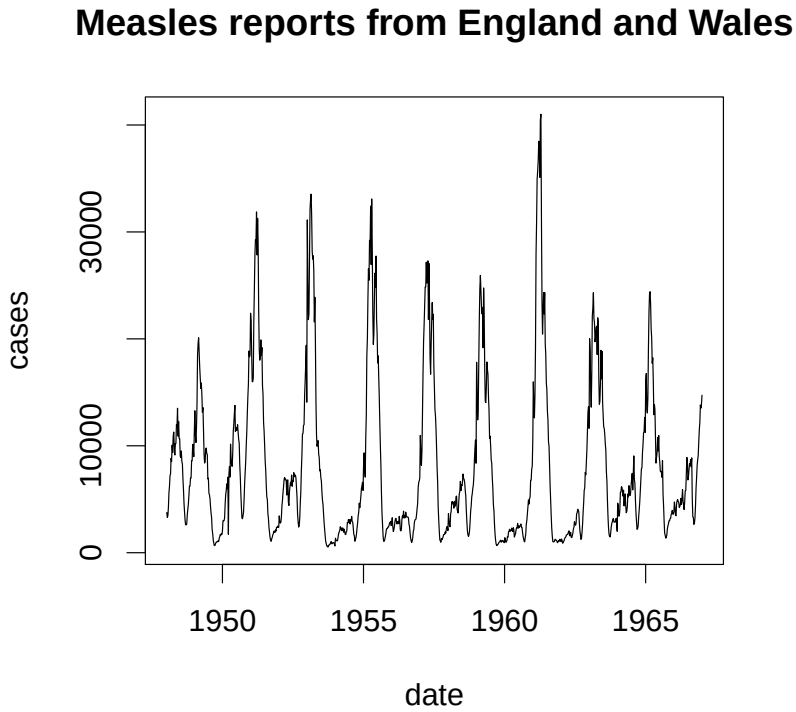
Time distributions and coronavirus control

Jonathan Dushoff, McMaster University

Cornell CAM Colloquium, Oct 2020

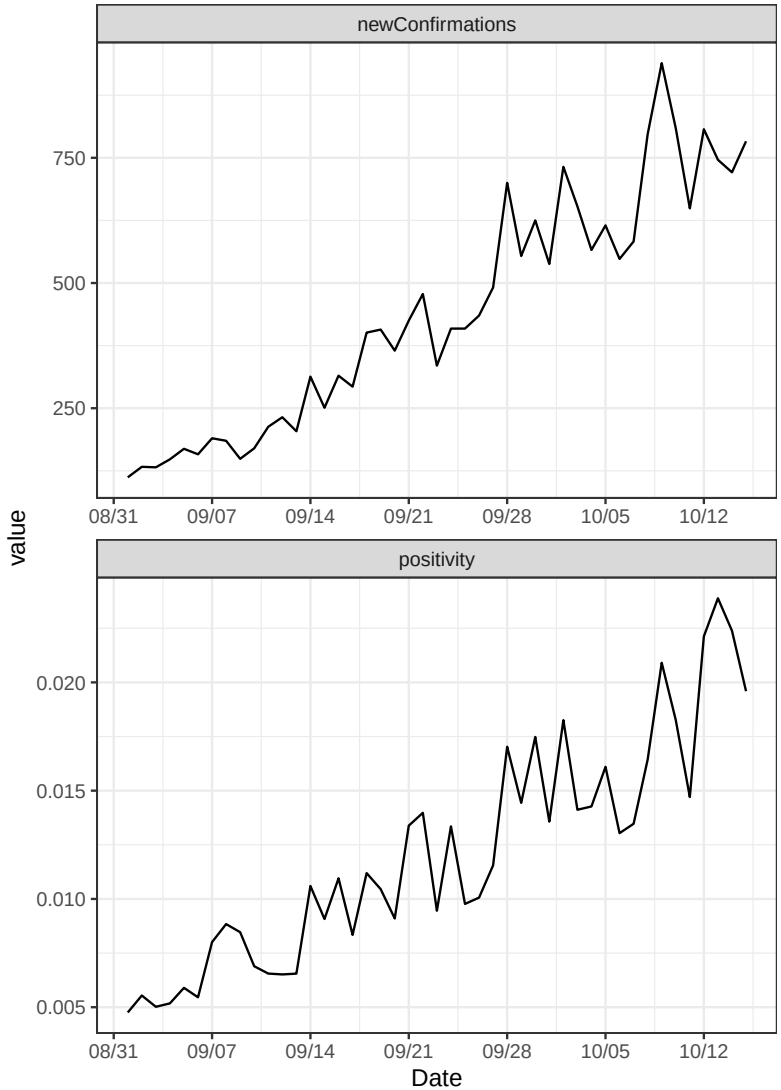
What is dynamical modeling?



- A way to connect scales
- Start with rules about how things change in short time steps
  - Usually based on *individuals*
- Calculate results over longer time periods
  - Usually about *populations*

Covid modeling questions

- How far and fast would it spread if unchecked?
- How hard is it to eliminate?
- How are we doing on control in a particular place and time?



https://wzmli.github.io/COVID19-Canada

Outline

Modeling disease spread

Linking strength and speed

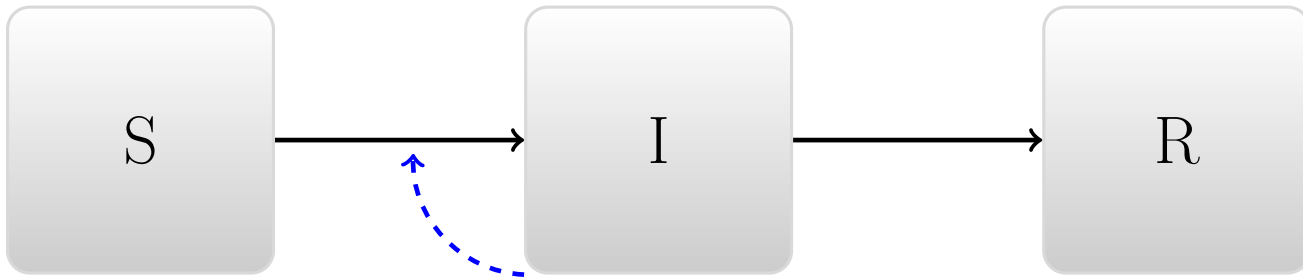
Estimating transmission intervals
- Generations through time
- Generations in space
- Serial intervals

The speed paradigm

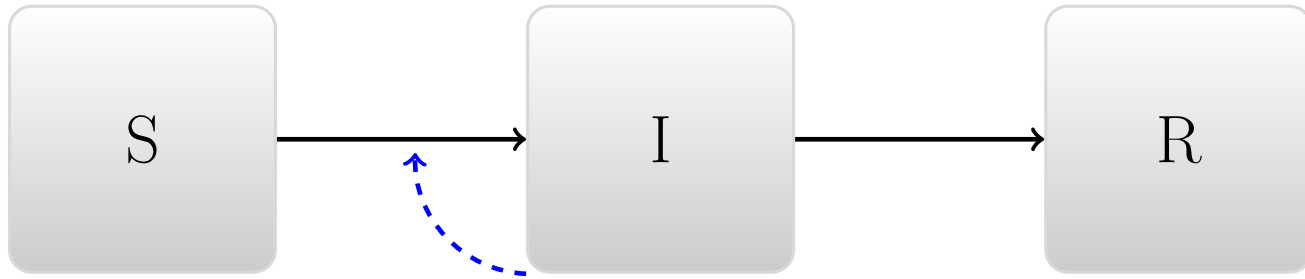
Real-time evaluation

Simple dynamical models use compartments

Divide people into categories:



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



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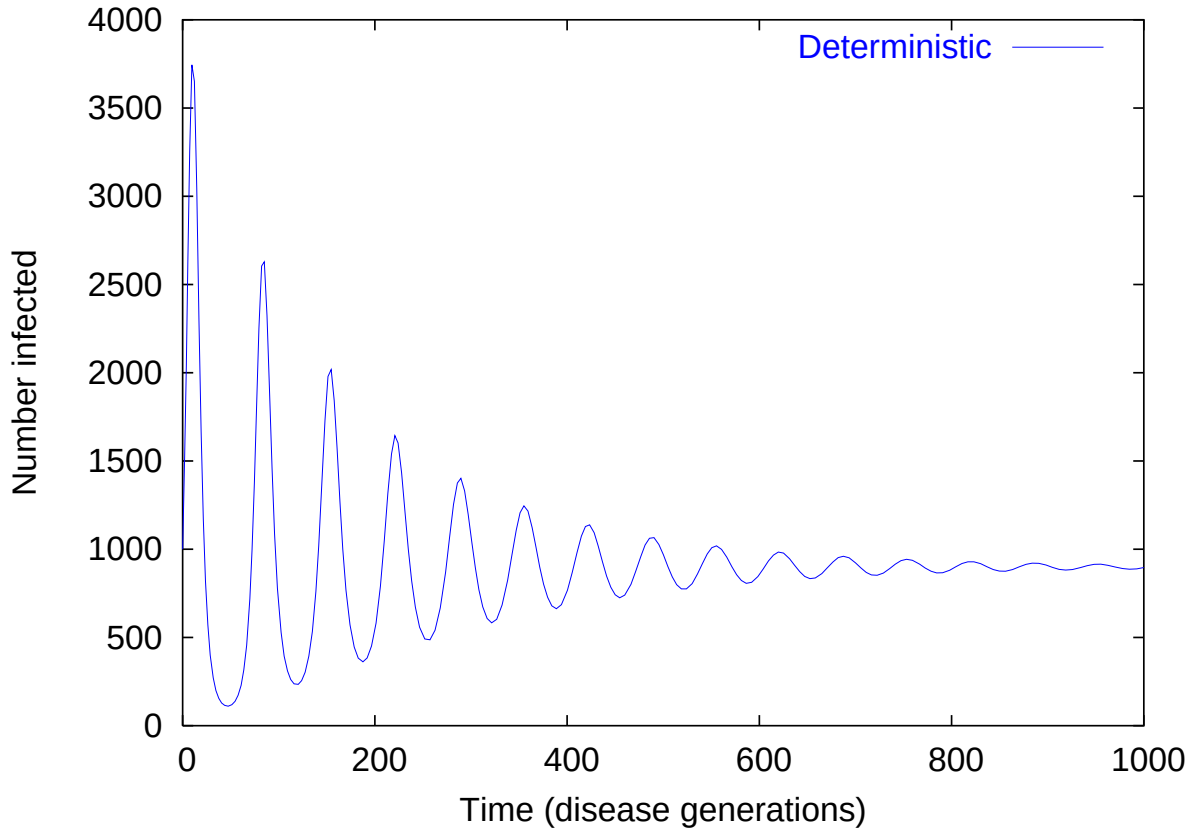
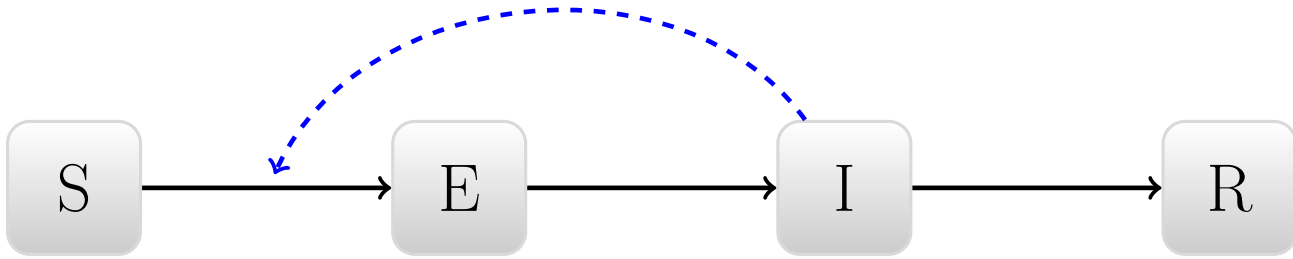
\end{aligned}
$$

