptible to analysis.

Network SIR epidemic model



D= degree of typical individual

$p_k = \mathrm{P}(D = k) \quad (k = 0, 1, \dots)$

$\tilde{D}$= degree of typical neighbour

$\mathrm{P}(\tilde{D} = k) = k p_k / \mathrm{E}[D] \quad (k = 0, 1, \dots)$

- $R_0 = p\mathrm{E}[\tilde{D} - 1] = p\left(\mathrm{E}[D] + \frac{\mathrm{Var}(D)}{\mathrm{E}[D]} - 1\right)$,

  where p is the probability that an infective infects a given neighbour.

- $R_0 = \infty$ (so critical vaccination coverage is 1) if $\mathrm{Var}(D) = \infty$, even if $\mathrm{E}[D] < \infty$.

- What does this mean for finite populations?

(Andersson (1999), Newman (2002))

Finite populations

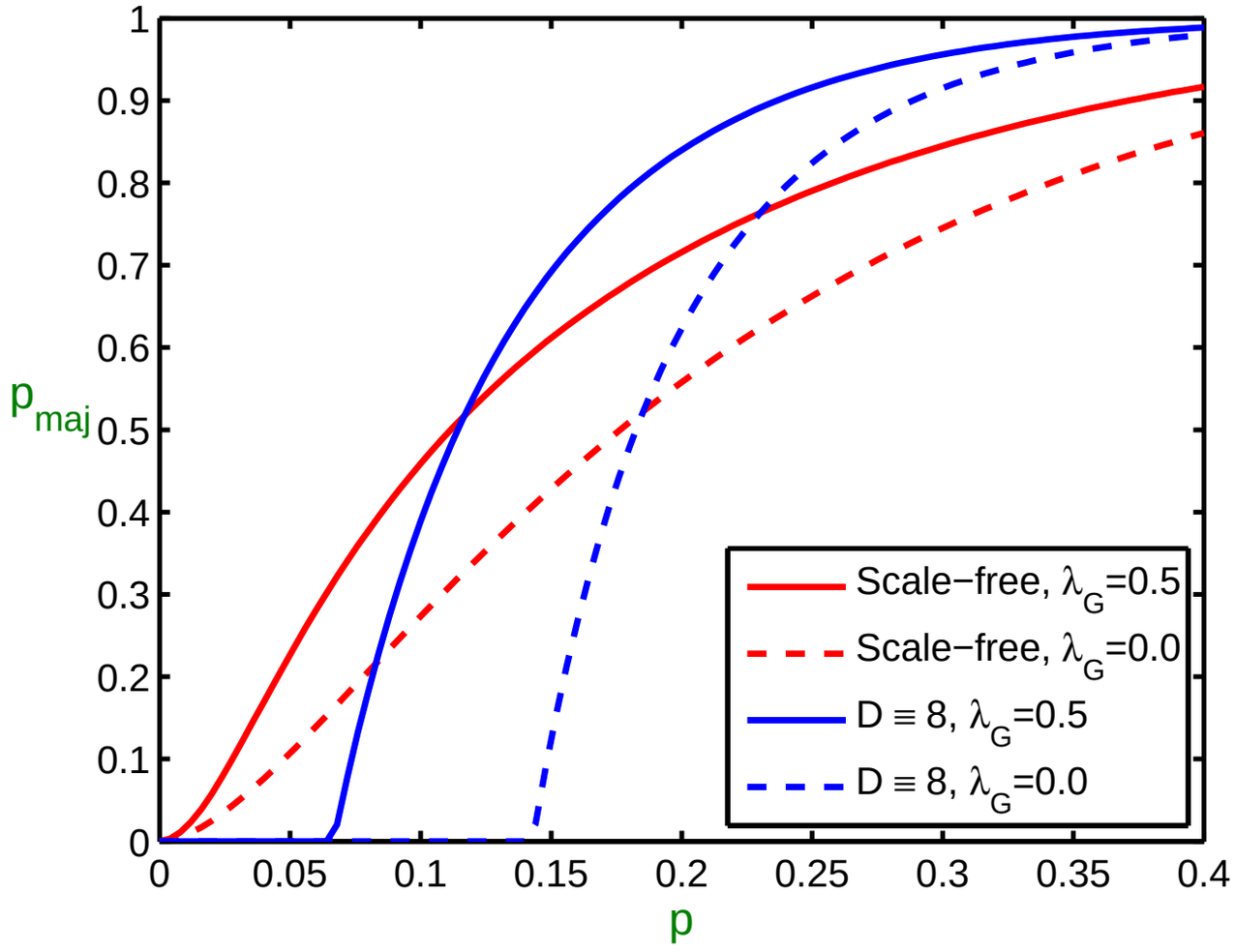
- For homogeneously mixing finite populations, Ross (2011) defines R_0 to be the expected number of infections (rather than infectious contacts) made by a typical infective in an otherwise fully susceptible population.
- This yields a sharper upper bounding branching process but the interpretation of minor and major outbreaks still essentially requires the population size $n \to \infty$.
- Aim of control is often to reduce R_0 to 1 but how appropriate is this for finite populations? As $n \to \infty$,
  - When $R_0 = 1$, mean size of epidemic $\to \infty$.
  - For $R_0 = 1 + \varepsilon$, mean fraction infected by major outbreak $\approx \frac{2\varepsilon}{(1+\varepsilon)^2}$ is small.
- Nasell (1995) defined the threshold value of R_0 to be when the final size distribution changes from being unimodal to bimodal and conjectured that this threshold $\approx 1 + \rho/n^{\frac{1}{3}}$ for large n, though a formal proof is still open.
- No sharp change at threshold, so control $\mathrm{P}(\text{size} > \text{specified value})$ instead?

