

R₀ and other reproduction numbers for households models

... and epidemic models with other social structures

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- Introduction
 - *R*₀ in simple models
 - *R*₀ in other models
- Households models
 - Reproduction numbers
 - Definition of *R*₀
 - Generalisations
- Comparison between reproduction numbers
 - Fundamental inequalities
 - Insight
- Conclusions

*R*₀ in simple models*R*₀ in other models

INTRODUCTION



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SIR full dynamics



Imperial College London Basic reproduction number R₀

Naïve definition:

" Average number of new cases generated by a typical case, throughout the entire infectious period, in a large and otherwise fully susceptible population "

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Requirements:

- 1) New real infections
- 2) Typical infector
- 3) Large population
- 4) Fully susceptible

Imperial College London Branching process approximation

- Follow the epidemic in generations:
 - $X_n^{(N)}$ = number of infected cases in generation n (pop. size N)

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• For every fixed *n*,

$$\lim_{N\to\infty} X_n^{(N)} = X_n$$

where X_n is the *n* -th generation of a simple Galton-Watson branching process (BP)

► Let ξ be the random number of children of an individual in the BP, and let $\mathbb{P}(\xi = k) = \xi_k, \forall k = 0, 1, ...$ be the offspring distribution.

> Define

$$\boldsymbol{R}_0 = \mathbb{E}\big[\boldsymbol{\xi}_k\big]$$

➢ We have "linearised" the early phase of the epidemic



Properties of *R*₀

- Threshold parameter:
 - If $\boldsymbol{R}_0 \leq 1$, only small epidemics
 - If $R_0 > 1$, possible large epidemics
- Probability of a large epidemic
- ➢ Final size:

$$1-z=e^{-R_0z}$$

Critical vaccination coverage:

$$\boldsymbol{p}_{C} = 1 - \frac{1}{\boldsymbol{R}_{0}}$$

 \succ If $X_0 = 1$, then

$$\boldsymbol{R}_{0} = \mathbb{E}[\boldsymbol{X}_{1}] = \lim_{N \to \infty} \mathbb{E}[\boldsymbol{X}_{n}^{(N)}]$$







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Outline

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Imperial College London Multitype epidemic model

- Different types of individuals
- Define the next generation matrix (NGM):

$$\boldsymbol{K} = \begin{pmatrix} \boldsymbol{k}_{11} & \boldsymbol{k}_{12} & \cdots & \boldsymbol{k}_{1n} \\ \boldsymbol{k}_{21} & \boldsymbol{k}_{22} & \vdots \\ \vdots & \ddots & \vdots \\ \boldsymbol{k}_{n1} & \cdots & \cdots & \boldsymbol{k}_{nn} \end{pmatrix}$$

where k_{ij} is the average number of type-*i* cases generated by a type-*j* case, throughout the entire infectious period, in a fully susceptible population

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Properties of the NGM:

- Non-negative elements
- We assume positive regularity



- > Single dominant eigenvalue Λ , which is positive and real
- \succ "Dominant" eigenvector V has non-negative components
- > For (almost) every starting condition, after a few generations, the proportions of cases of each type in a generation converge to the components of the dominant eigenvector V, with per-generation multiplicative factor Λ

> Define $\boldsymbol{R}_0 = \boldsymbol{\Lambda}$

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Interpret "typical" case as a linear combination of cases of each type given by V



Start the BP with a j -case:

- > $X_n(j;i)$ = number of *i* -cases in generation *n*
- *X_n*(*j*) = $\sum_{i} X_n(j;i)$ = total number of cases in generation *n* ▶ Then:

$$\boldsymbol{R}_{0} \coloneqq \lim_{n \to \infty} \lim_{N \to \infty} \sqrt[n]{\mathbb{E}\left[\boldsymbol{X}_{n}^{(N)}(\boldsymbol{j})\right]}$$

Compare with single-type model:

$$\boldsymbol{R}_{0} \coloneqq \lim_{N \to \infty} \mathbb{E} \Big[\boldsymbol{X}_{1}^{(N)} \Big]$$