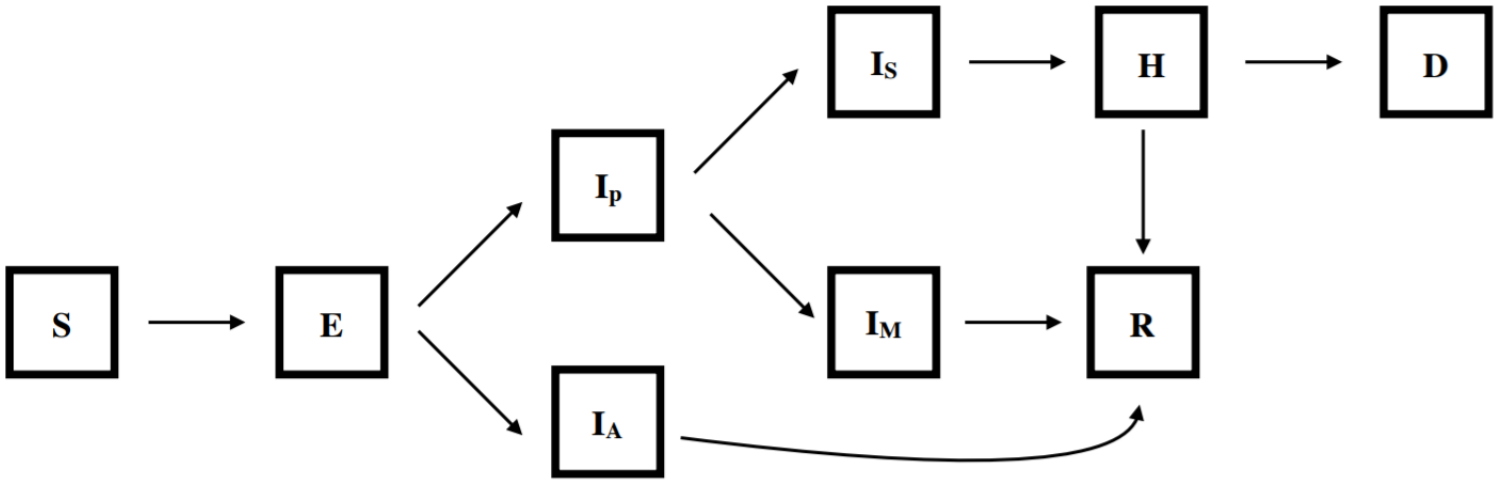
Deterministic implementation



Box models



More detailed dynamics

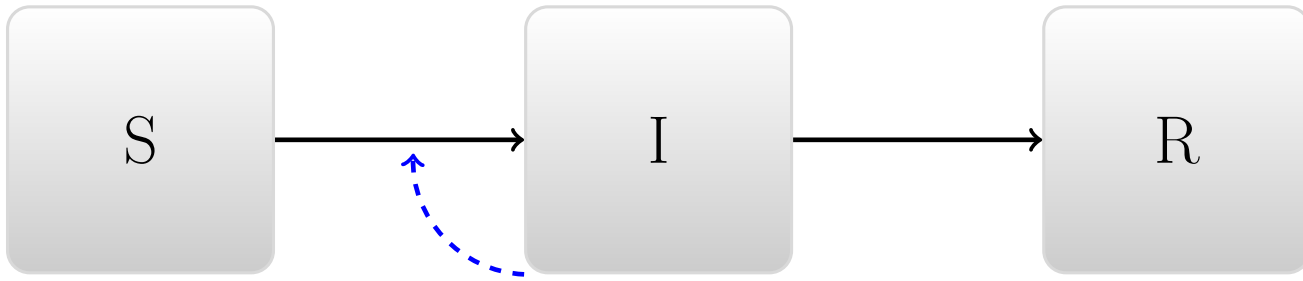


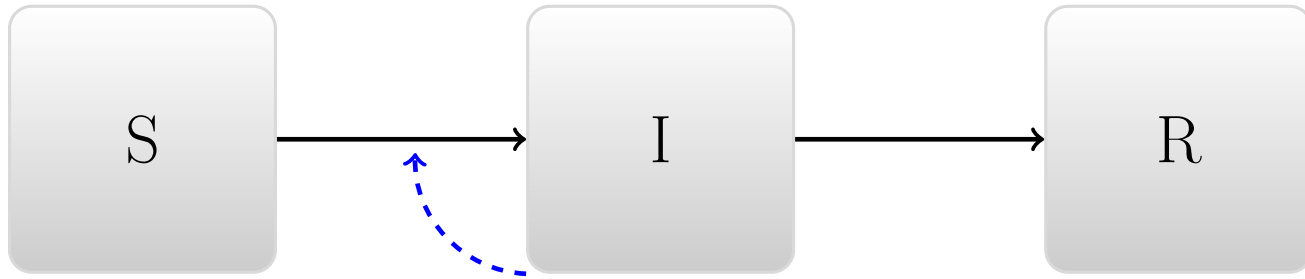
S = susceptible
E = exposed

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/


S
I
R



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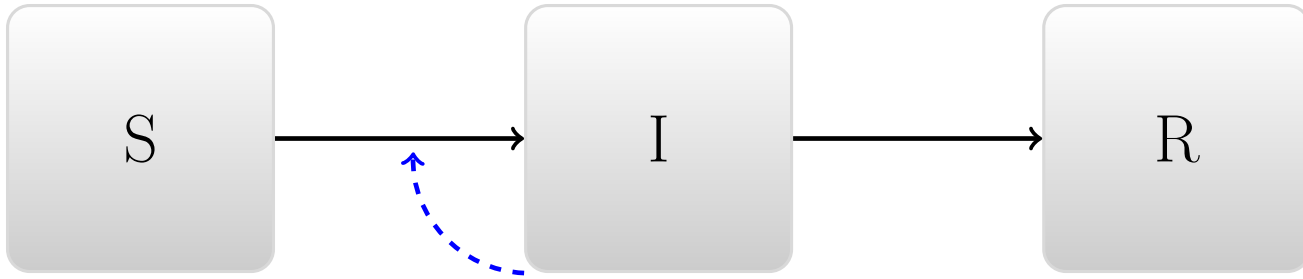
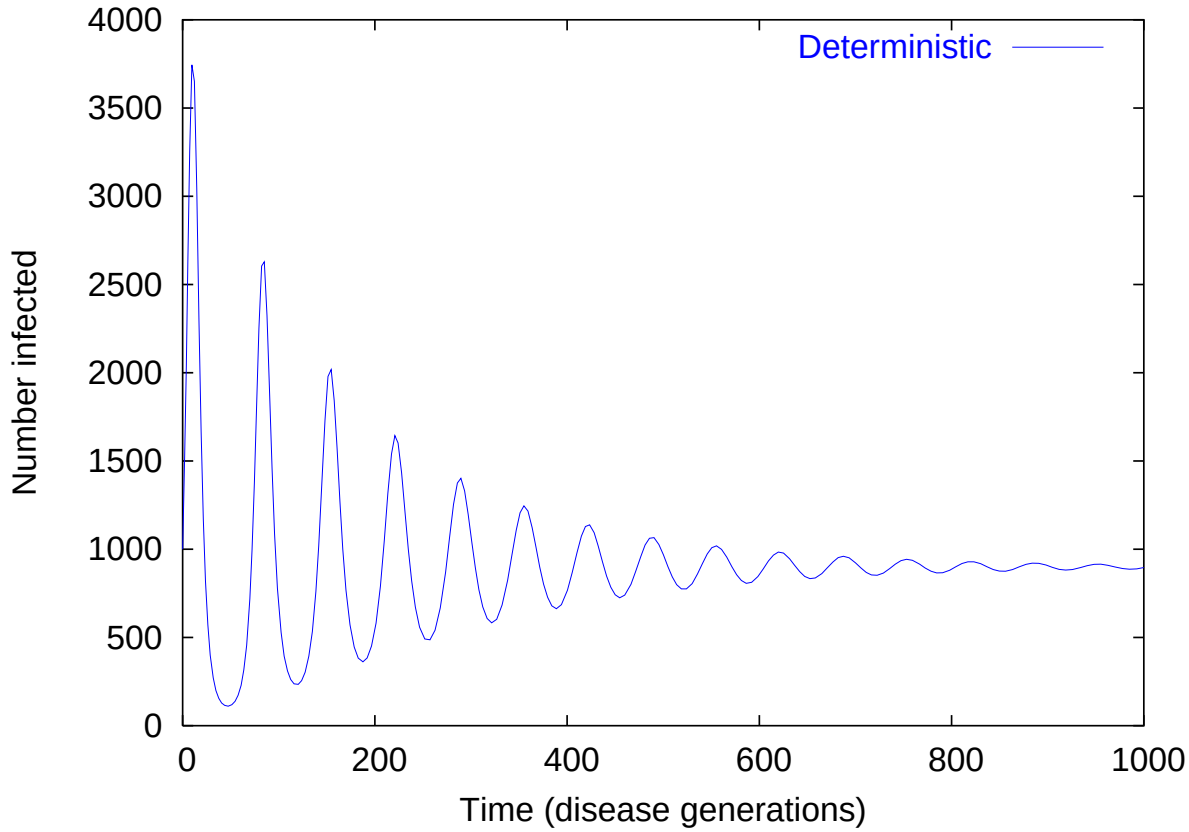
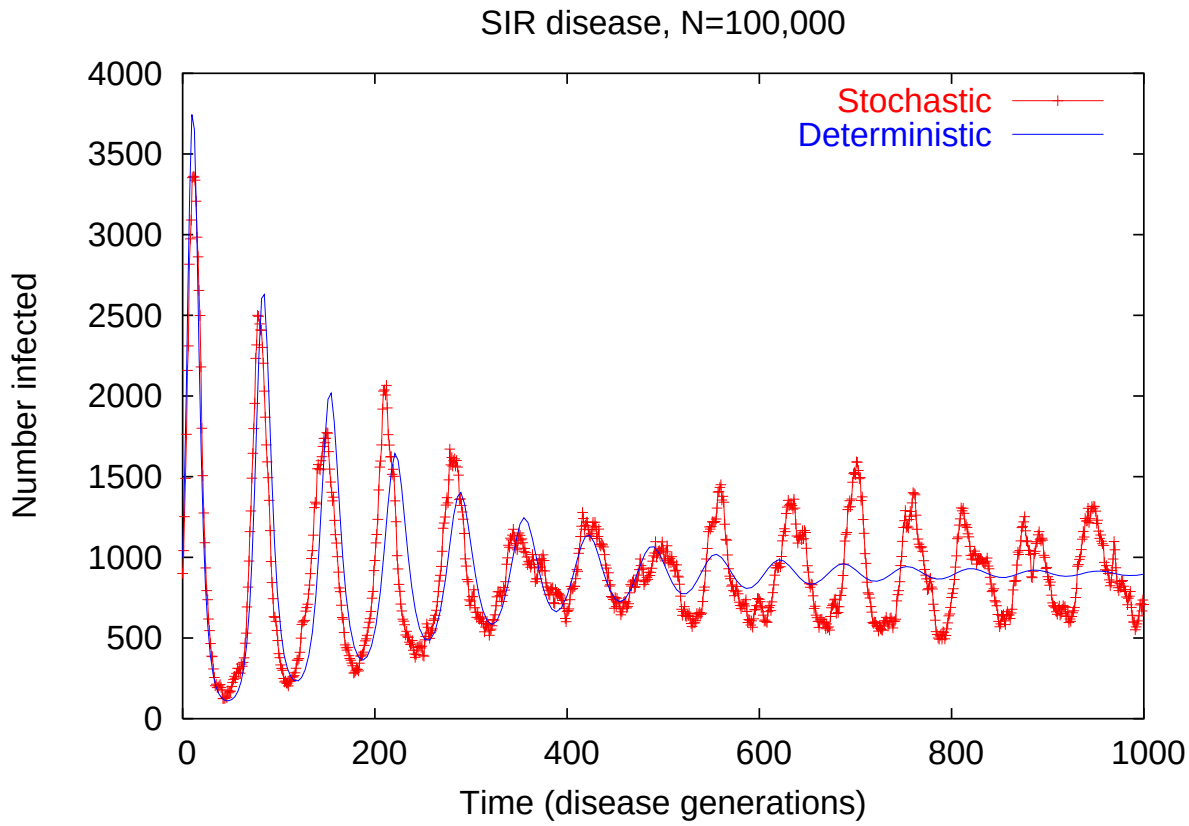


Event	**transition**	**rate**
Infection	$S \to I$	$R_0 SI/N$
Recovery	$I \to R$	$(1-\rho)I$
Rebirth	$R \to S$	ρR
Rebirth	$I \to S$	ρI

Deterministic implementation



Individual-based implementation

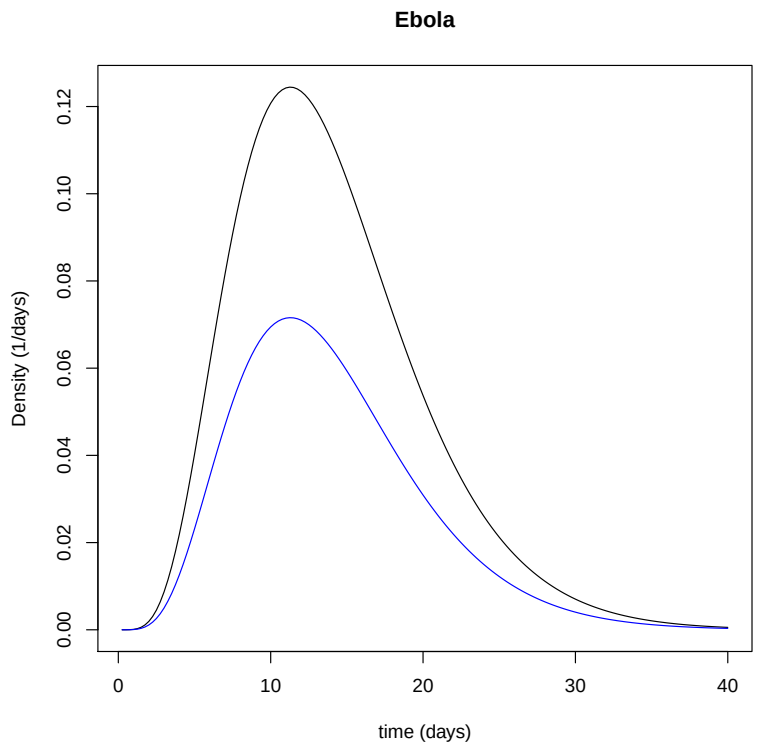


Renewal equation

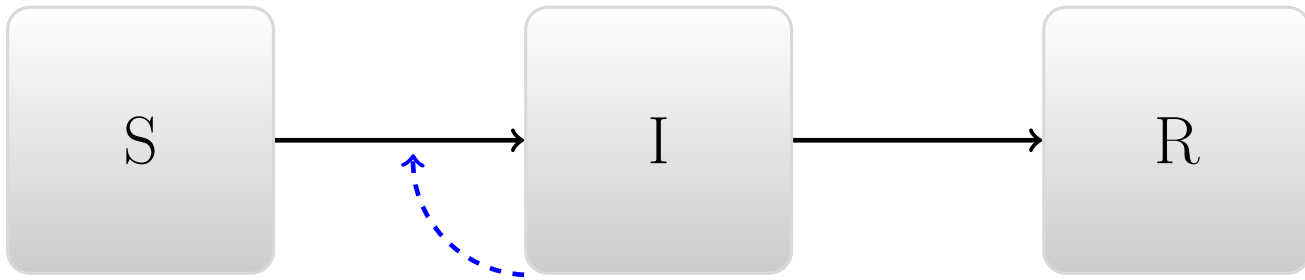
- A broad framework that covers a wide range of underlying models
- $i(t) = S(t) \int k(\tau) i(t-\tau)\, d\tau$
  - $i(t)$ is the *rate* of new infections (per-capita incidence)
  - $S(t)$ is the proportion of the population susceptible
  - $k(\tau)$ measures how infectious a person is (on average) at time τ after becoming infected
- For invasion, treat S as constant