Network epidemic models

Areas in need of further work include

- Dynamic networks, including effect of epidemic on network.
- Clustered networks
  - Mathematically tractable models have tree-like local structure at some level
  - There exist distinct network models having the same degree distribution, clustering coefficient and degree correlation but yielding differing epidemic properties, so caution is required when extrapolating results to real-life networks.
- Non-SIR models, e.g. SIS, SIRS.
- Casual contacts.

Effect of casual contacts



Asymptotic probability of a major outbreak, p_{maj}, for constant-degree and scale-free ($\mathrm{P}(D=k) \propto k^{-2.466956}\ (k=3,4,\ldots)$) networks with $\mathrm{E}[D]=8$ when $I \equiv 1$ and infectives make casual contacts at rate λ_G. (Ball and Neal (2008))

Estimation in an emerging epidemic

- Suppose that infectives have iid infectiousness profiles $\{\Lambda(a) : a \geq 0\}$; an infective with infectious age a creates new infectives at rate $\Lambda(a)$.
- Thus $\Lambda(a)$ is the (possibly random) intensity of the point process ξ governing births in the general branching process that approximates the homogeneously mixing epidemic.
- Real time growth rate r satisfies $\int_0^\infty \mathrm{e}^{-ra}\mathrm{E}[\Lambda(a)]\mathrm{d}a = 1$.
- $R_0 = \int_0^\infty \mathrm{E}[\Lambda(a)]\mathrm{d}a$.
- "Infectious contact interval" W has pdf $w(t) = \mathrm{E}[\Lambda(t)]/R_0$ $(t > 0)$.
- Let $M_W(\theta) = \mathrm{E}[\mathrm{e}^{-\theta W}] = \frac{1}{R_0}\int_0^\infty \mathrm{e}^{-\theta t}\mathrm{E}[\Lambda(t)]\mathrm{d}t$. Then $R_0 M_W(r) = 1$.
- Thus if the distribution of W is known and the real time growth rate r is observed, an estimate of R_0 is given by $1/M_W(r)$.

(Wallinga and Lipsitch (2007))

