Transmission intervals and COVID control

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Arizona State University Mathematical Biology Seminar
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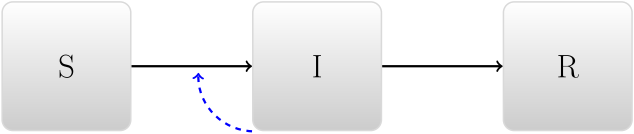
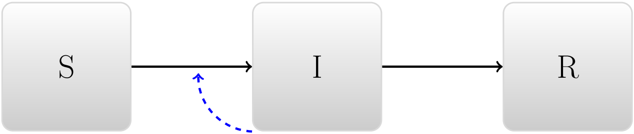
Outline

Simple dynamical models use compartments

Divide people into categories:

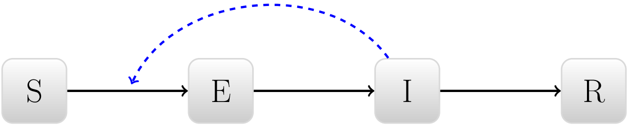


- Susceptible $\to$ Infectious $\to$ Recovered
- Individuals recover independently
- Individuals are infected by infectious people

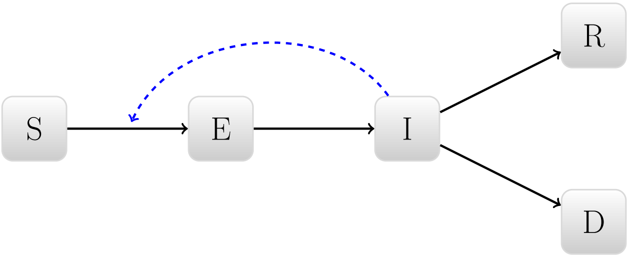


$$
\begin{aligned}
\frac{dS}{dt} &= \mu N - \beta \frac{SI}{N} - \mu S \\
\frac{dI}{dt} &= \beta \frac{SI}{N} - \gamma I - \mu R \\
\frac{dR}{dt} &= \gamma I - \mu R
\end{aligned}
$$

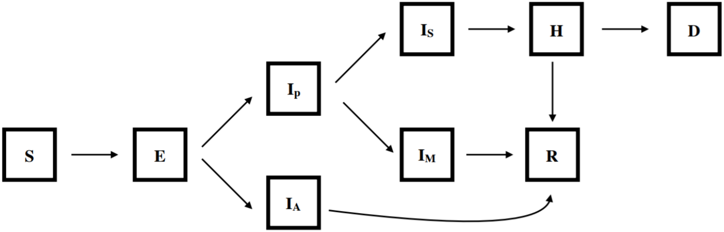
Delayed infectiousness



Ebola



Coronavirus



S = susceptible
E = exposed

I_P = pre-symptomatic
I_A = asymptomatic
I_S = symptomatic, severe case
I_M = symptomatic, minor case

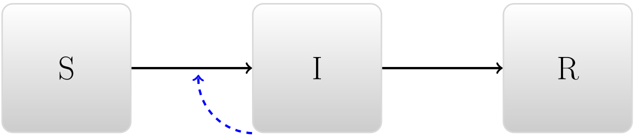
H = hospitalized
R = recovered
D = dead

Childs et al., http://covid-measures.stanford.edu/

BRIDGE Renewal-equation framework

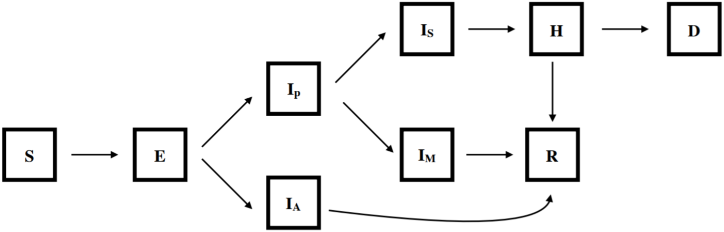
- A broad framework that covers a wide range of underlying models
- $i(t) = \int k(\tau, t) i(t - \tau) \, d\tau$
  - $i(t)$ is the *rate* of new infections (per-capita incidence)
  - $k(\tau)$ measures how infectious a person is (on average) at time τ after becoming infected
- k changes through time
  - proportion susceptible, control measures
  - we often think about counterfactuals with fixed $k(\tau)$

MATH Cohort modeling



- Create ODEs to follow a *cohort* of people infected at the same time
- Transform ODE model to renewal-equation model

MATH Cohort modeling



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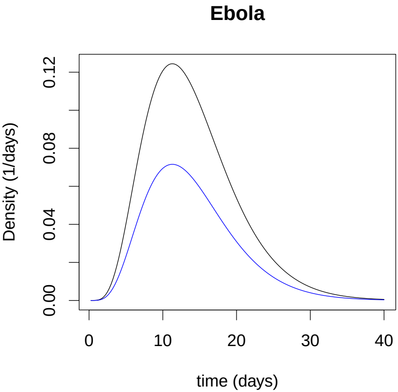
BRIDGE Transmission kernel