Infection kernel

- $k(\tau)$ is the expected rate at which you infect at time τ after being infected
- $\int_\tau k(\tau)d\tau$ is the expected number of people infected:
  - $\mathcal{R}$ the effective reproductive number
- $k(\tau)/\mathcal{R}$ is a distribution:
  - $g(\tau)$, the *intrinsic* generation distribution

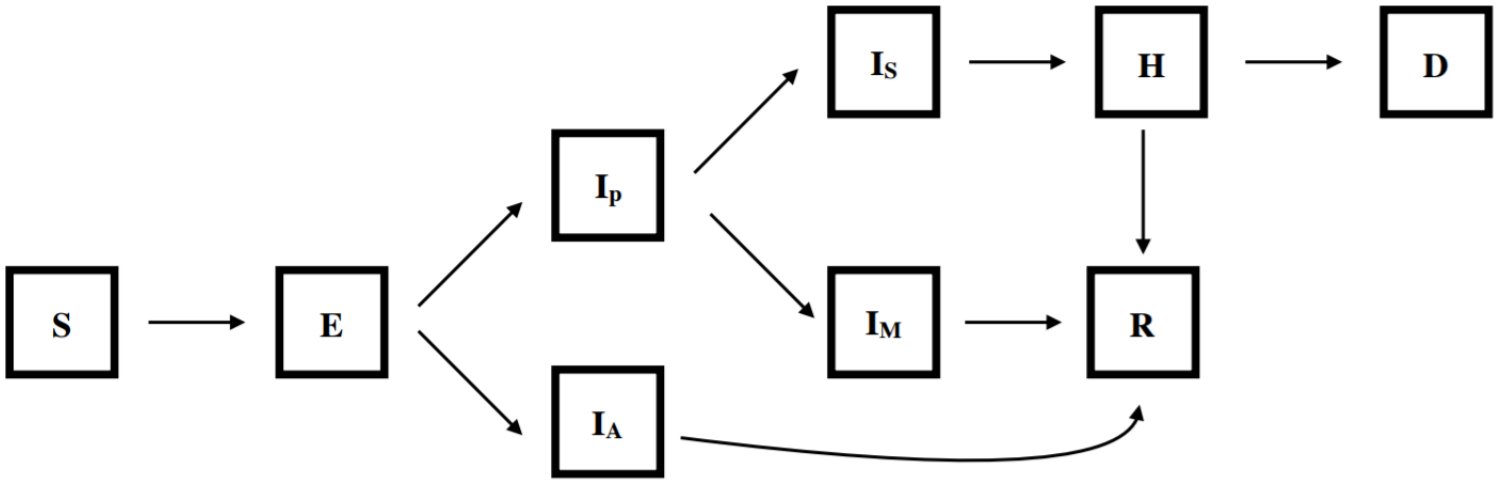


Linear chain trick



- Create ODEs to follow a *cohort* of people infected at the same time

Linear chain trick



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

How long until the bus comes?

Mean of a self-weighted quantity

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

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

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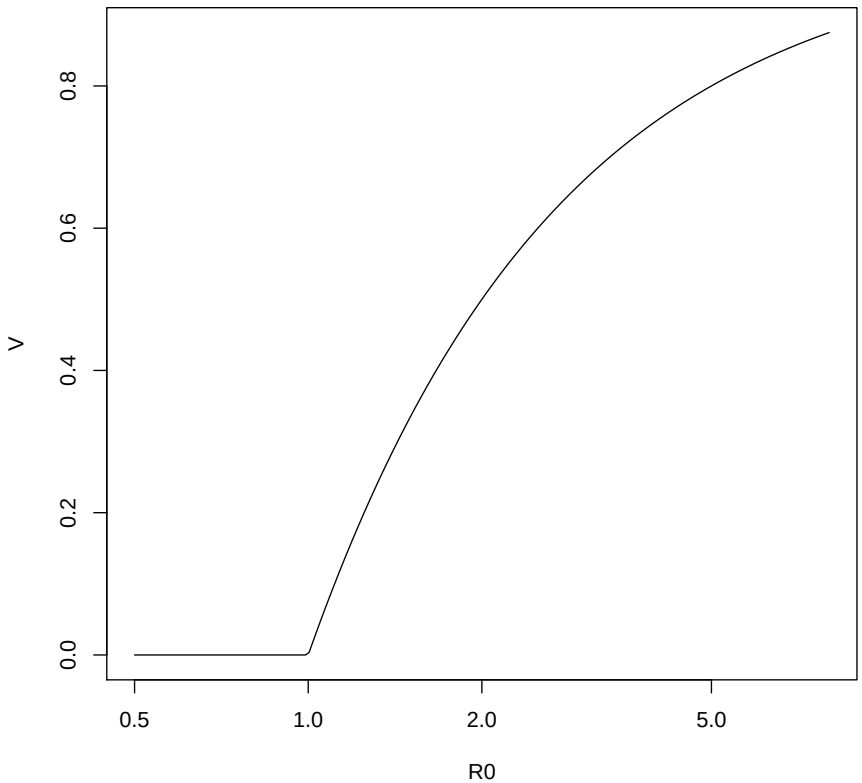
Lessons from simple models

- Exponential invasion potential
- Tendency to oscillate
- Thresholds

Strength

- We describe epidemic strength with big $\mathcal{R}$
- Number of new cases per case
- Uncontrolled, initial value of $\mathcal{R}$ is called $\mathcal{R}_0$.

$\mathcal{R}$ and control



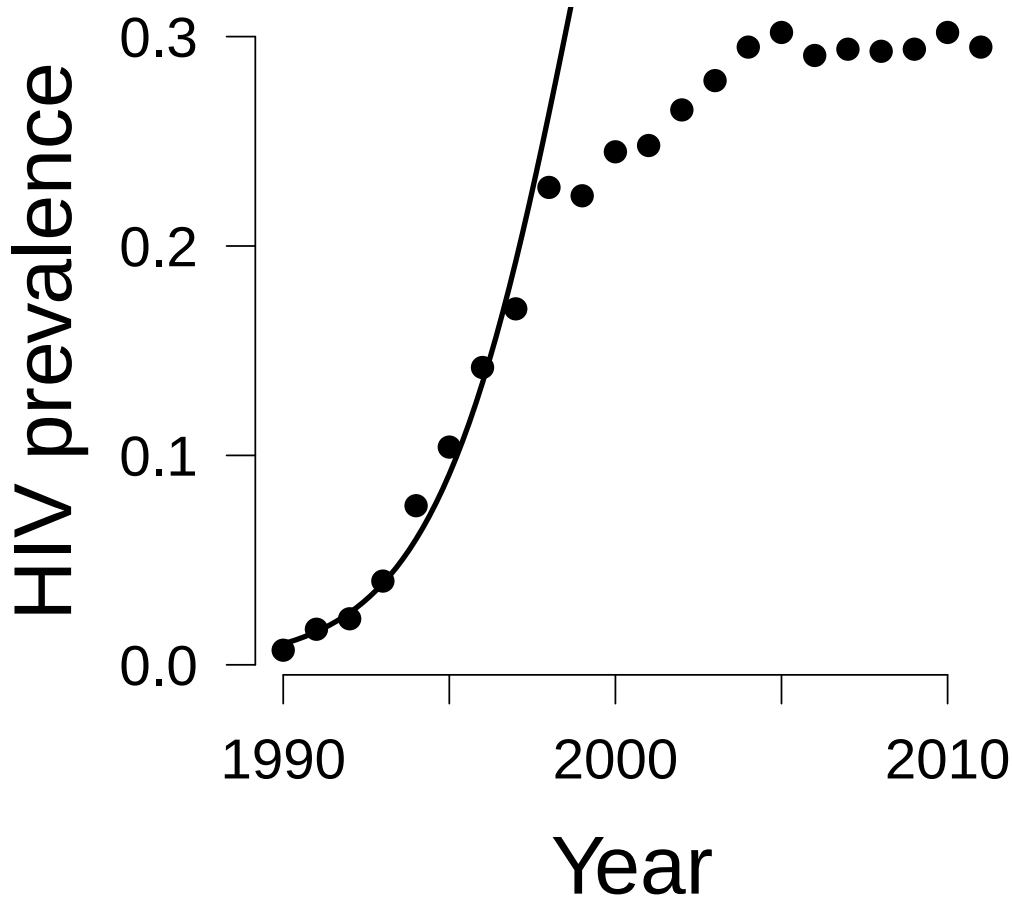
Herd immunity

- If we have $\mathcal{R}$ new cases per case when everyone is susceptible
- And 1 case per case (on average) at equilibrium:
  - Proportion susceptible at equilibrium is $S = 1/\mathcal{R}$
  - Proportion affected at equilibrium is $V = 1 - 1/\mathcal{R}$

Speed

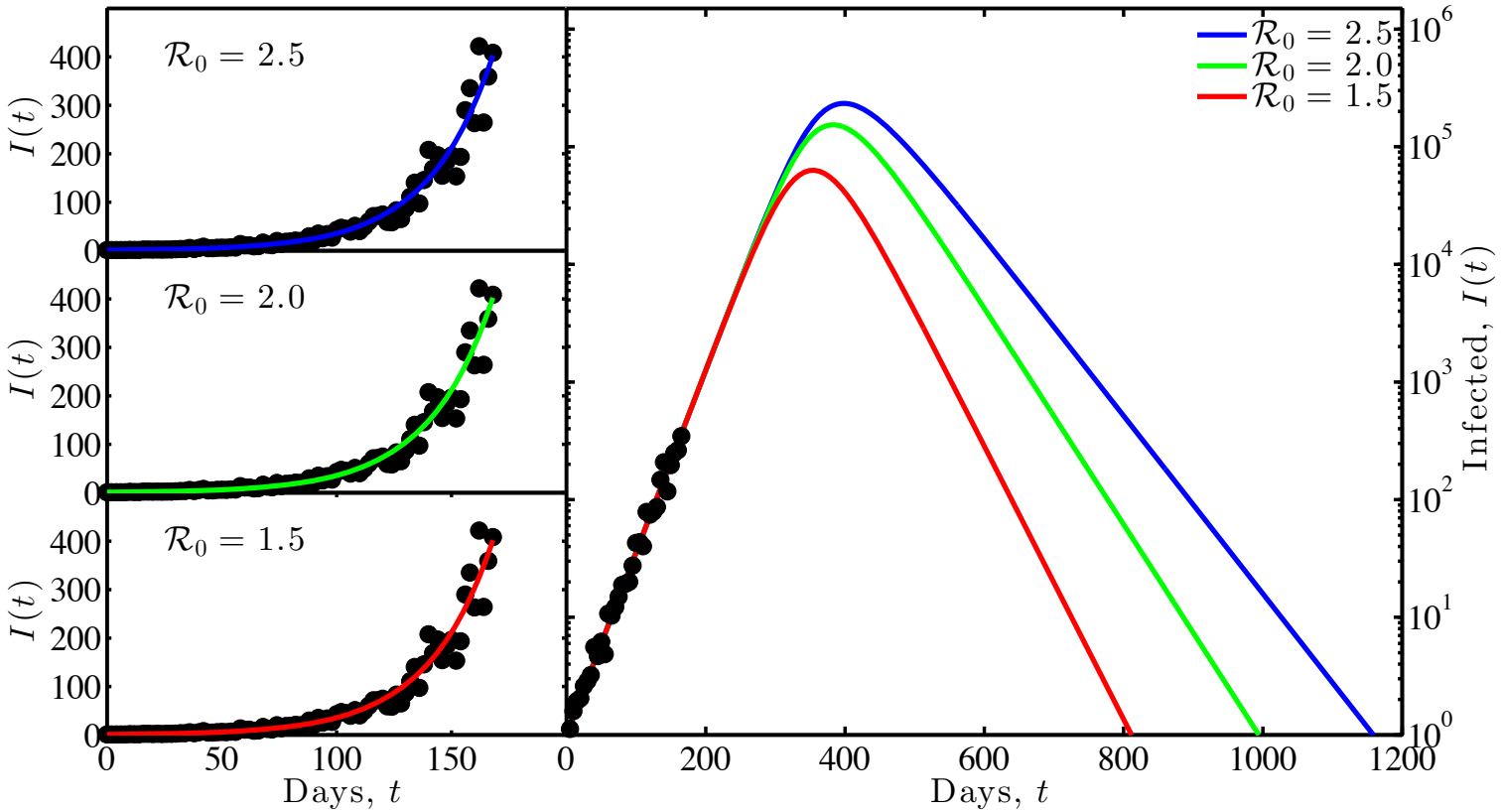
- We measure epidemic speed using little r:
  - The ratio of the *change* in disease impact to the *amount* of disease impact
  - *Units*: [1/time]
  - Disease increases like e^{rt}
- Time scale is $C = 1/r$