Imperial College London Basic reproduction number R₀

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Network models

- People connected by a static network of acquaintances
- Simple case: no short loops, i.e. locally tree-like
 - Repeated contacts
 - First case is special
 - $\mathbb{E}[X_1] = 1$ is not a threshold
 - Define:

$$\boldsymbol{R}_0 = \mathbb{E} \big[\boldsymbol{X}_2 \mid \boldsymbol{X}_1 = 1 \big]$$

- Difficult case: short loops, clustering
 - Maybe not even possible to use branching process approximation or define *R*₀







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Reproduction numbers Definition of **R**₀ Generalisations

HOUSEHOLDS MODELS



Model description



Imperial College London Example: sSIR households model

- > Population of m households with of size n_H
- > Upon infection, each case i:
 - remains infectious for a duration $I_i \sim I$, iid $\forall i$
 - makes infectious contacts with each household member according to a homogeneous Poisson process with rate λ_L
 - makes contacts with each person in the population according to a homogeneous Poisson process with rate λ_G/N

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- Contacted individuals, if susceptible, become infected
- Recovered individuals are immune to further infection



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Imperial College London Household reproduction number R_{*}

- Consider a within-household epidemic \succ started by one initial case
- Define: >
 - μ_L = average household final size, excluding the initial case
 - μ_G = average number of global infections an individual makes
- "Linearise" the epidemic process at the level of households:

$$\boldsymbol{R}_* \coloneqq \boldsymbol{\mu}_G \left(1 + \boldsymbol{\mu}_L \right)$$



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Imperial College London Individual reproduction number R₁

Attribute all further cases in a household to the primary case

$$\boldsymbol{M}_{\boldsymbol{I}} = \begin{pmatrix} \boldsymbol{\mu}_{\boldsymbol{G}} & \boldsymbol{\mu}_{\boldsymbol{G}} \\ \boldsymbol{\mu}_{\boldsymbol{L}} & \boldsymbol{0} \end{pmatrix}$$

> R_I is the dominant eigenvalue of M_I :

$$\boldsymbol{R}_{\boldsymbol{I}} = \frac{\boldsymbol{\mu}_{\boldsymbol{G}}}{2} \left(1 + \sqrt{1 + \frac{4\boldsymbol{\mu}_{\boldsymbol{L}}}{\boldsymbol{\mu}_{\boldsymbol{G}}}} \right)$$

More weight to the first case than it should be



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Imperial College London Individual reproduction number R₁

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More weight to the first case than it should be



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Imperial College London Further improvement: R₂



Approximate tertiary cases:

- μ_1 = average number of cases infected by the primary case
- Assume that each secondary case infects b further cases
- Choose $\boldsymbol{b} = 1 \boldsymbol{\mu}_1 / \boldsymbol{\mu}_L$, such that

$$\mu_1(1+b+b^2+b^3+...)=\frac{\mu_1}{1-b}=\mu_L,$$

so that the household epidemic yields the correct final size

> Then:

$$\boldsymbol{M}_2 = \begin{pmatrix} \boldsymbol{\mu}_G & \boldsymbol{\mu}_G \\ \boldsymbol{\mu}_1 & \boldsymbol{b} \end{pmatrix}$$

and \boldsymbol{R}_2 is the dominant eigenvalue of \boldsymbol{M}_2

Opposite approach: *R*_{*HI*}

All household cases contribute equally

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$$\boldsymbol{R}_{HI} \coloneqq \boldsymbol{\mu}_{G} + \frac{\boldsymbol{\mu}_{L}}{1 + \boldsymbol{\mu}_{L}}$$

Less weight on initial cases than what it should be



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Opposite approach: *R*_{*HI*}

All household cases contribute equally

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$$\boldsymbol{R}_{HI} \coloneqq \boldsymbol{\mu}_{G} + \frac{\boldsymbol{\mu}_{L}}{1 + \boldsymbol{\mu}_{L}}$$