- Area is $\mathcal{R}$
- Distribution is the generation interval

Outline

Transmission intervals

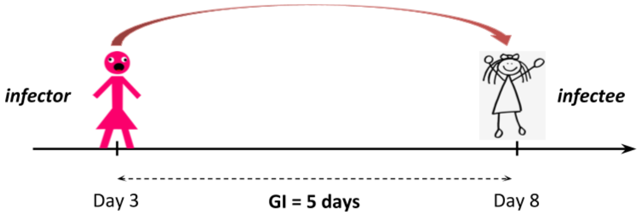
- Sort of the poor relations of disease-modeling world
- Ad hoc methods
- Error often not propagated

How long is a disease generation? (present)

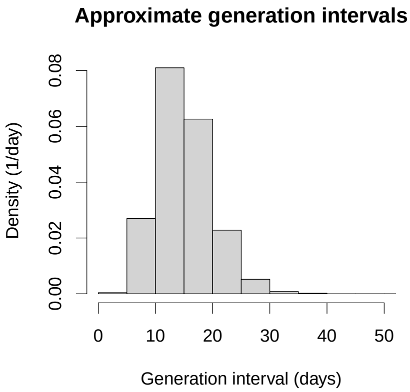
Definition

Generation Interval:

Interval between the time that an individual is infected by an infector and the time this infector was infected



Generation-interval distributions



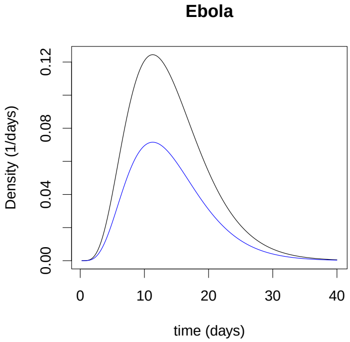
- The generation distribution measures generations of the disease
    - Interval between "index" infection and resulting infection
- Link r (exponential growth rate) and $\mathcal{R}$ (effective reproductive number)

REGULAR Transmission intervals drive epidemics

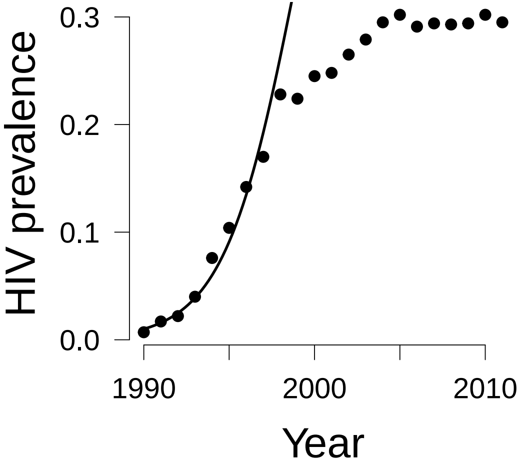
- Population-level *Speed* of spread r is a product:
  - Something about *Strength* $\mathcal{R}$
  - $\times$
  - Something about *Quickness*: Individual-level speed of transmission $g(\tau)$

Mechanistic perspective

- $\mathcal{R}$ is known
- Quicker generations $\implies$ faster population-level spread

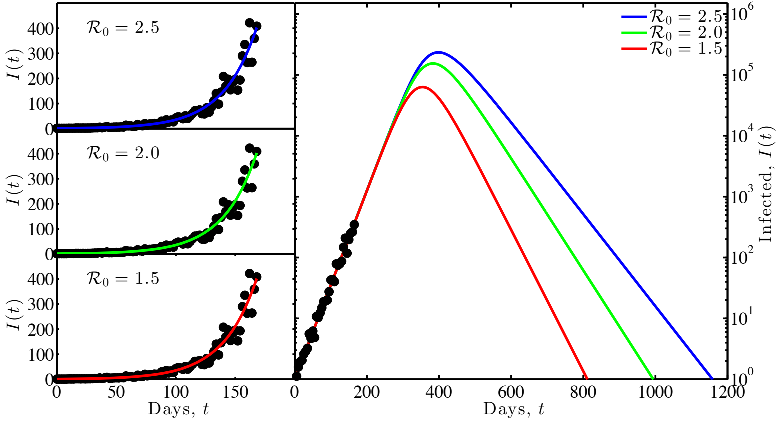


HIV in sub-Saharan Africa



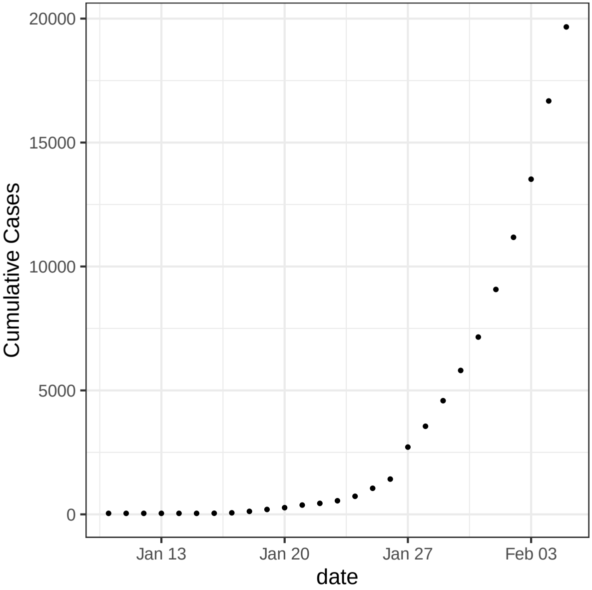
$C \approx 18\,\mathrm{month}$. Faster than expected.