HIV in sub-Saharan Africa



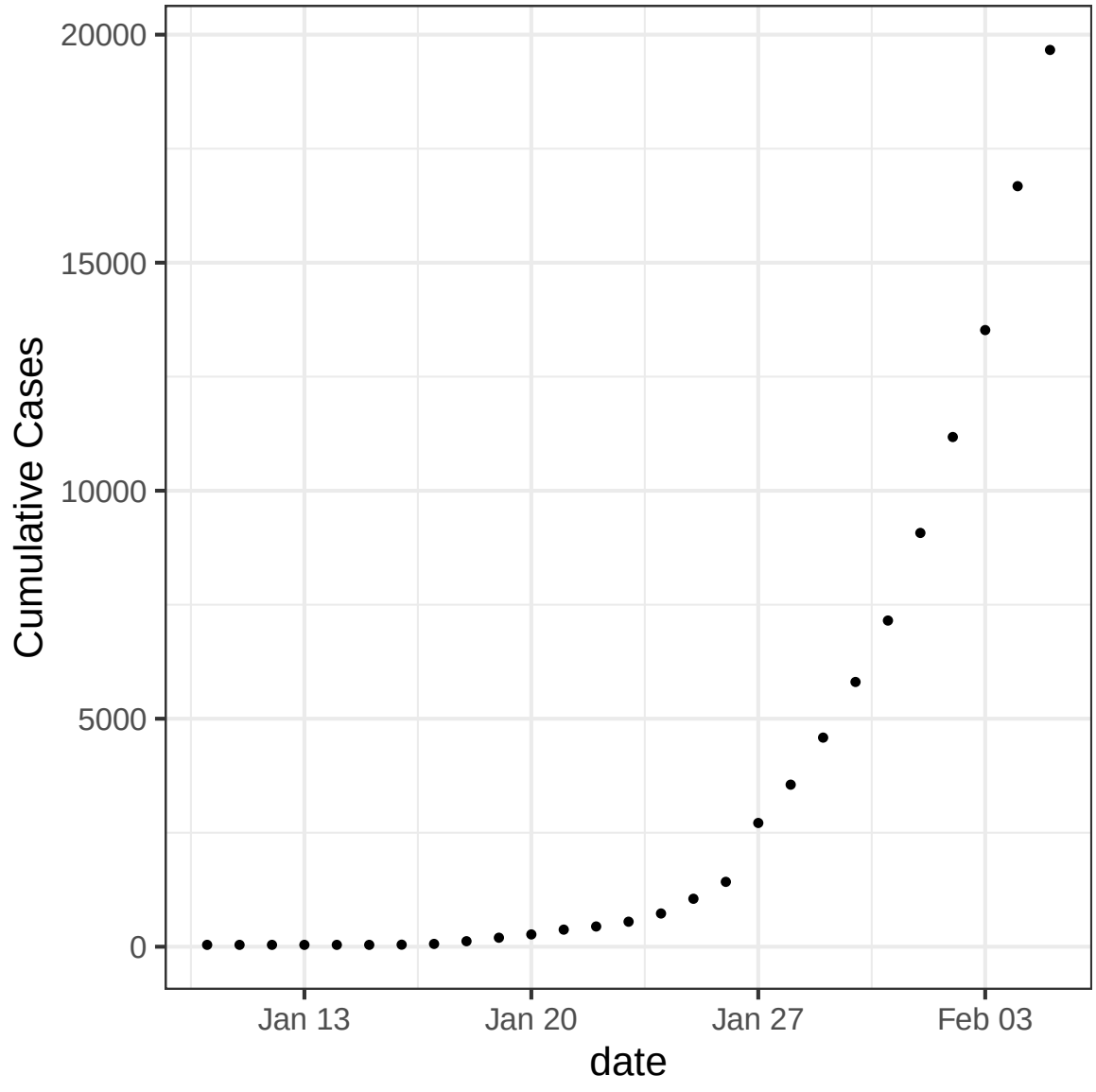
$C \approx 18\,\mathrm{month}$. Faster than expected.

Ebola outbreak



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

Coronavirus speed



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

Coronavirus

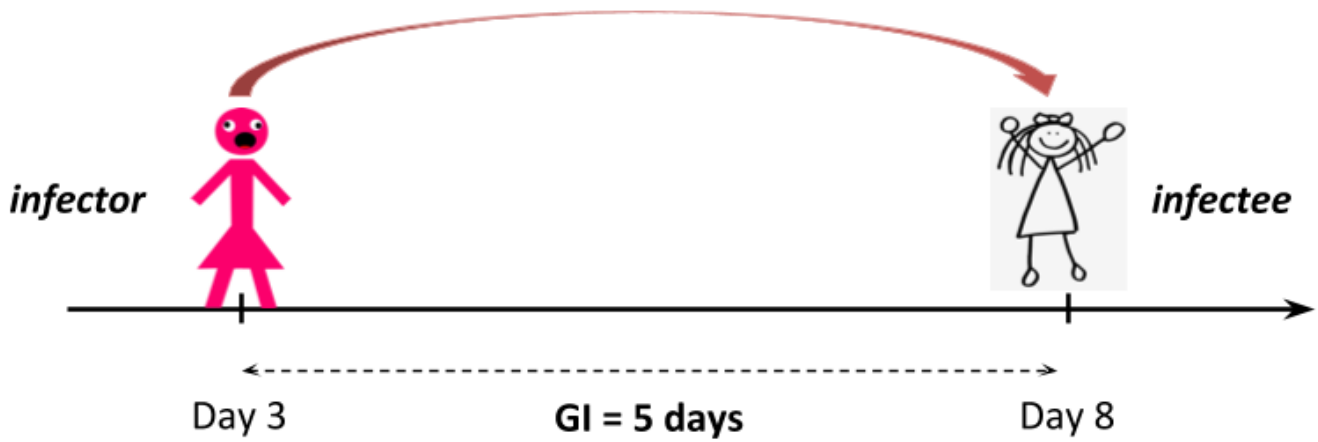
- What we see clearly is r
- What we rush to calculate is $\mathcal{R}$
- How do we do this?
- *Why* do we do this?

How long is a disease generation? (present)

Definition

Generation Interval:

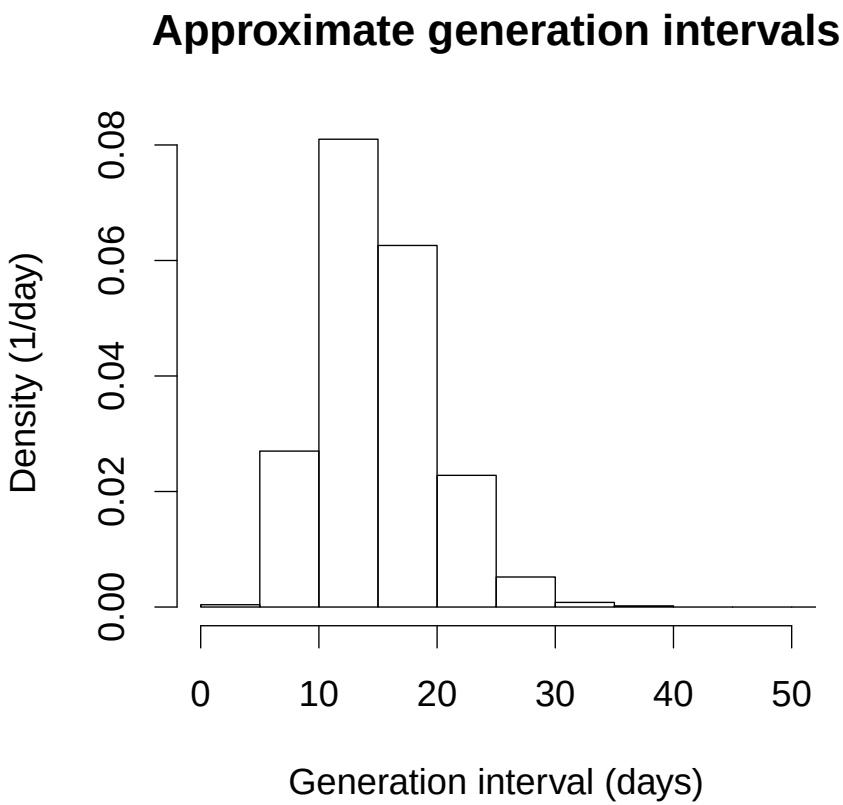
Interval between the time that an individual is infected by an infector and the time this infector was infected



Generation intervals

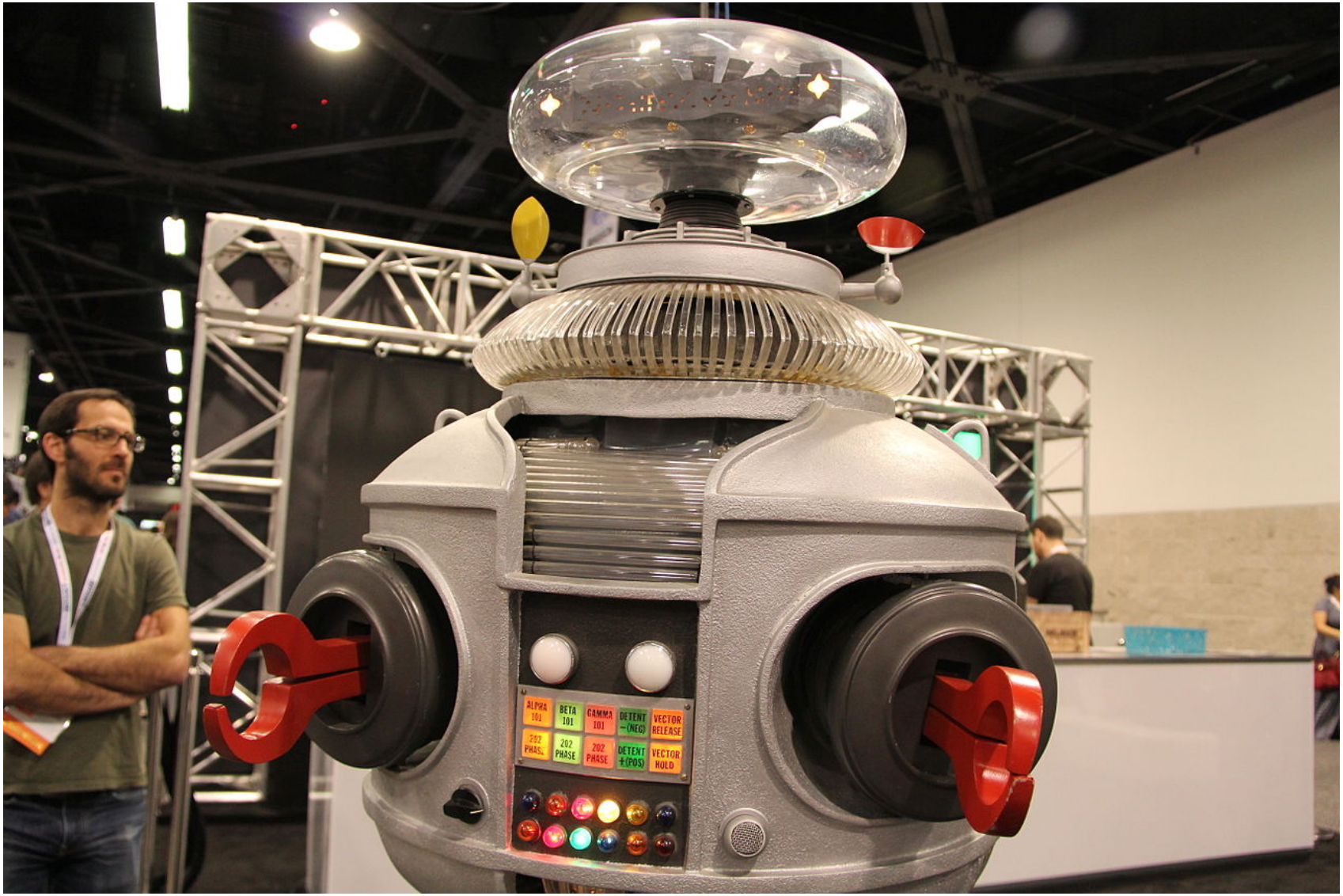
- Sort of the poor relations of disease-modeling world
- Ad hoc methods
- Error often not propagated

Quickness: $g(\tau)$



- The generation distribution measures generations of the disease
  - Interval between "index" infection and resulting infection
- Does "quick" disease (short generations) mean more danger or less danger?