Households model

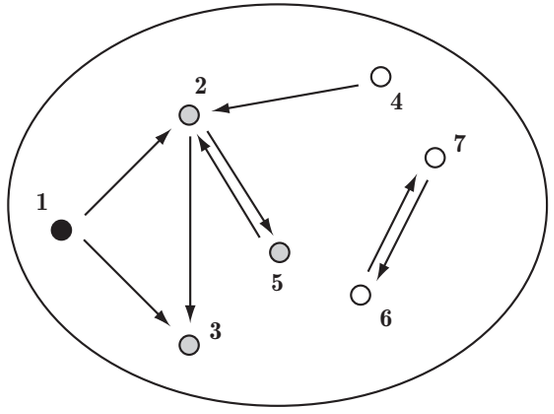
- Infectiousness profile $\{\Lambda_0(a) : a \geq 0\}$ satisfying $\mathrm{E}[\int_0^\infty \Lambda_0(a)\mathrm{d}a] = 1$.
- Infective with infectious age a makes global contacts at rate $\mu_G\Lambda_0(a)$ and contacts any given susceptible in its household independently at rate $\lambda_L\Lambda_0(a)$.
- Global contacts emanate from a typical single-household epidemic t time units after that household was infected at expected rate $\beta_H(t) = \mu_G w_H(t)$, where $w_H(t)$ depends only on household structure and within-household disease dynamics.
- For $\theta \geq 0$, let $M_H(\theta) = \int_0^\infty \mathrm{e}^{-\theta t} w_H(t)\mathrm{d}t$. Then

$$R_* = \int_0^\infty \beta_H(t)\mathrm{d}t = \mu_G M_H(0) \qquad \text{and} \qquad \mu_G \int_0^\infty \mathrm{e}^{-rt} w_H(t)\mathrm{d}t = 1.$$

- Thus if $M_H(\theta)$ $(\theta \geq 0)$ is known and the real time growth rate r is observed, $\hat{\mu}_G = 1/M_H(r)$ and $\hat{R}_* = M_H(0)/M_H(r)$. (Fraser (2007))

Two challenges

- Estimating $(\lambda_L, \Lambda_0(\cdot))$ in an emerging epidemic.
- Determining $M_H(\theta)$ from λ_L and distribution of $\{\Lambda_0(a) : a \geq 0\}$.
  - matrix methods exist for Markov models (e.g. with exponential latent and infectious periods) – Goldstein et al. (2009) and Pellis et al. (2011).
  - simulate single-household epidemics – can be computationally expensive
  - Fraser (2007) developed a closed-form approximate method which assumes that a typical household-generation-k infective is infected at time $W_1 + W_2 + \cdots + W_k$ after the household was infected, where $W_1, W_2, \cdots, W_k \overset{\text{iid}}{\sim} W$ and W has pdf $w(t) = \mathrm{E}[\Lambda_0(t)]$ $(t > 0)$. Works well if household size or var(W) is sufficiently small.