REGULAR Ebola outbreak



$C \approx 1\,\mathrm{month}$. Slower than expected.

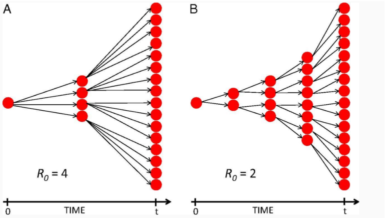
REGULAR Coronavirus speed



$C \approx 5\,\mathrm{day}$. Coronavirus!

Phenomenological perspective

- Population-level speed r is observed
- Quicker generations (low $\bar{G}$) $\implies$ *lower* $\mathcal{R}$



Powers et al., *https://www.pnas.org/content/111/45/15867*

Generation interval

- One generation:
  - Latent period (time until infectiousness) $+$
  - Infectious waiting time (time until infection)
- Infectious waiting time
  - Drawn at random from infectious period
  - Equal to infectious period *only* when we assume a Markovian process
  - Common source of confusion for people with ODE background

MATH How long until the bus comes?

MATH Mean of a self-weighted quantity

- Infectious period of an infector
  - Activity level of an interactor, in HIV models
- $\mu(1 + \frac{\sigma^2}{\mu^2}) = \mu(1 + \kappa)$
- Time until bus comes: $\mu(1 + \kappa)/2$
- Exponential distribution: $\kappa = 1$

REGULAR Transmission intervals

- Generation interval: infection $\implies$ infection
  - Drives epidemic, often unobserved
- Serial interval: symptoms $\implies$ symptoms
  - Observable. . . , may be hard to define
- Other:
  - diagnosis $\implies$ diagnosis
  - notification $\implies$ notification
- Some cases are never symptomatic, or never diagnosed

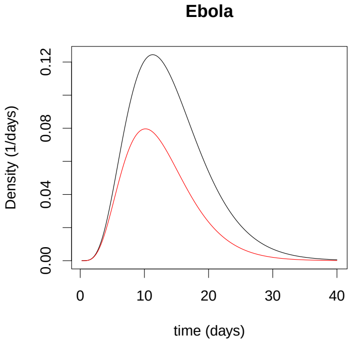
Outline

Euler-Lotka equation

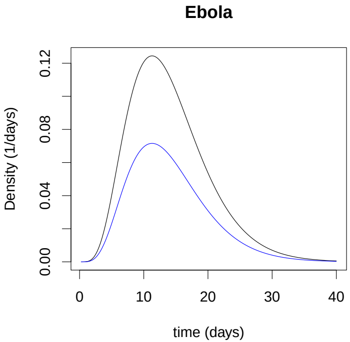
- If we assume k is not changing through time, we expect exponential growth
- $1 = \int k(\tau) \exp(-r\tau)\, d\tau$
  - i.e., the total of *discounted* contributions is 1
- $1/\mathcal{R} = \int g(\tau) \exp(-r\tau)\, d\tau$
- Note that $b(\tau) = k(\tau) \exp(-r\tau)$ is also a distribution
  - The initial "backwards" generation interval

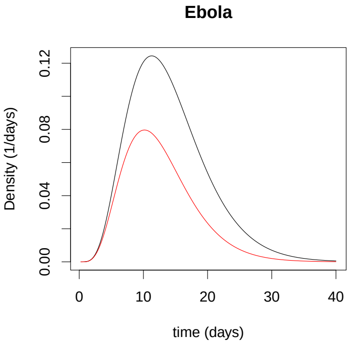
MATH Interpretation: generating functions

- $1/\mathcal{R} = \int g(\tau)\exp(-r\tau)\,d\tau$
- $\mathcal{R} = 1/M(-r)$
- *J Wallinga, M Lipsitch; DOI: 10.1098/rspb.2006.3754*



Interpretation: strength and speed





- $k(\tau) = \mathcal{R}g(\tau)$
- Strength decomposition
- $k(\tau) = \exp(r\tau)b(\tau)$
- Speed decomposition

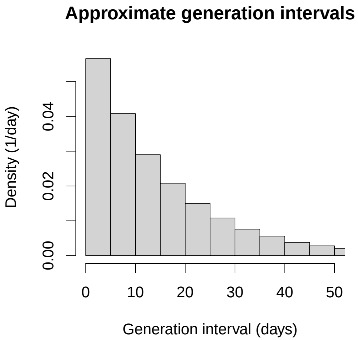
Compound-interest interpretation

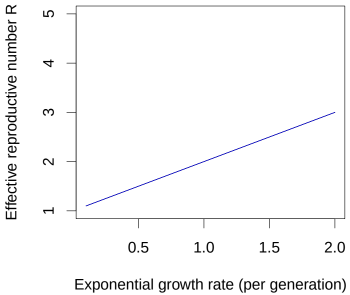
- $\mathcal{R} = (1 + r\kappa\bar{G})^{1/\kappa} \equiv X(r\bar{G}; 1/\kappa)$
- κ is the 'effective dispersion'
  - Equal to the squared coefficient of variation when G is gamma-distributed
- X is the compound-interest approximation to the exponential
  - Linear when $\kappa = 1$ (i.e., when g is exponential)
  - Approaches exponential as $\kappa \to 0$
- *Park et al., Epidemics DOI:10.1101/312397*