Less weight on initial cases than what it should be



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Imperial College Vaccine-associated MRC London reproduction numbers R_V and R_{VL}

Perfect vaccine

- > Assume $R_* > 1$
- Define p_C as the fraction of the population that needs to be vaccinated to reduce R_* below 1

> Then

$$\boldsymbol{R}_{V} \coloneqq 1 - \frac{1}{\boldsymbol{p}_{C}}$$

Leaky vaccine

- > Assume $R_* > 1$
- Define E_c as the critical vaccine efficacy (in reducing susceptibility) required to reduce R_* below 1 when vaccinating the entire population

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> Then

$$\boldsymbol{R}_{VL} \coloneqq 1 - \frac{1}{\boldsymbol{E}_C}$$



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Naïve approach: next generation matrix



- Consider a within-household epidemic started by a single initial case. Type = generation they belong to.
- > Define $\mu_0 = 1, \mu_1, \mu_2, ..., \mu_{n_H-1}$ the expected number of cases in each generation
- \succ Let μ_G be the average number of global infections from each case
- The next generation matrix is:

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$$\boldsymbol{K} = \begin{pmatrix} \boldsymbol{\mu}_{G} & \boldsymbol{\mu}_{G} & \boldsymbol{\mu}_{G} & \boldsymbol{\mu}_{G} & \boldsymbol{\mu}_{G} \\ \boldsymbol{\mu}_{1} & & & 0 \\ & \boldsymbol{\mu}_{2}/\boldsymbol{\mu}_{1} & & & \vdots \\ & & \ddots & & & \vdots \\ & & & \boldsymbol{\mu}_{n_{H}-1}/\boldsymbol{\mu}_{n_{H}-2} & 0 \end{pmatrix}$$

Imperial College London More formal approach (I)



Notation:

- $x_{n,i}$ = average number of cases in generation *n* and householdgeneration *i*
- $x_n = \sum_{i=0}^{n_H-1} x_{n,i}$ = average number of cases in generation n and any household-generation

1

System dynamics:

Derivation:

$$x_{n,0} = \mu_G \sum_{i=0}^{n_H^{-1}} x_{n-1,i}$$

$$x_{n,i} = \mu_i x_{n-i,0} \qquad 1 \le i \le n_H - 1$$

$$x_{n,0} = \mu_G x_{n-1} \qquad 1 \le i \le n_H - 1$$

$$x_{n,i} = \mu_i \mu_G x_{n-i-1} \qquad 1 \le i \le n_H - 1$$

$$x_n = \sum_{i=0}^{n_H^{-1}} x_{n,i} = \mu_G \sum_{i=0}^{n_H^{-1}} \mu_i x_{n-i-1}$$

i=0

Imperial College More formal approach (II)

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System dynamics:

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$$\underline{\mathbf{x}}^{(n)} = A_{n_H} \underline{\mathbf{x}}^{(n-1)}$$

 $\boldsymbol{A}_{n_{H}} = \begin{pmatrix} \boldsymbol{\mu}_{G} \,\boldsymbol{\mu}_{0} & \boldsymbol{\mu}_{G} \,\boldsymbol{\mu}_{1} & \boldsymbol{\mu}_{G} \,\boldsymbol{\mu}_{2} & \cdots & \boldsymbol{\mu}_{G} \,\boldsymbol{\mu}_{n_{H}-1} \\ 1 & & 0 \\ & 1 & & \vdots \\ & & \ddots & & \vdots \\ & & & 1 & 0 \end{pmatrix}$ where

Imperial College London More formal approach (III)



Let A = dominant eigenvalue of A_{n_H} V = $(v_0, v_1, ..., v_{n_H-1})$ = "dominant" eigenvector Then, for $n \to \infty$: $\underline{x}^{(n)} / \|\underline{x}^{(n)}\| \to V$ $\|\underline{x}^{(n)}\| / \|\underline{x}^{(n-1)}\| \to \Lambda$ $x_n / x_{n-1} \to \Lambda$