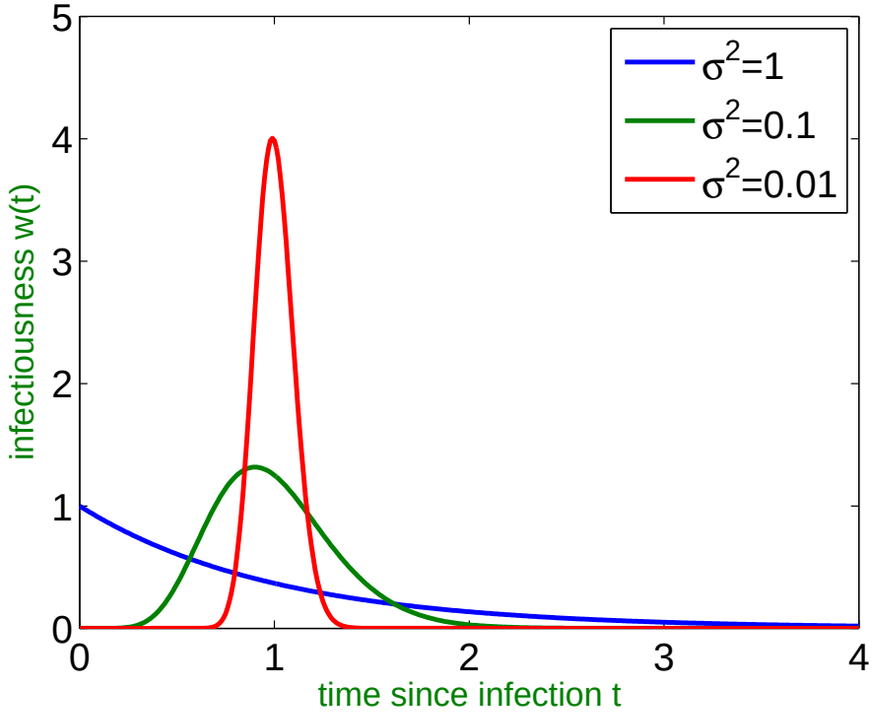


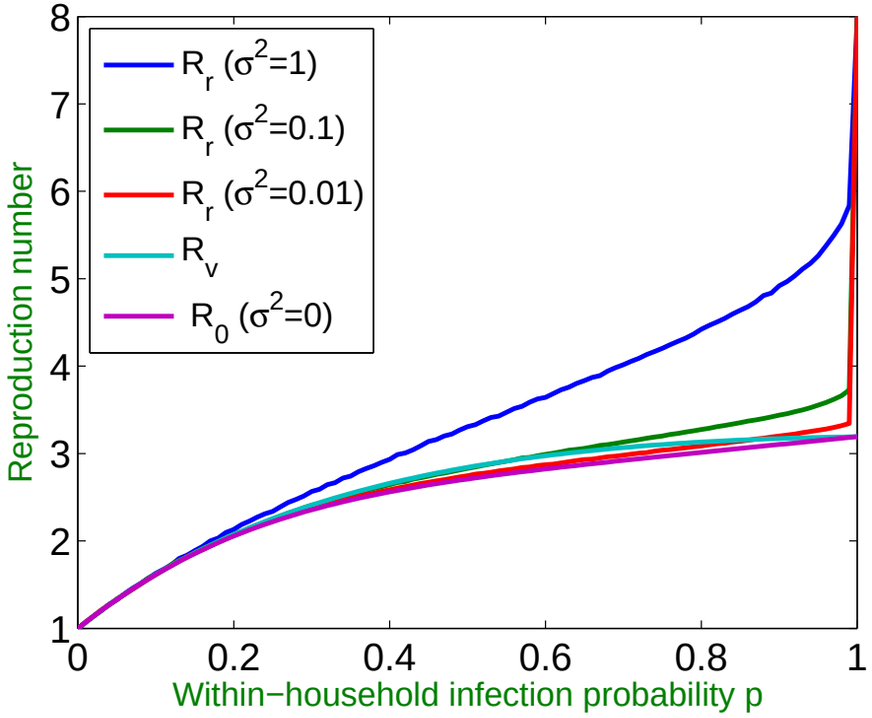
Households model

Goldstein et al. (2009) introduced the following reproduction numbers:

- Exponential-growth-associated reproduction number $R_r = 1/M_W(r)$
  - yields R_0 if model is homogeneously mixing,
  - yields households model R_0 (Pellis et al. (2012)) if Fraser (2007) approximation is used.
- Perfect-vaccine-associated reproduction number $R_V = (1 - c_V)^{-1}$, where c_V is the critical vaccination coverage assuming individuals are chosen uniformly at random for vaccination. (Note that $c_V = 1 - R_V^{-1}$).