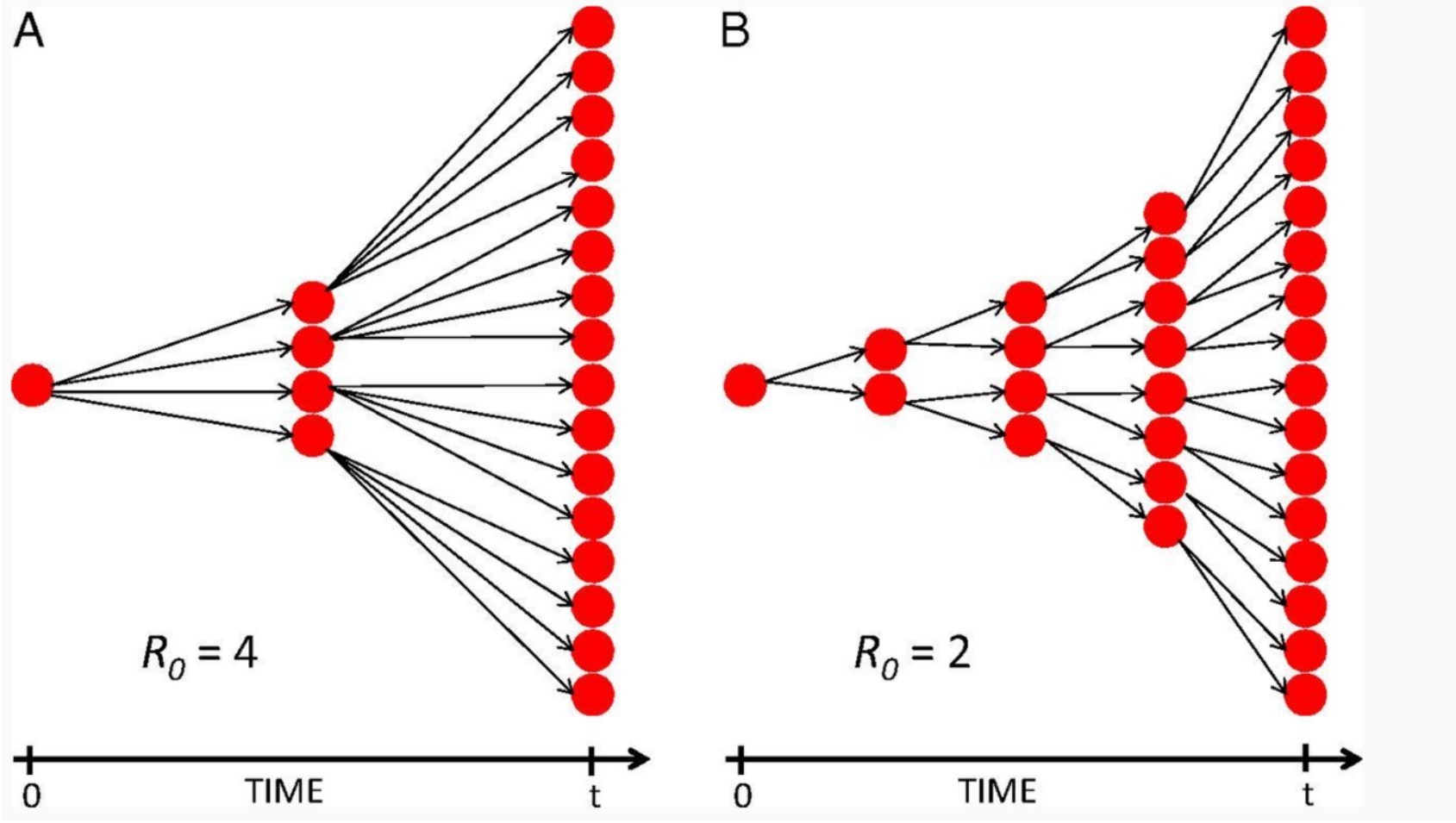
Danger?


ALPHA 101
BETA 101
GAMMA 101
DETENT −(NEG)
VECTOR RELEASE
202 PHAS..
202 PHASE
202 PHASE
DETENT +(POS)
VECTOR HOLD

Conditional effect of quickness

- *Given* the reproductive number $\mathcal{R}$
  - quicker disease means faster growth rate r
  - More danger
- *Given* the growth rate r
  - quicker disease means *smaller* $\mathcal{R}$
  - Less danger

Generations and $\mathcal{R}$

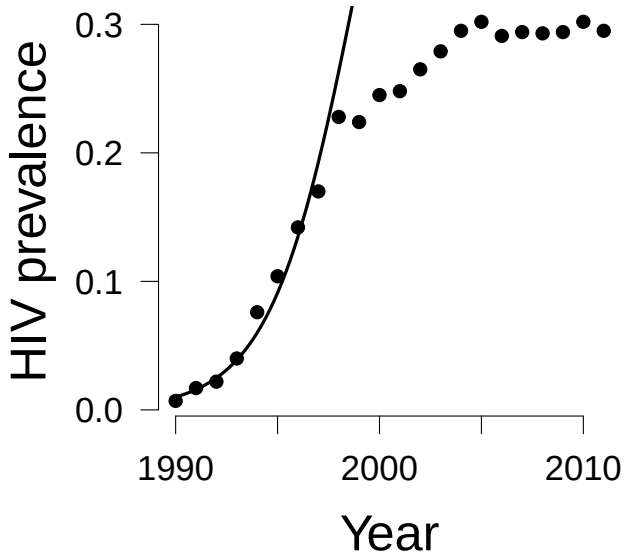


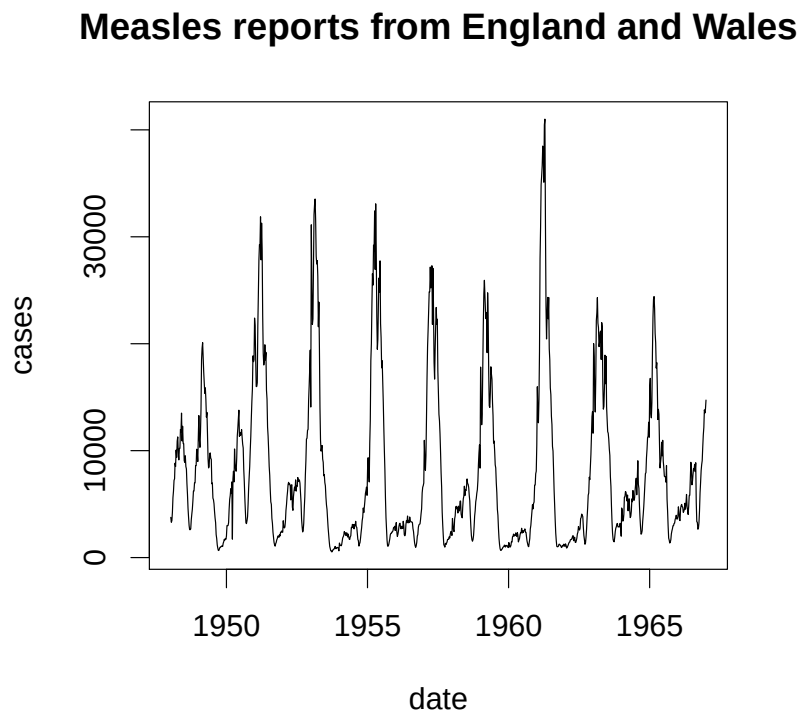
Powers et al., https://www.pnas.org/content/111/45/15867

Linking framework

- Epidemic speed (r) is a *product*:
  - (something to do with) quickness $\times$
  - (something to do with) epidemic strength
- Strength ($\mathcal{R}$) is therefore (sort-of) a quotient
  - More quickness implies less strength
  - . . . if speed is known

Speed and strength



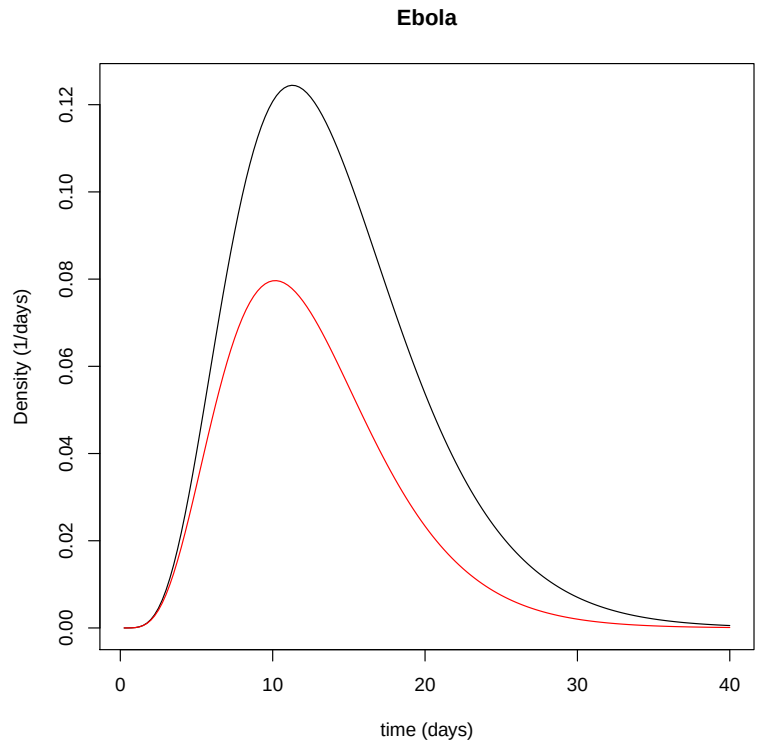


Euler-Lotka equation

- If we neglect S, 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

Interpretation: generating functions

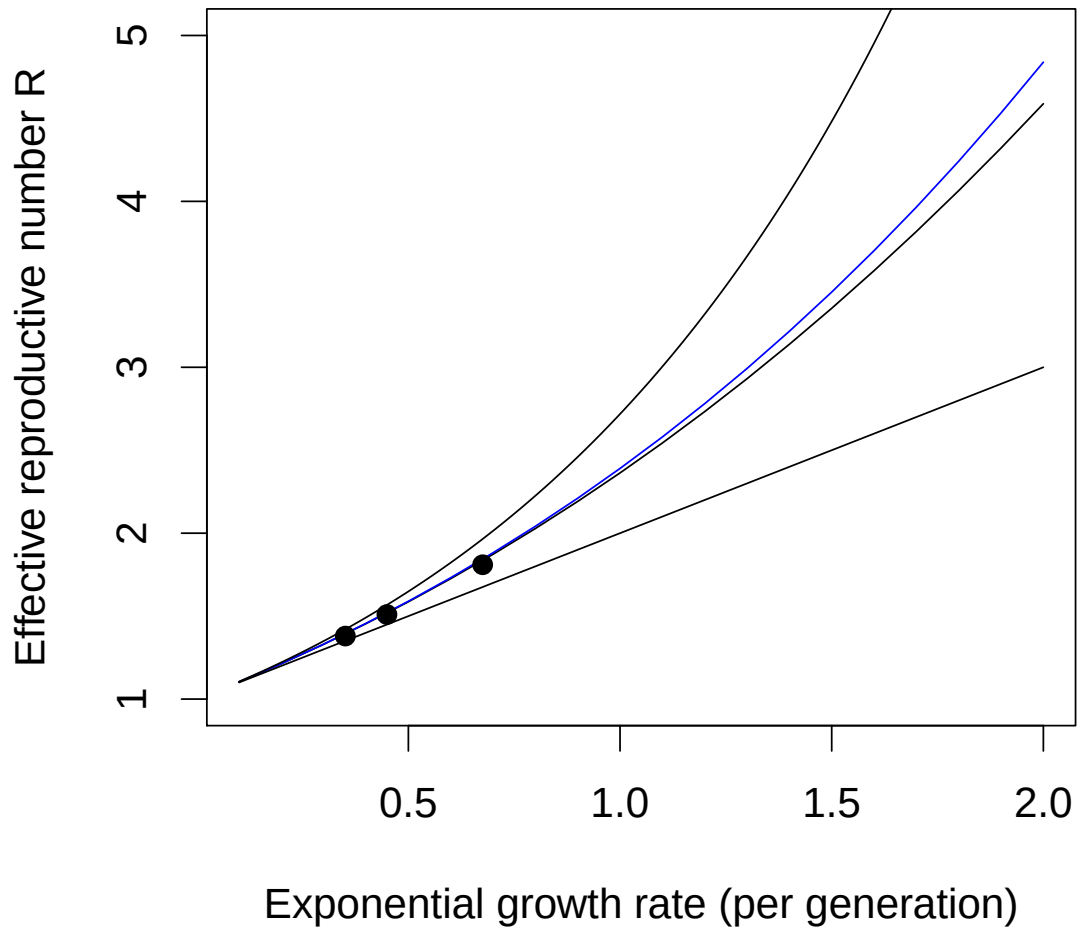
- $1/\mathcal{R} = \int g(\tau) \exp(-r\tau)\, d\tau$
- $\mathcal{R} = 1/M(-r)$
- *J Wallinga, M Lipsitch; DOI: 10.1098/rspb.2006.3754*