Product framework

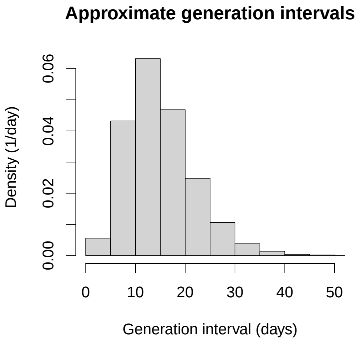
- Quicker generations (small $\bar{G}$) mean faster r for fixed $\mathcal{R}$
  - $\implies$ Weaker $\mathcal{R}$ for fixed r
- More variation κ means more "compounding" of infections
  - $\implies$ quicker spread, when epidemic is growing
- $r = (1/\bar{G}) \times \ell(\mathcal{R}; \bar{\kappa})$ *is the sense in which* r *is actually a product*

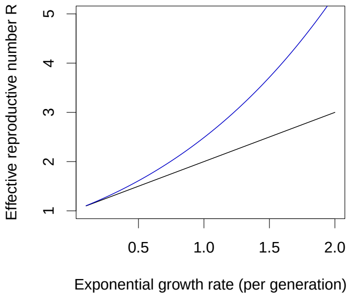
Moment approximation



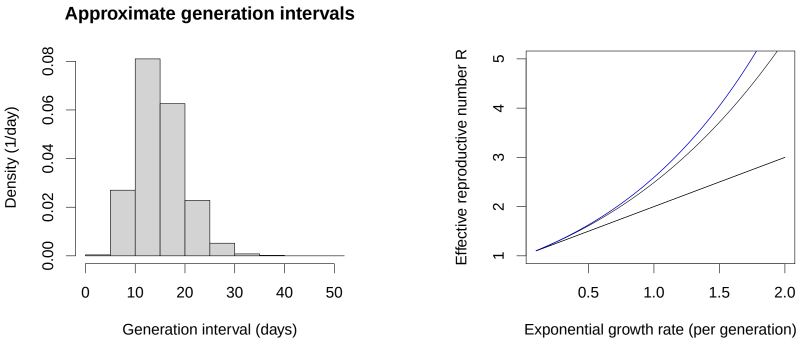


Moment approximation





Moment approximation



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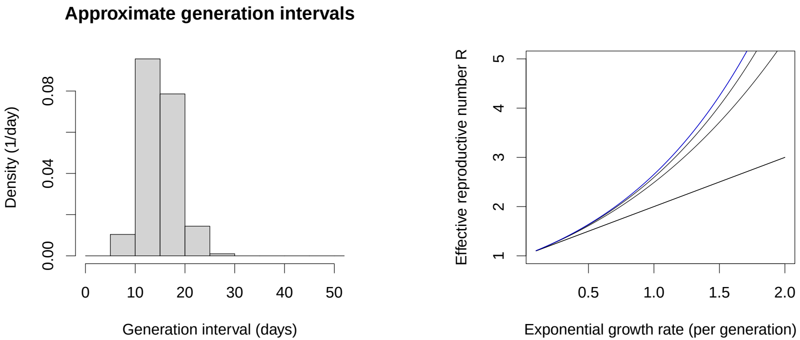
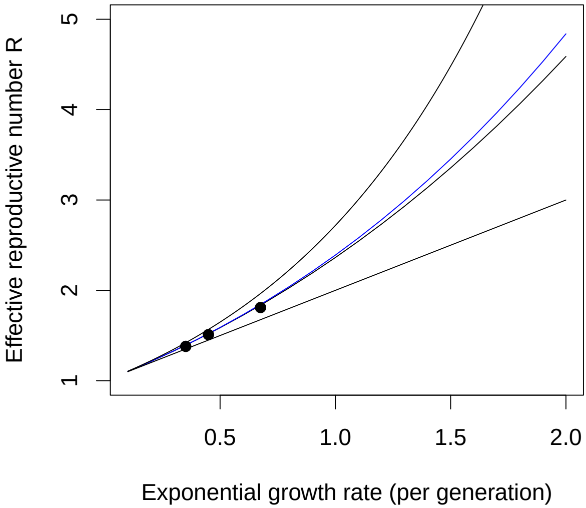