Households model reproduction numbers





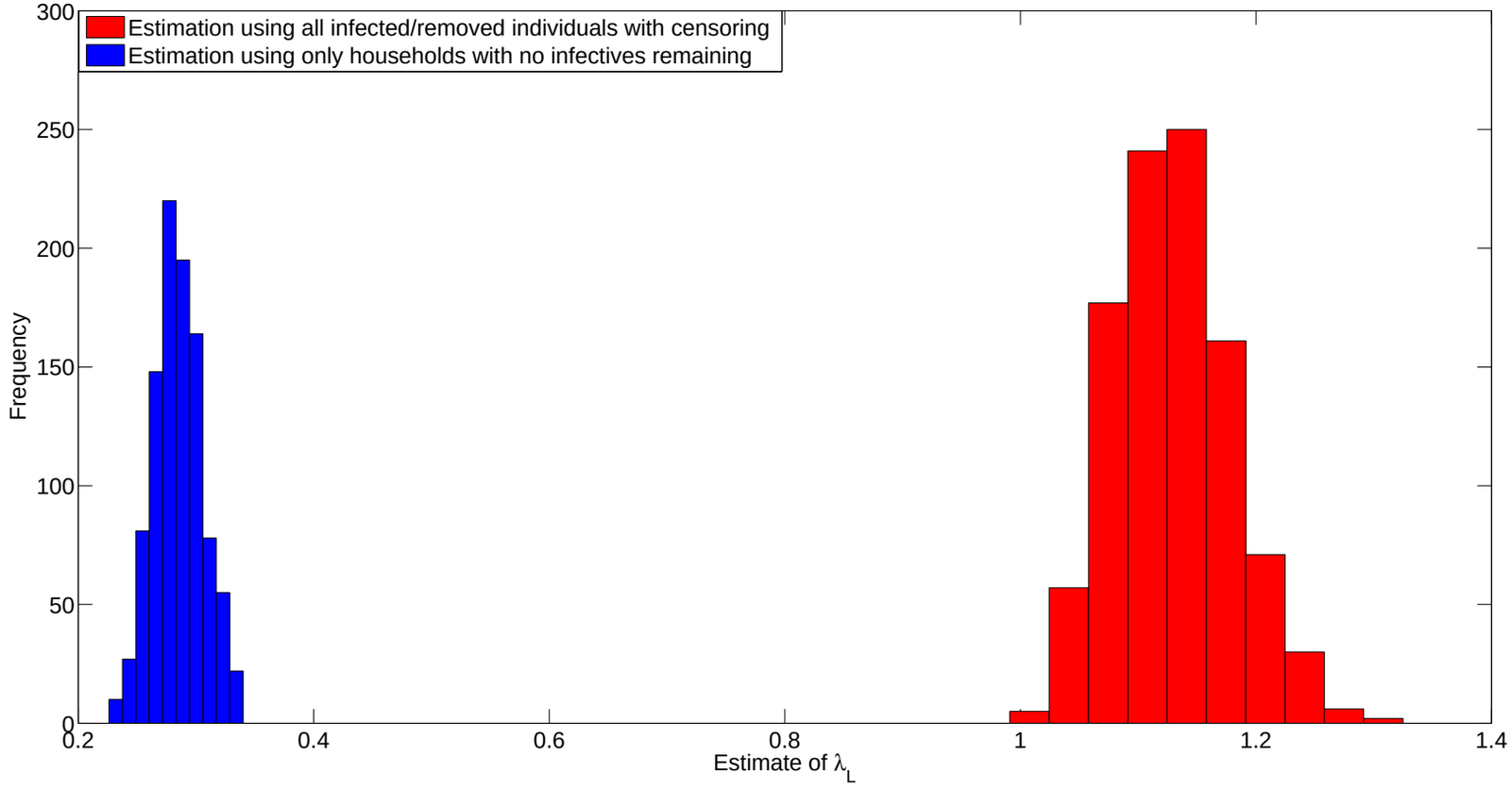
Reproduction numbers (right panel) for households model with $\mu_G = 1$, household size $= 8$ and non-random infectiousness profile $\Lambda_0(t) \equiv w(t)$ (left panel) that follows a gamma distribution with mean 1.

Estimation in an emerging epidemic

- Consider an SIR epidemic among $5,000,000$ households, with sizes distributed uniformly on 1 to 5, in which a typical infective makes global contacts at overall rate λ_G and contacts a given susceptible in its own household at rate λ_L, throughout and infectious period that has an exponential distribution with mean 1.
- After $1,000$ individuals have become infected
  - estimate real time growth rate empirically
  - estimate λ_L by fitting final size distribution of single-household epidemics, with one initial infective, to observed household outbreaks
  - estimate λ_G and hence R_* using (exact) Fraser's method.