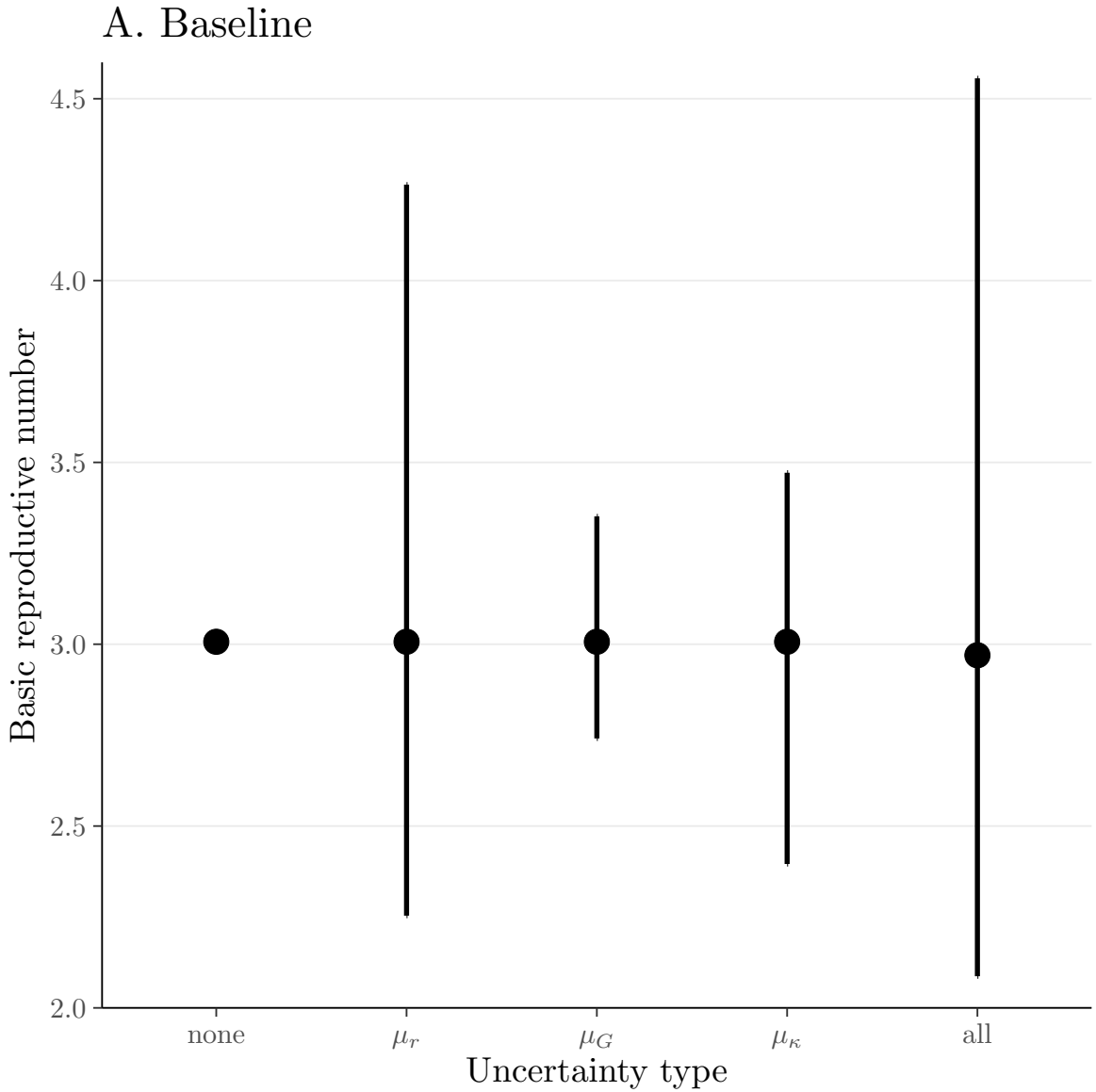
Compound-interest interpretation

- $\mathcal{R} = (1 + r\kappa\bar{G})^{1/\kappa} \equiv X(r\bar{G}; 1/\kappa)$
- 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*

Approximating the $r\mathcal{R}$ relationship



Propagating error



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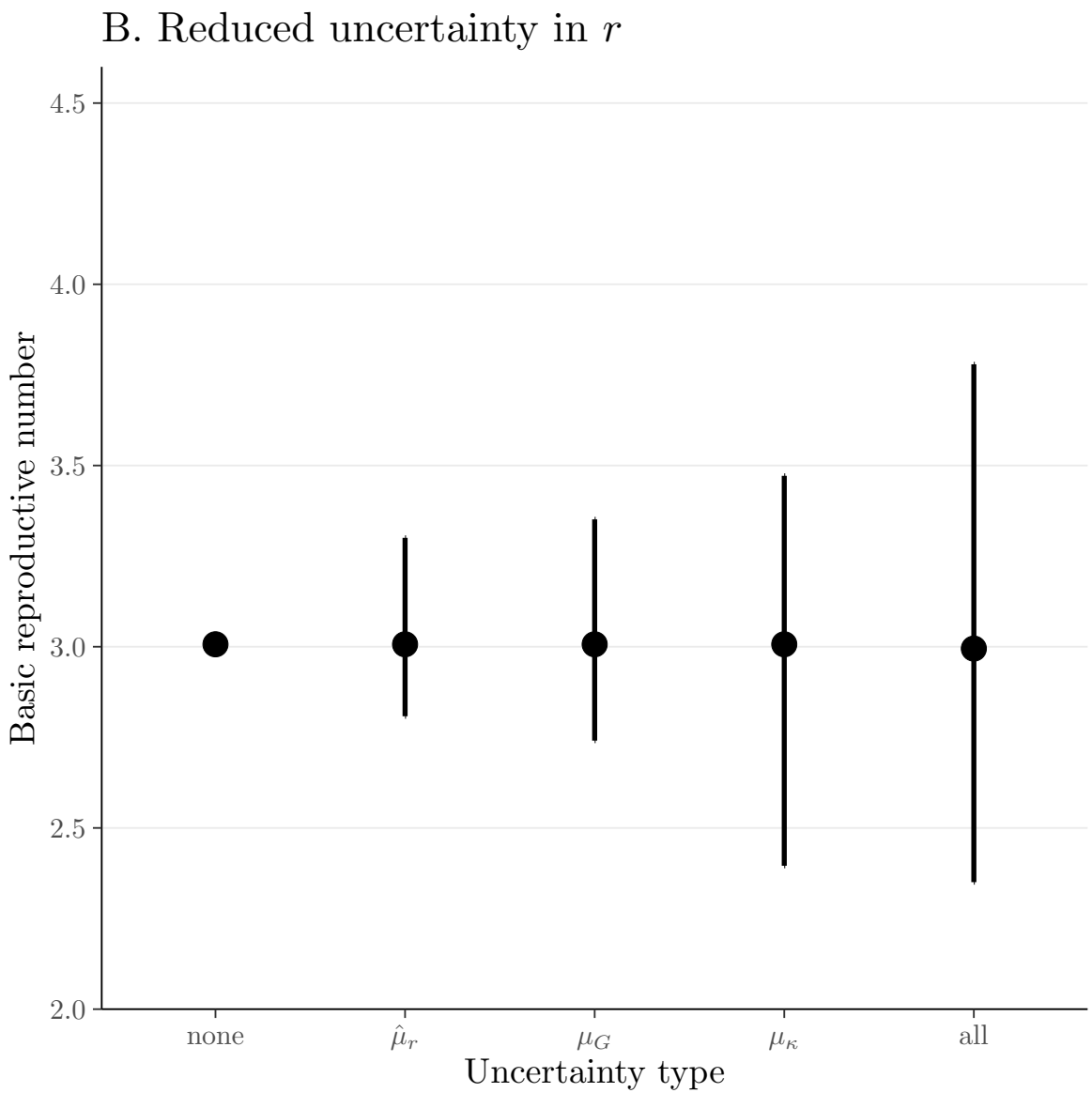

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Real-time evaluation

Estimating transmission intervals

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Generations through time

- Generation intervals can be estimated by:
  - Observing patients:
    - How long does it take to become infectious?
    - How long does it take to recover?
    - What is the time profile of infectiousness/activity?
  - Contact tracing
    - Who (probably) infected whom?
    - When did each become infected?
    - — or ill (serial interval)?

Which is the real interval?

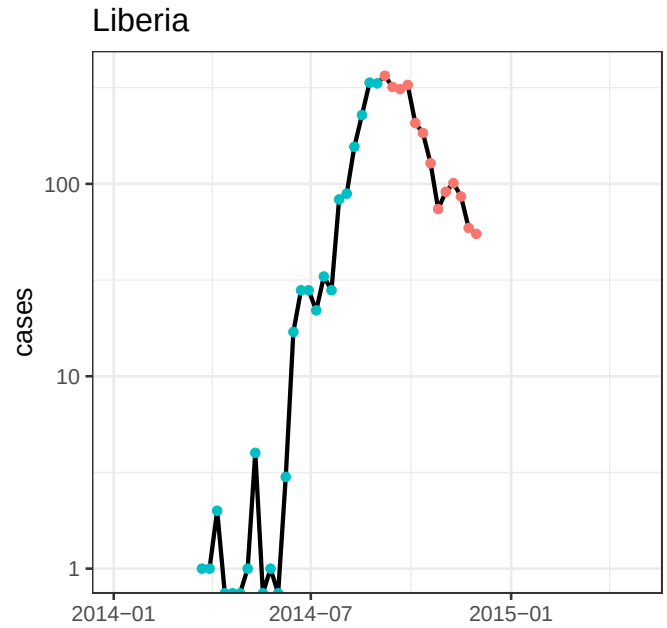
- Contact-tracing intervals look systematically different, depending on when you observe them.
- Observed in:
  - Real data, detailed simulations, simple model
- Also differ from intrinsic (infector centered) estimates