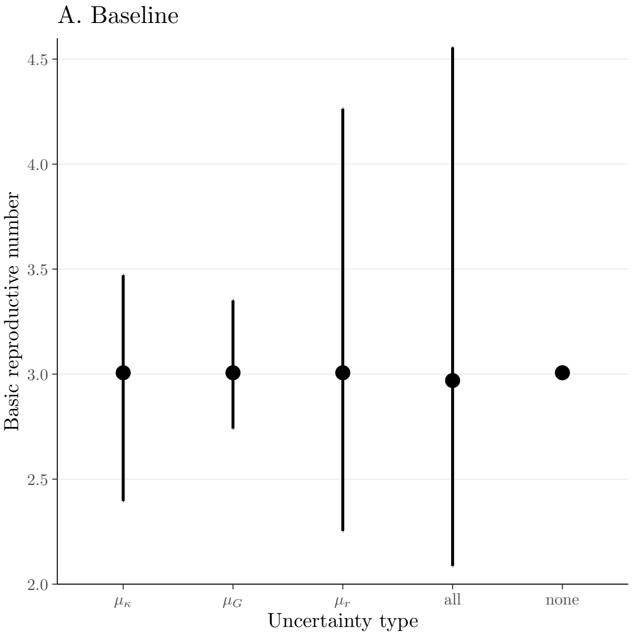
Approximating the $r\mathcal{R}$ relationship



Heuristics for $\mathcal{R}$

- Mechanistic: $\mathcal{R} = DcpS/N$
  - Duration of infectiousness, contact rate, probability of transmission, proportion susceptible
- Phenomenological: $X(r\bar{G}; 1/\kappa)$
  - Rate of exponential growth, mean generation interval, effective dispersion of generation interval

Propagating error



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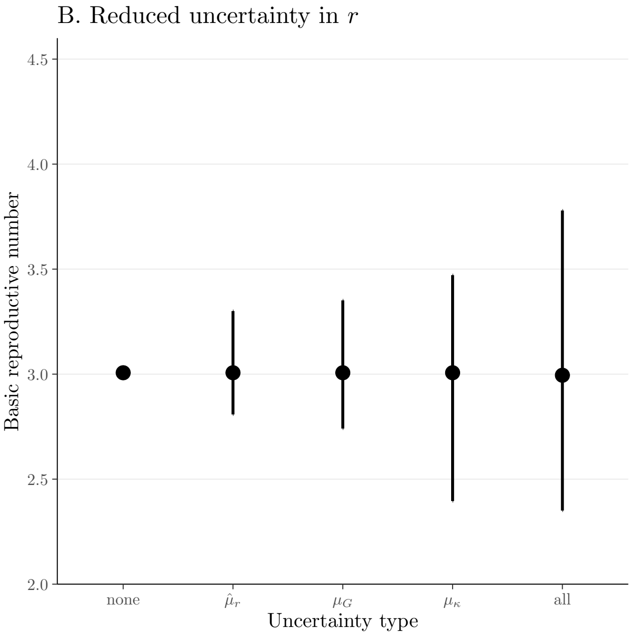
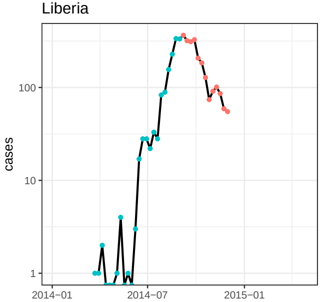
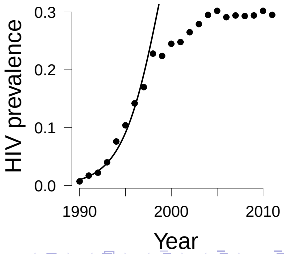


Outline

Growing epidemics

- Measured generation intervals look *shorter* at the beginning of an epidemic
  - A disproportionate number of people are infectious right now
  - They haven't finished all of their transmitting
  - We are biased towards observing faster events

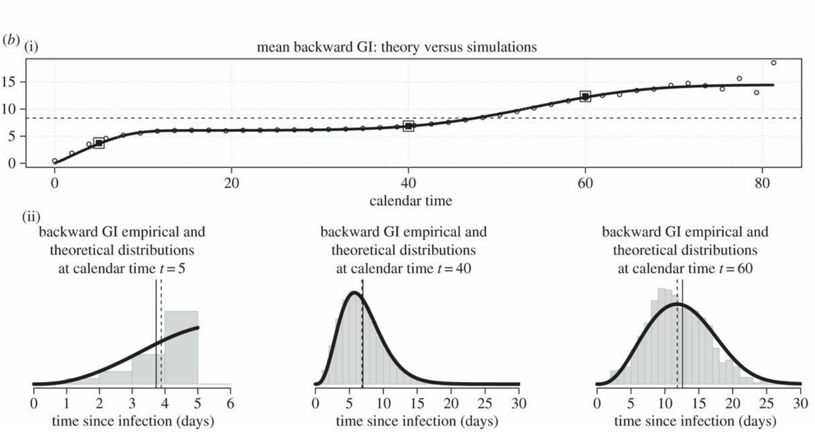




Types of interval

- Define:
  - *Intrinsic interval*: How infectious is a patient at time τ after infection?
  - *Forward interval*: When will the people infected today infect others?
  - *Backward interval*: When did the people who infected people today themselves become infected?
  - *Censored interval*: What do all the intervals observed up until a particular time look like?
    - Like backward intervals, if it's early in the epidemic