> Therefore:

$$\boldsymbol{\Lambda} = \boldsymbol{R}_0$$



Similarity

	Recall:		Define:					
K =	$\begin{pmatrix} \mu_G & \mu_G \\ \mu_1 & \\ \mu_2 / \mu_2 \end{pmatrix}$	μ_{G} μ_{1} \ddots	μ_{G}	$ \begin{array}{c} \mu_{G} \\ 0 \\ \vdots \\ \vdots \\ 0 \end{array} $	S -	$= \begin{pmatrix} \mu_0 \\ \mu \end{pmatrix}$	μ _{n_H-2}	
$A_{n_H} =$	$\begin{pmatrix} \boldsymbol{\mu}_{G}\boldsymbol{\mu}_{0} & \boldsymbol{\mu}_{0} \\ 1 & & \end{pmatrix}$	$\mu_{G} \mu_{1} \mu_{G} \mu_{2}$ $1 \qquad \ddots$	$\mu_{H}^{-1}/\mu_{n_{H}}$	$ \begin{array}{c} \mu_{G} \mu_{n_{H}-1} \\ 0 \\ \vdots \\ 0 \end{array} \right) $		Then: rSo: ho(K	$X = SA_{n_H}S^{-1}$	μ_{n_H-1}


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Generalisations

This approach can be extended to:

- Variable household size
- Household-network model
- Model with households and workplaces
- ... (probably) any structure that allows an embedded branching process in the early phase of the epidemic

... all signals that this is the "right" approach!

Imperial College London Households-workplaces model



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Model description

Assumptions:

- Each individual belongs to a household and a workplace
- > Rates λ_H , λ_W and λ_G of making infectious contacts in each environment
- No loops in how households and workplaces are connected, i.e. locally tree-like





Construction of R₀

- > Define $\mu_0^H = 1, \mu_1^H, \mu_2^H, ..., \mu_{n_H-1}^H$ and $\mu_0^W = 1, \mu_1^W, \mu_2^W, ..., \mu_{n_W-1}^W$ for the households and workplaces generations
- \blacktriangleright Define $n_T = n_H + n_W$
- > Then R_0 is the dominant eigenvalue of

$$A_{n_{H}} = \begin{pmatrix} c_{0} & c_{1} & \cdots & c_{n_{T}-3} & c_{n_{T}-2} \\ 1 & & & 0 \\ & 1 & & & \vdots \\ & & \ddots & & \vdots \\ & & & 1 & 0 \end{pmatrix},$$

where
$$c_k = \mu_G \sum_{\substack{i+j=k \ 0 \le i \le n_H - 1 \ 0 \le j \le n_W - 1}} \mu_i^H \mu_j^W + \sum_{\substack{i+j=k+1 \ 1 \le i \le n_H - 1 \ 1 \le j \le n_W - 1}} \mu_i^H \mu_j^W, \quad 0 \le k \le n_T - 2$$

Fundamental inequalities Insight

COMPARISON BETWEEN REPRODUCTION NUMBERS



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➢ Goldstein et al (2009) showed that

$$\mathbf{R}_* = 1 \iff \mathbf{R}_{VL} = 1 \iff \mathbf{R}_r = 1 \iff \mathbf{R}_V = 1 \iff \mathbf{R}_{HI} = 1$$

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$$egin{array}{rcl} R_{*} &\geq R_{VL} &\geq R_{V} &\geq R_{HI} \ R_{*} &\geq R_{r} \end{array}$$

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$$R_* \geq R_V \geq R_{HI}$$

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To which we added

 $\Leftrightarrow \quad \boldsymbol{R}_{I} = 1 \quad \Leftrightarrow \quad \boldsymbol{R}_{0} = 1 \quad \Leftrightarrow \quad \boldsymbol{R}_{2} = 1$

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To which we added

 \Leftrightarrow $\boldsymbol{R}_{I} = 1 \Leftrightarrow$ $\boldsymbol{R}_{0} = 1 \Leftrightarrow$ $\boldsymbol{R}_{2} = 1$

In a growing epidemic:

 $R_* \geq R_V \geq R_{HI}$

➢ Goldstein et al (2009) showed that

 $\mathbf{R}_* = 1 \iff \mathbf{R}_{VL} = 1 \iff \mathbf{R}_r = 1 \iff \mathbf{R}_V = 1 \iff \mathbf{R}_{HI} = 1$

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 $\Leftrightarrow \quad \boldsymbol{R}_{I} = 1 \quad \Leftrightarrow \quad \boldsymbol{R}_{0} = 1 \quad \Leftrightarrow \quad \boldsymbol{R}_{2} = 1$

In a growing epidemic:

 $R_* \geq R_I \geq R_V \geq R_0 \geq R_2 \geq R_{HI}$

Goldstein et al (2009) showed that

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To which we added

 $\Leftrightarrow \mathbf{R}_{\mathbf{I}} = 1 \quad \Leftrightarrow \quad \mathbf{R}_0 = 1 \quad \Leftrightarrow \quad \mathbf{R}_2 = 1$

In a growing epidemic:

 $R_* \geq R_I \geq R_V \geq R_0 \geq R_2 \geq R_{HI}$

To which we added that, in a **declining** epidemic:

$$R_* \leq R_I \leq R_V \leq R_0 \leq R_2 \leq R_{HI}$$



Practical implications

>
$$\mathbf{R}_{V} \ge \mathbf{R}_{0}$$
, so vaccinating $\mathbf{p} = 1 - \frac{1}{\mathbf{R}_{0}}$ is not enough

➢ Goldstein et al (2009):

$$R_* \geq R_V \geq R_{HI}$$

> Now we have sharper bounds for R_V :

$$R_* \geq R_I \geq R_V \geq R_0 \geq R_{HI}$$



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> Recall that \mathbf{R}_0 is the dominant eigenvalue of

$$\boldsymbol{A}_{n_{H}} = \begin{pmatrix} \boldsymbol{\mu}_{G} \,\boldsymbol{\mu}_{0} & \boldsymbol{\mu}_{G} \,\boldsymbol{\mu}_{1} & \boldsymbol{\mu}_{G} \,\boldsymbol{\mu}_{2} & \cdots & \boldsymbol{\mu}_{G} \,\boldsymbol{\mu}_{n_{H}-1} \\ 1 & & & 0 \\ & 1 & & & \vdots \\ & & \ddots & & \vdots \\ & & & \ddots & & \vdots \\ & & & & 1 & 0 \end{pmatrix}$$

> From the characteristic polynomial, we find that R_0 is the only positive root of

$$\boldsymbol{g}_{0}(\boldsymbol{\lambda}) = 1 - \sum_{i=0}^{n_{H}-1} \frac{\boldsymbol{\mu}_{G} \boldsymbol{\mu}_{i}}{\boldsymbol{\lambda}^{i+1}}$$

Imperial College London Discrete Lotka-Euler equation

Continuous-time Lotka-Euler equation:

$$\int_{0}^{+\infty} \boldsymbol{\beta}_{\boldsymbol{H}}(\boldsymbol{\tau}) \mathbf{e}^{-r\boldsymbol{\tau}} \mathrm{d}\boldsymbol{\tau} = 1$$

Discrete-generation Lotka-Euler equation:

$$\boldsymbol{\beta}_{H}(\boldsymbol{\tau}) = \boldsymbol{\beta}_{k} \boldsymbol{\delta}_{k}(\boldsymbol{\tau}) \qquad \Rightarrow \qquad \sum_{k=0}^{+\infty} \boldsymbol{\beta}_{k} \left(\mathbf{e}^{r} \right)^{-k} = 1$$

•
$$\beta_0 = 0$$

• $\beta_k = \mu_G \mu_{k-1}$ for $k = 1, 2, ..., n_H$
• $\beta_k = 0$ for $k > n_H$

> Therefore, $\mathbf{R}_0 = \mathbf{e}^r$ is the solution of

$$\sum_{i=0}^{n_{H}-1} \frac{\mu_{G} \mu_{i}}{R_{0}^{i+1}} = 1$$

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Imperial College London Fundamental interpretation

> For each reproduction number R_A , define a r.v. X_A describing the generation index of a randomly selected infective in a household epidemic

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> Distribution of X_A is $\mathbb{P}\{X_A = i\} = \frac{\mu_i^A}{1 + \mu_L}, \quad 0 \le i \le +\infty$



CONCLUSIONS

Imperial College London Why so long to come up with R₀?