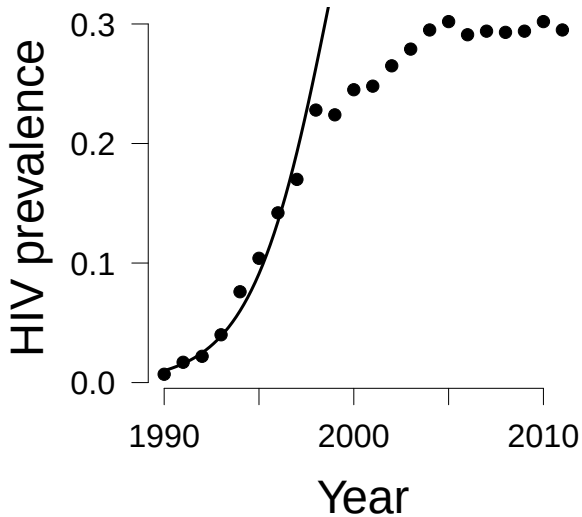
Types of interval

- 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

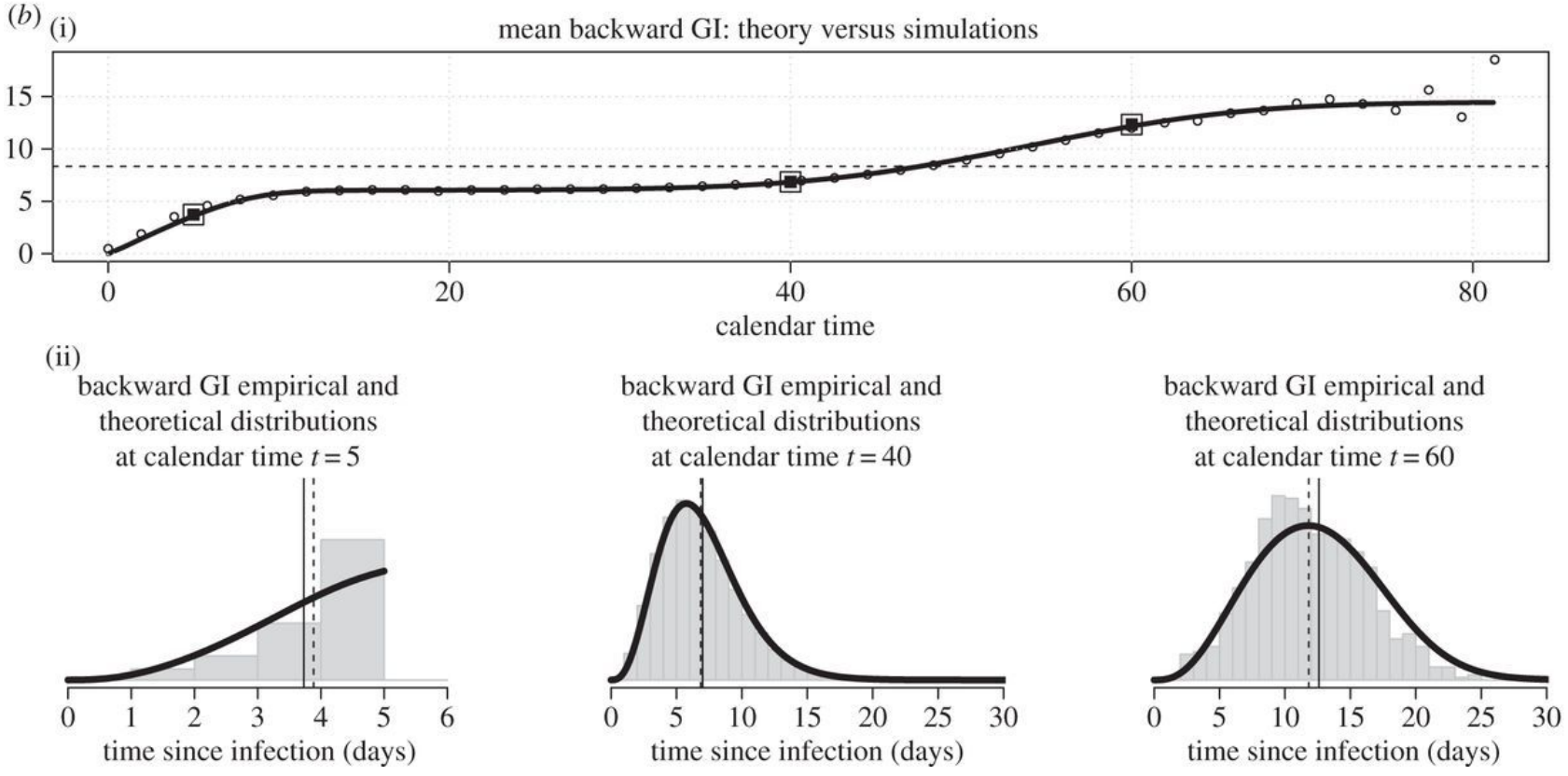
Growing epidemics

- 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





Backward intervals



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

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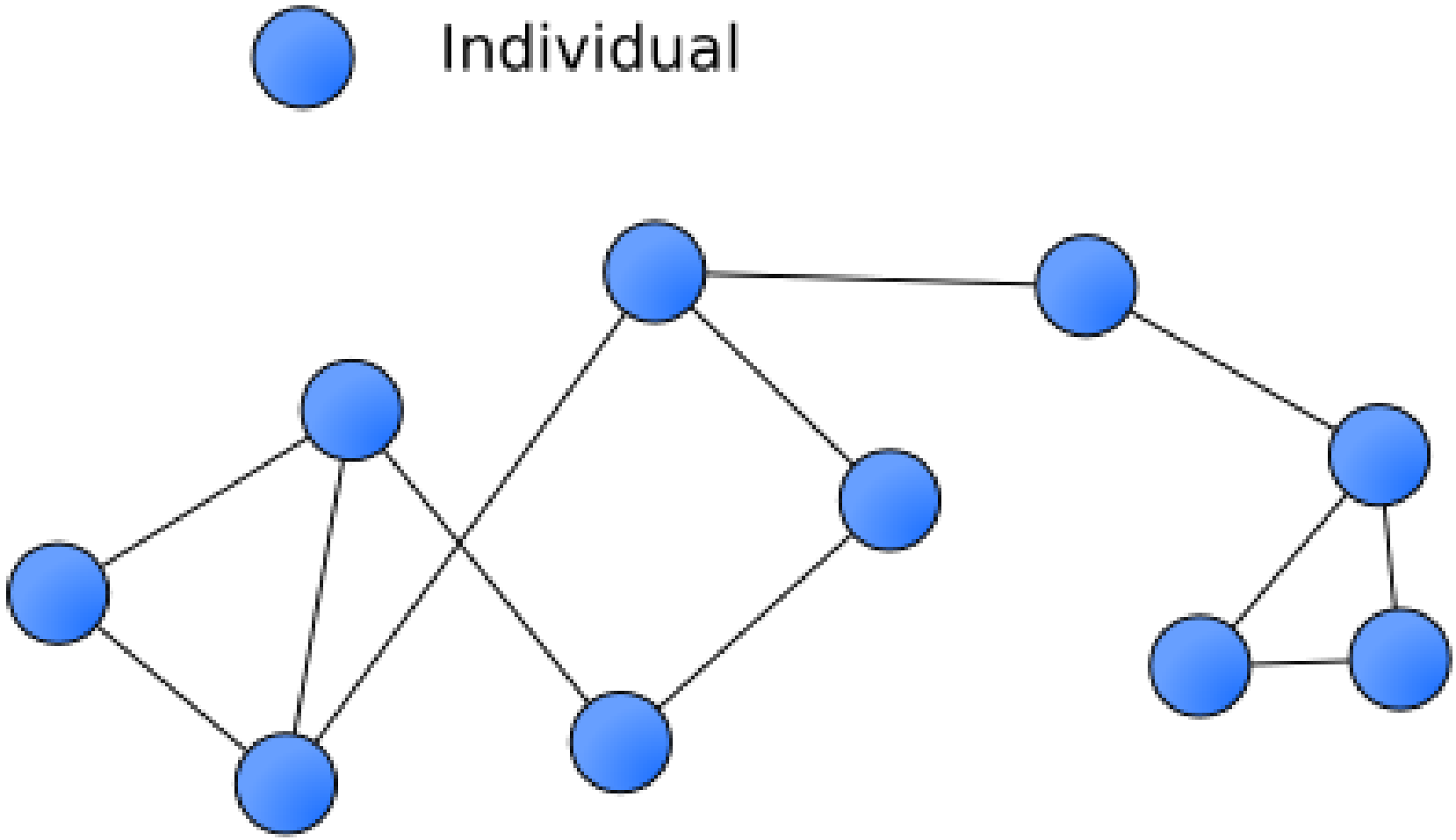
Generations in space

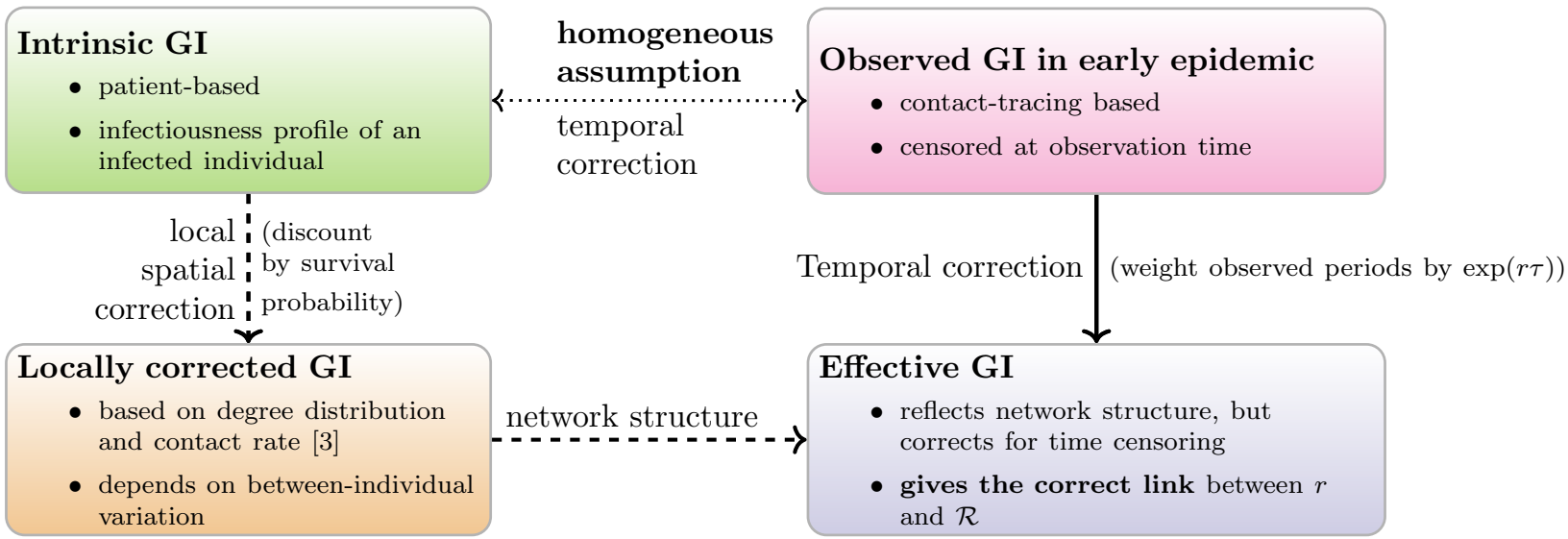
- How do local interactions affect realized generation intervals?



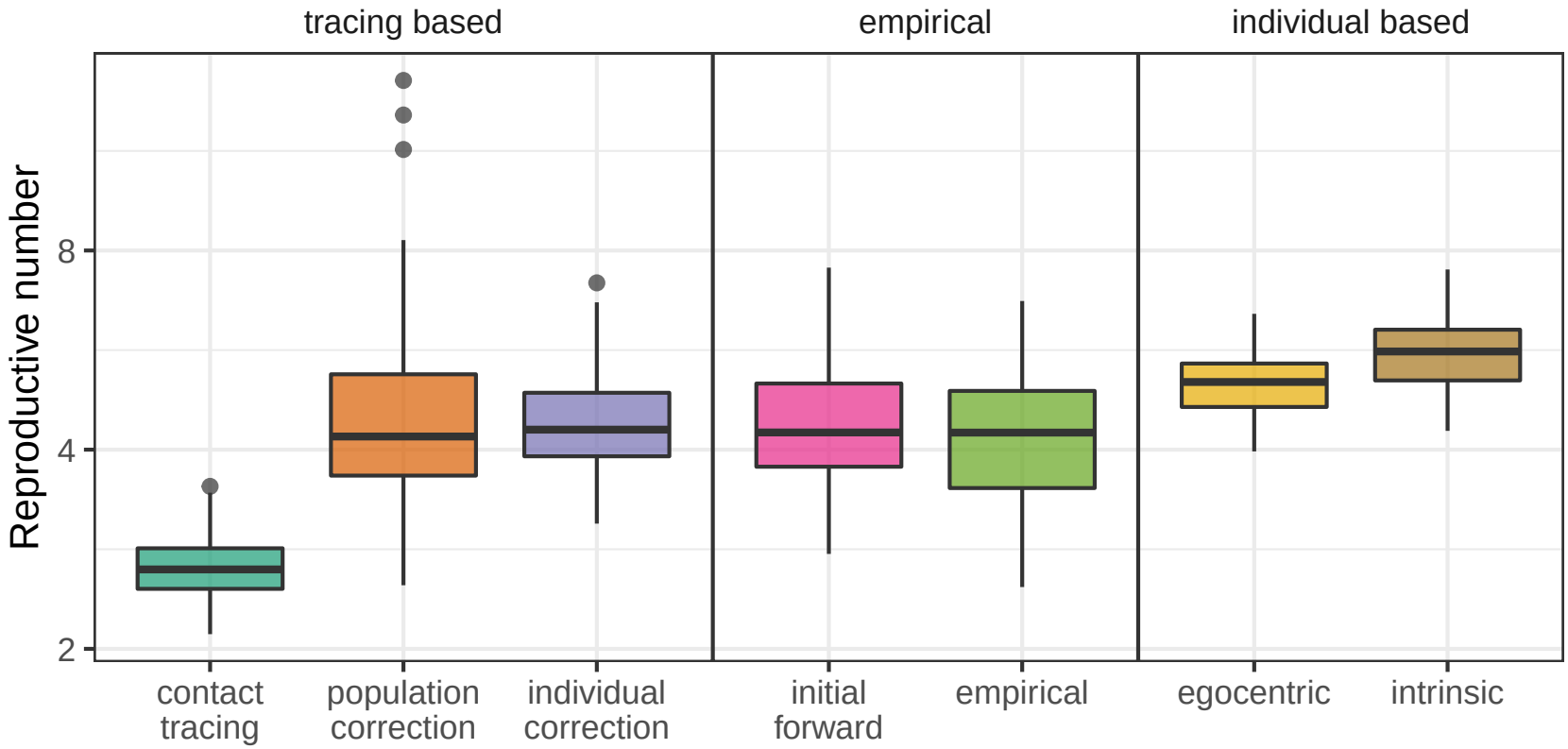
Generation-interval perspective

- Modelers don't usually question the intrinsic generation interval
- But spatial network structure does change generation intervals:
  - Local interactions
  - $\Longrightarrow$ wasted contacts
  - $\Longrightarrow$ shorter generation intervals
  - $\Longrightarrow$ smaller estimates of $\mathcal{R}$.