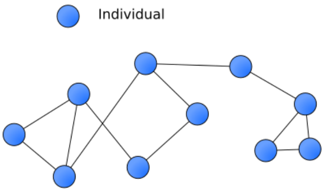
Correcting backward intervals



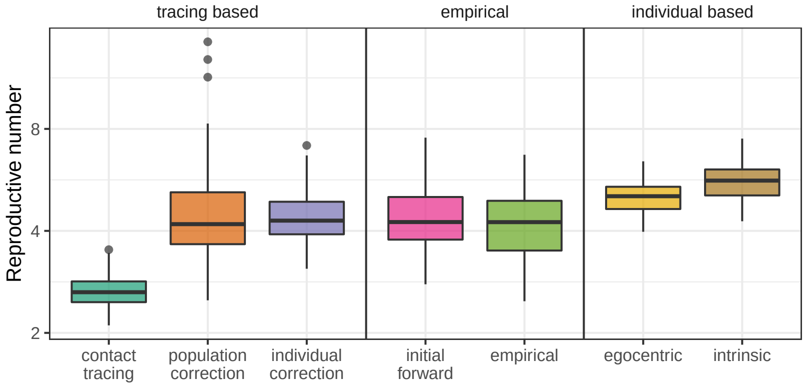
Champredon and Dushoff, 2015. DOI:10.1098/rspb.2015.2026

Generations in space

- Local interactions
- $\implies$ wasted contacts
- $\implies$ realized generation intervals smaller than intrinsic
- $\implies$ intrinsic GIs over-estimate $\mathcal{R}$
- *Trapman et al., 2016. JRS Interface DOI:10.1098/rsif.2016.0288*



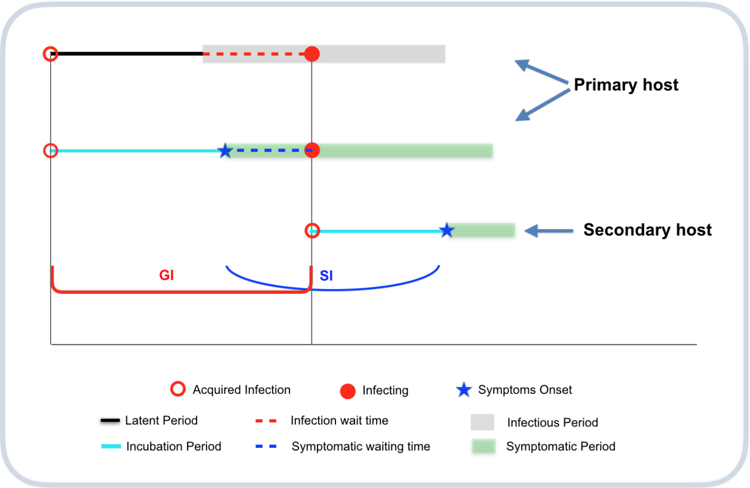
Outbreak estimation



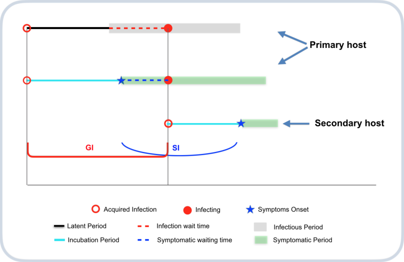
Park et al. JRSI, DOI: 10.1098/rsif.2019.0719

Outline

Serial-interval distributions

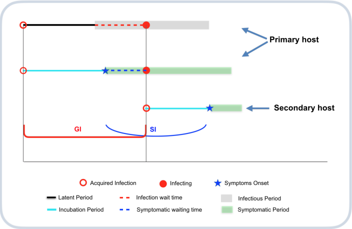


Serial intervals are proxies



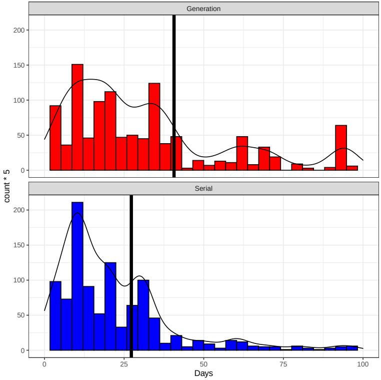
- Serial intervals measure generations of the same process as generation intervals
  - Should have the same mean
  - But often larger variance (flu example)

The serial-mean paradox



- Empirically, even the means are not the same!
- Generation interval:
  - Latent + infectious waiting, or
  - Incubation + Symptomatic waiting ... of infector
- Serial interval:
  - Symptomatic waiting (infector) + Incubation (infectee)