- > Typical infective:
 - "Suitable" average across all cases during a household epidemic

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$$\boldsymbol{K} = \begin{pmatrix} \boldsymbol{\mu}_{G} & \boldsymbol{\mu}_{G} & \boldsymbol{\mu}_{G} & \boldsymbol{\mu}_{G} & \boldsymbol{\mu}_{G} \\ \boldsymbol{\mu}_{1} & & & 0 \\ & \boldsymbol{\mu}_{2}/\boldsymbol{\mu}_{1} & & \vdots \\ & & \ddots & & \vdots \\ & & & \boldsymbol{\mu}_{n_{H}}/\boldsymbol{\mu}_{n_{H}-1} & 0 \end{pmatrix}$$

- Types are given by the generation index:
 - not defined a priori
 - appear only in real-time
- "Fully" susceptible population:
 - the first case is never representative
 - need to wait at least a few full households epidemics



Conclusions

- > After more than 15 years, we finally found R_0
- General approach
 - clarifies relationship between all previously defined reproduction numbers for the households model
 - works whenever a branching process can be imbedded in the early phase of the epidemic, i.e. when we can use Lotka-Euler for a "sub-unit"
- \succ Allows sharper bounds for R_V :

$$R_* \geq R_I \geq R_V \geq R_0 \geq R_{HI}$$



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 - Frank Ball
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 - Christophe Fraser
- Fundings:
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SUPPLEMENTARY MATERIAL



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- \pmb{R}_0 in simple models
- \boldsymbol{R}_0 in other models

INTRODUCTION

- Threshold property:
 - If $\mathbf{R}_0 \leq 1$ the BP goes extinct with probability 1 (small epidemic)
 - If $\mathbf{R}_0 > 1$ the BP goes extinct with probability given by the smallest solution $\mathbf{s} \in [0,1]$ of

$$s = \sum_{k=0}^{\infty} \xi_k s^k$$

Assume $X_0 = 1$. Then:

 $\succ \mathbb{E}[X_n] = (R_0)^n$ $\succ \sqrt[n]{\mathbb{E}[X_n]} = R_0$ $\succ \mathbb{E}[X_{n+1}] / \mathbb{E}[X_n] = R_0$



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Properties of R₀

- Threshold parameter:
 - If $\boldsymbol{R}_0 \leq 1$, only small epidemics
 - If $R_0 > 1$, possible large epidemics
- Probability of a large epidemic
- ➢ Final size:

$$1-z=e^{-R_0z}$$

Critical vaccination coverage:

$$\boldsymbol{p}_{C} = 1 - \frac{1}{\boldsymbol{R}_{0}}$$

 \succ If $X_0 = 1$, then

$$\boldsymbol{R}_{0} = \mathbb{E}[\boldsymbol{X}_{1}] = \lim_{N \to \infty} \mathbb{E}[\boldsymbol{X}_{n}^{(N)}]$$







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HOUSEHOLDS MODELS
Within-household epidemic

- Repeated contacts towards the same individual
 - Only the first one matters
- Many contacts "wasted" on immune people
 - Number of immunes changes over time -> nonlinearity
- Overlapping generations

Imperial College

London

Time of events can be important





Imperial College London Rank VS true generations

- ▹ sSIR model:
 - draw an arrow from individual to each other individual with probability $1 \exp\left(\frac{\lambda}{n-1}I_i\right)$

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- attach a weight given by the (relative) time of infection
- Rank-based generations = minimum path length from initial infective
- \blacktriangleright Real-time generations = minimum sum of weights