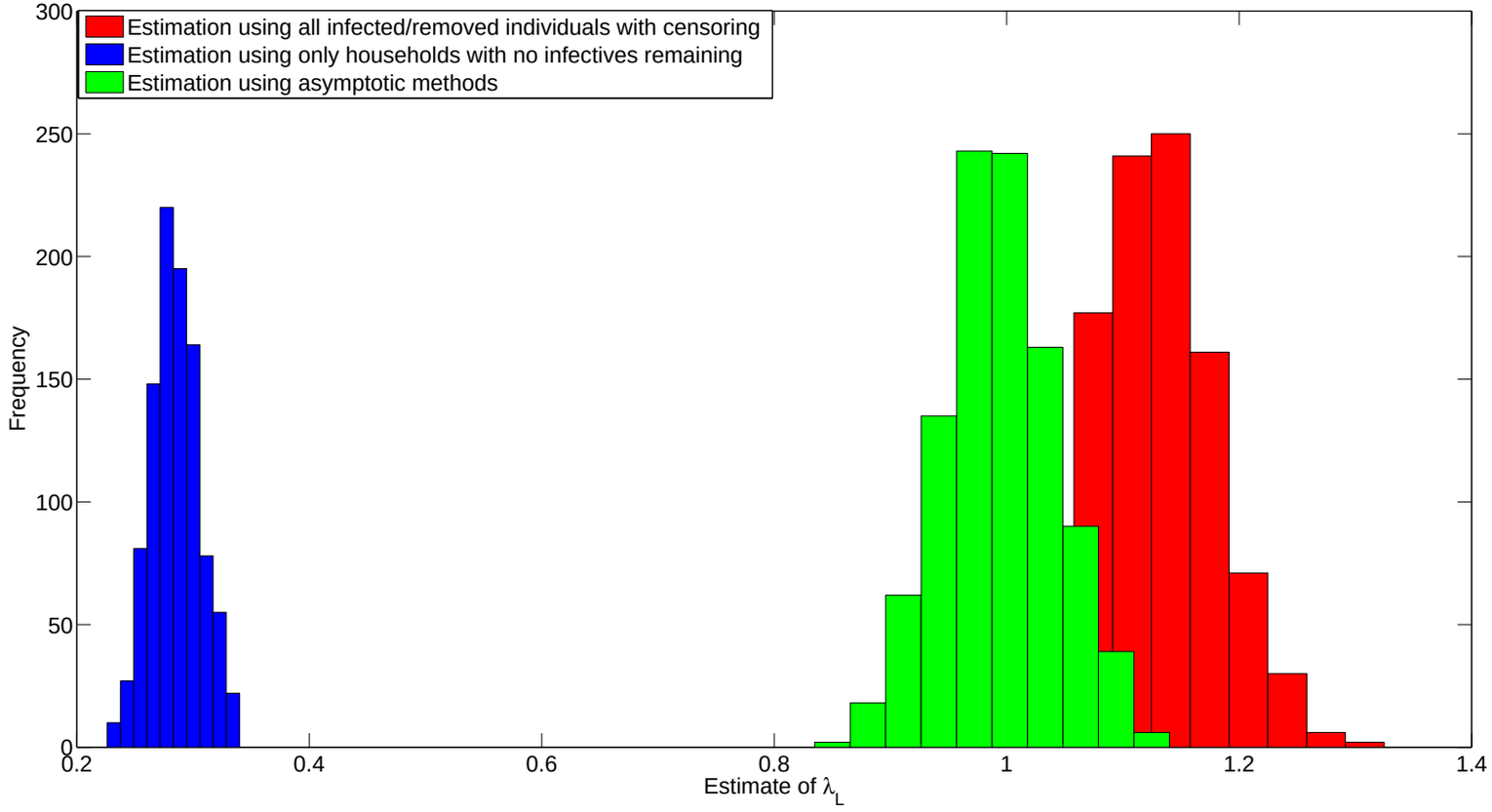
(Ball and Shaw (2013))

Estimation in an emerging epidemic



Histograms of estimates of within-household infection rate λ_L based on $1,000$ simulated epidemics with $\lambda_L = \lambda_G = 1$ that took off.

Estimation in an emerging epidemic



Histograms of estimates of within-household infection rate λ_L based on $1,000$ simulated epidemics with $\lambda_L = \lambda_G = 1$ that took off.

Estimation in an emerging epidemic

- Observed household final sizes do not follow the usual distribution owing to emerging nature of epidemic among population of households.
- “Correct" distribution can be obtained using asymptotic theory of multitype continuous time branching processes (Ball and Shaw (2013)).
- Similar issues arise more generally (i.e. outside of simple households models) in statistical analysis of emerging epidemics; data collected need to be modelled very carefully taking due account of the emerging nature of epidemic.

Closing remark

Branching processes have a very rich and well-developed theory, owing in part to their linear nature, and provide a fertile ground for investigating the early stages of epidemics in large populations.