Heterogeneity

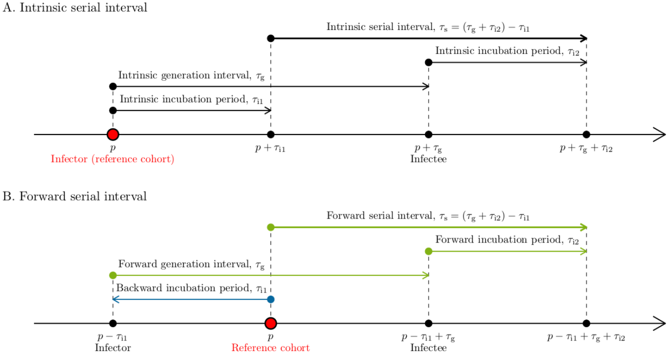


- Generation intervals include latent period of infectors only (often strongly weighted)
- Serial intervals average over infectees (everyone is infected once)
- Coronavirus: people diagnosed early are less likely to transmit
  - could bias GI estimates

The link paradox

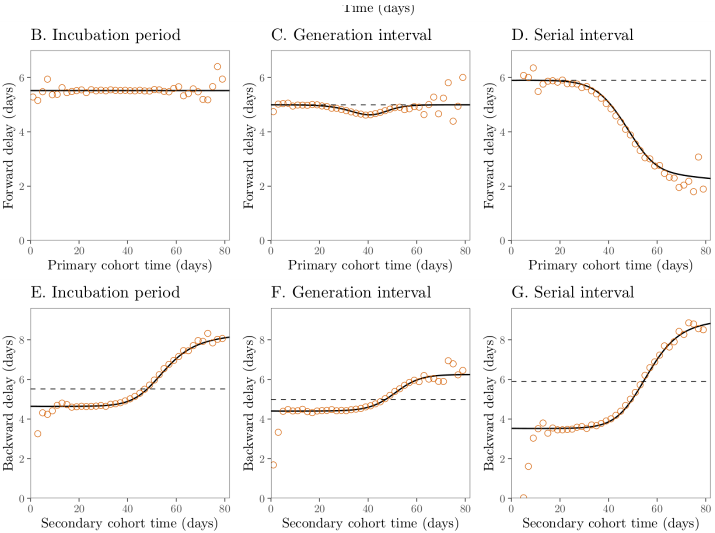
- Imagine a renewal process where symptoms in the infector cause symptoms in the infectee
  - Assume homogeneity
- This has to match the same $r\mathcal{R}$ link as the true (generation-interval driven) process
- But it also can't when the serial interval is broader than the generation interval
  - All else equal, a broader interval means lower $\mathcal{R}$.
  - Broader $\implies$ more compounding $\implies$ more quickness
  - $\implies$ less strength required to achieve observed speed

The forward serial interval



- Early in the epidemic, backward incubation periods are short
- $\Longrightarrow$ forward serial intervals are long

Observed epidemiological intervals

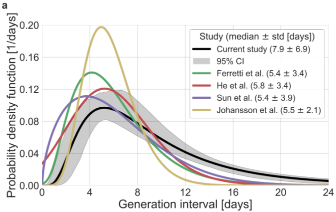


Park et al. https://doi.org/10.1101/2020.06.04.20122713

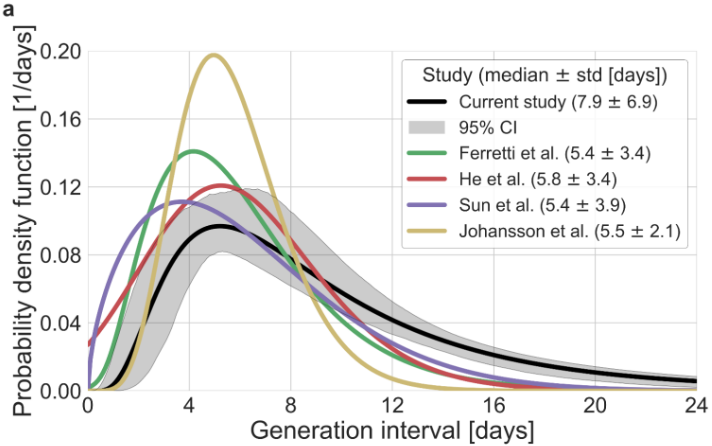
Outline

Unmitigated estimates

- Carefully curated pre-intervention intervals
- Bivariate fit to generation intervals and incubation periods
- Account for dynamical biases

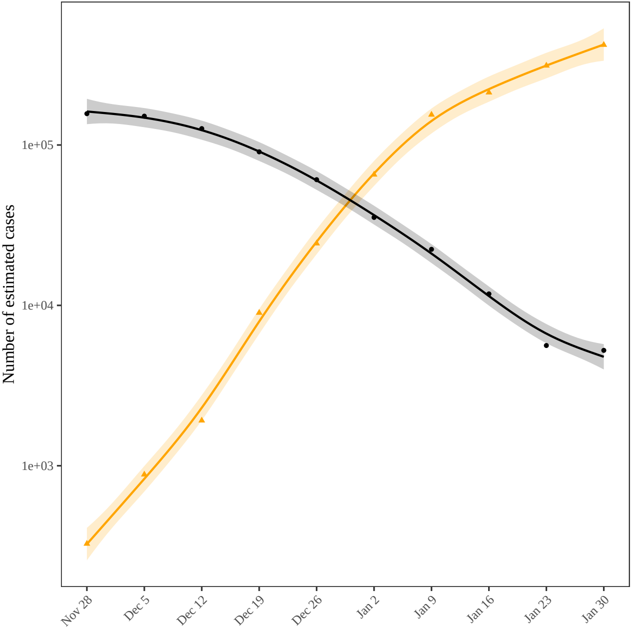


Unmitigated estimates

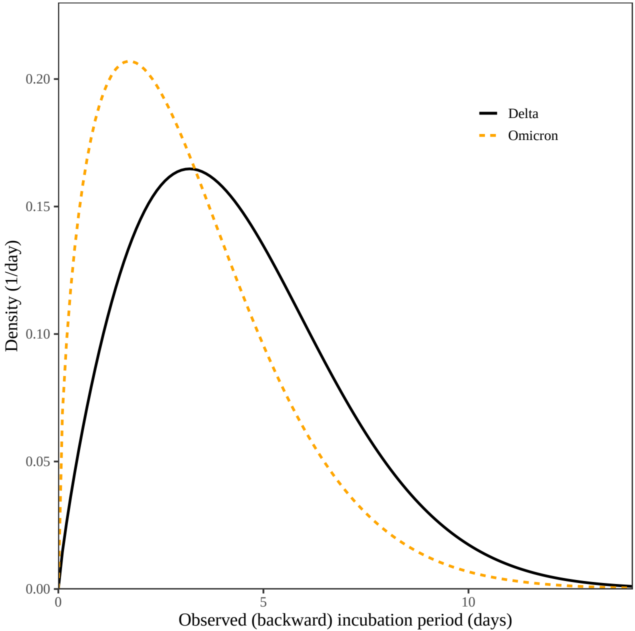


https://www.medrxiv.org/content/10.1101/2021.11.17.21266051v2

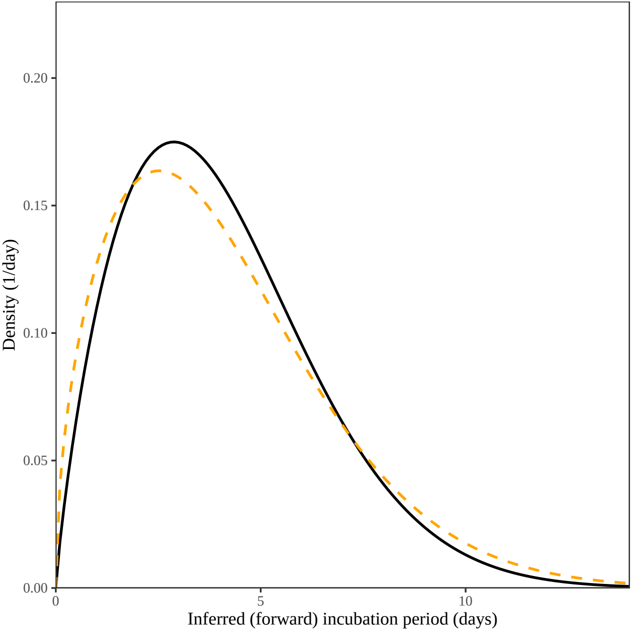
Intervals from the Netherlands



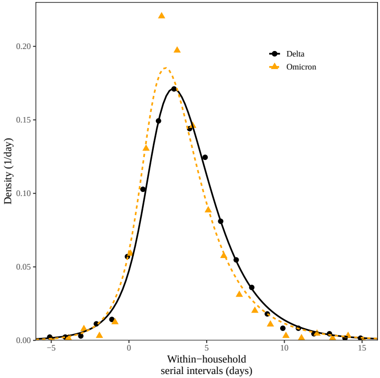
Fitted incubation periods

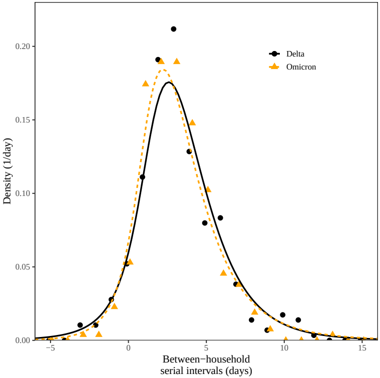


Dynamical correction



Observed and fitted transmission intervals





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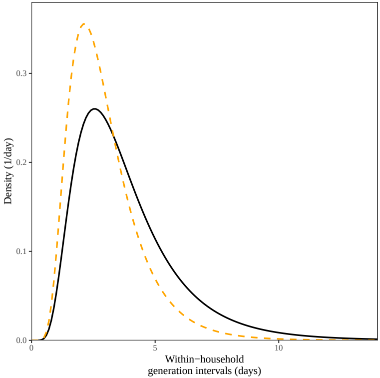

Outline

Summary

- Strength $\mathcal{R}$ and speed r are complementary ways to understand epidemic growth and control
- Transmission intervals are key to linking these measurements
  - Clear definitions
  - Combining different sources of information
  - Propagating error

Thanks

- Organizers and audience
- Collaborators:
  - Li, Park, Weitz, Bolker, Earn, Champredon, Gharouni, Papst, Hampson, So ...
  - ICI3D and SACEMA
- Funders: NSERC, CIHR, PHAC, WHO, McMaster