Observed and estimated intervals



Outbreak estimation



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

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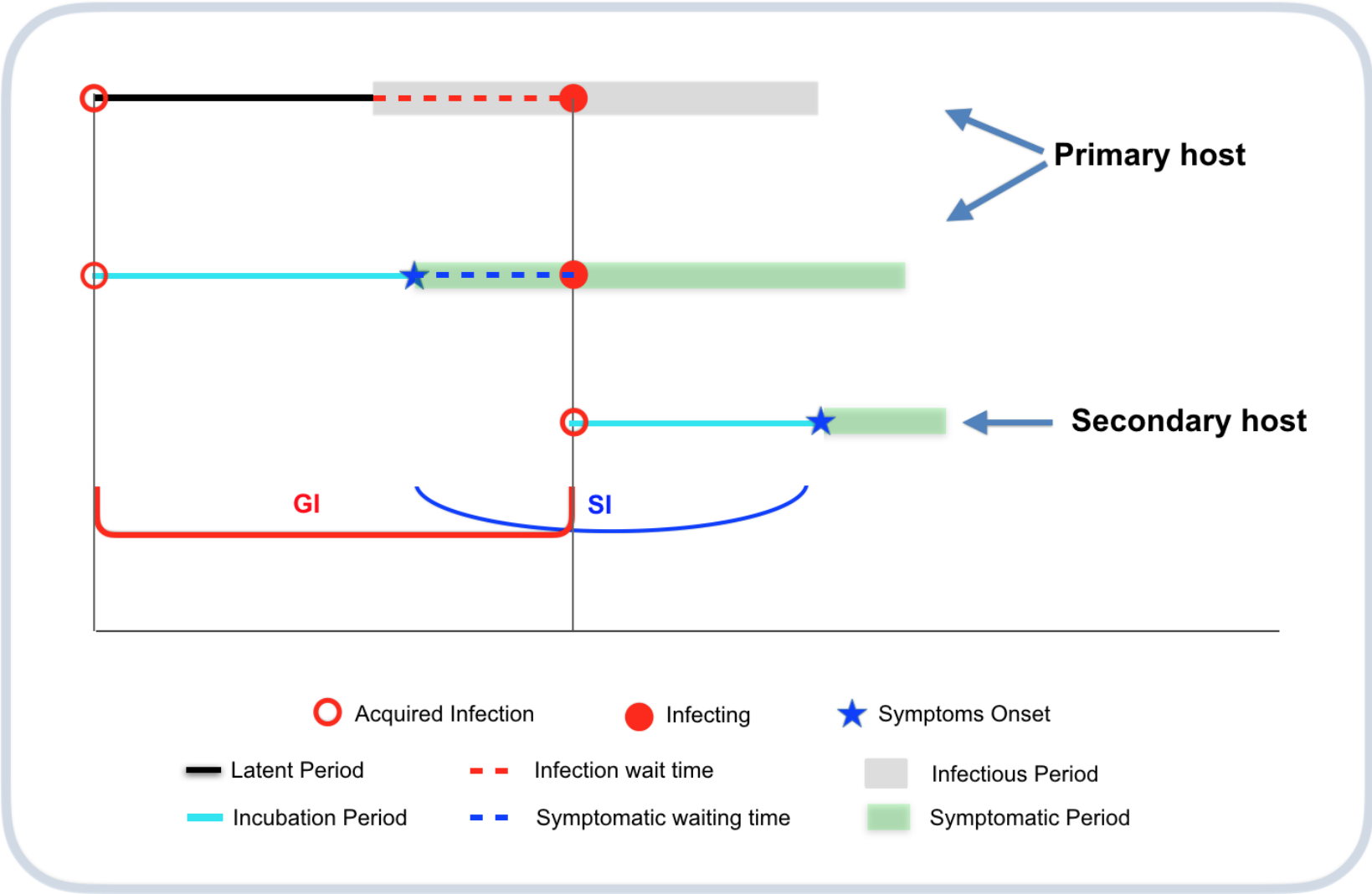
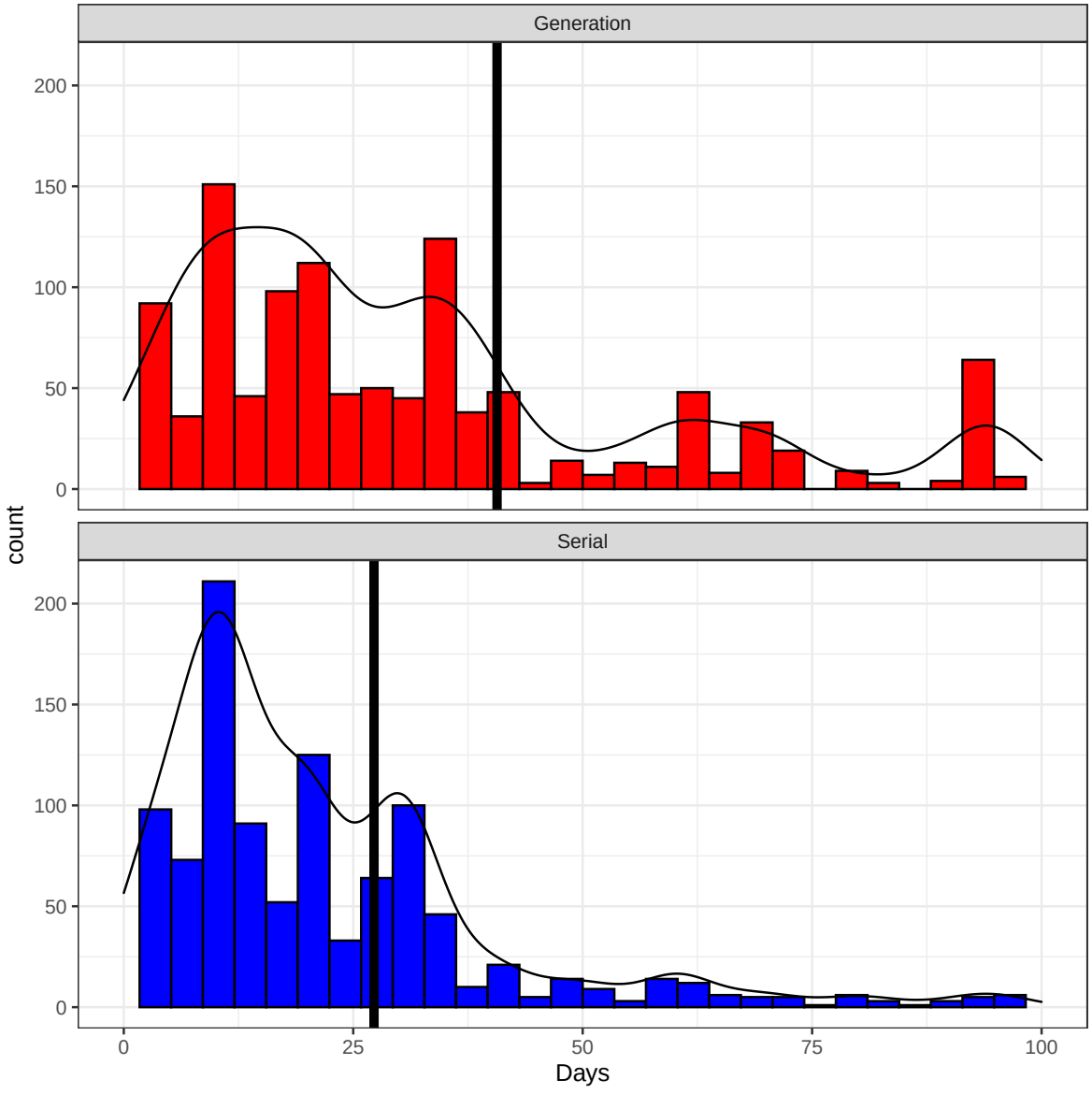


Serial intervals

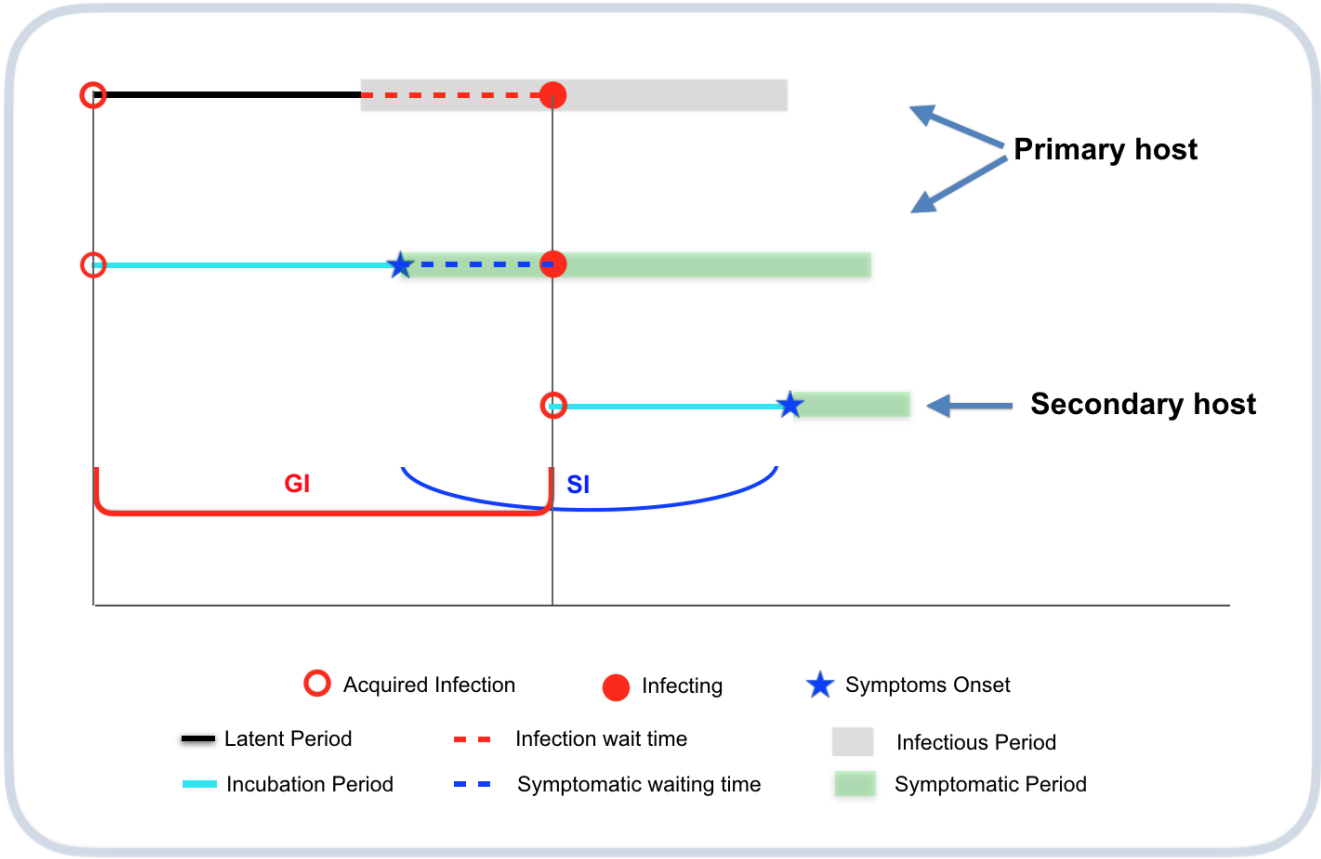
- Do serial intervals and generation intervals have the same distribution?
- It seems that they should: they describe generations of the same process
  - But serial intervals can be very different
  - Even negative! You might report to the clinic with flu before me, even though I infected you

Rabies

- If symptoms always start *before* infectiousness happens, then serial interval should equal generation interval:
  - incubation time + extra latent time + waiting time
  - extra latent time + waiting time + incubation time

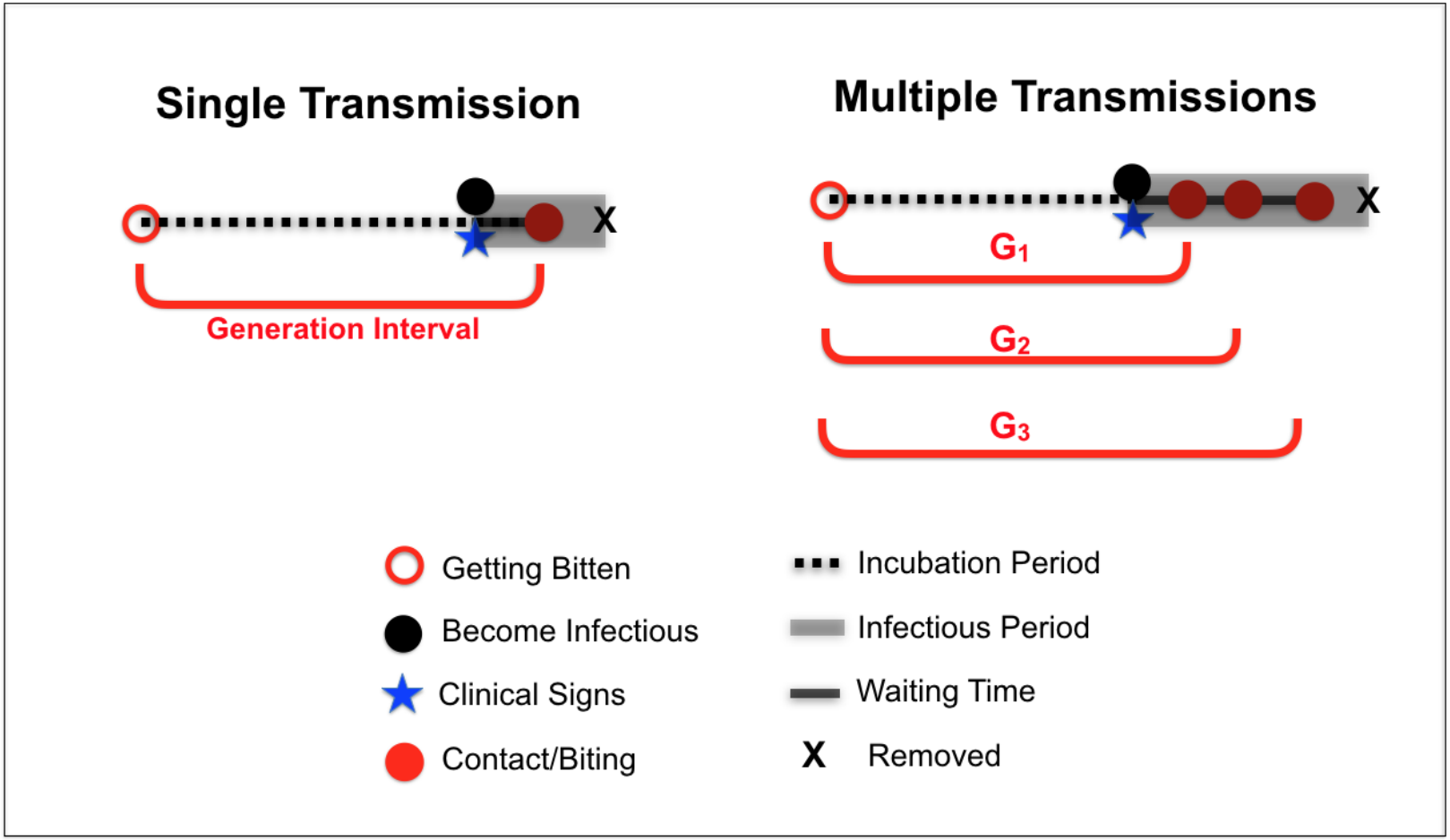

Generation
Serial
count
Days
0
50
100
150
200
0
25
50
75
100

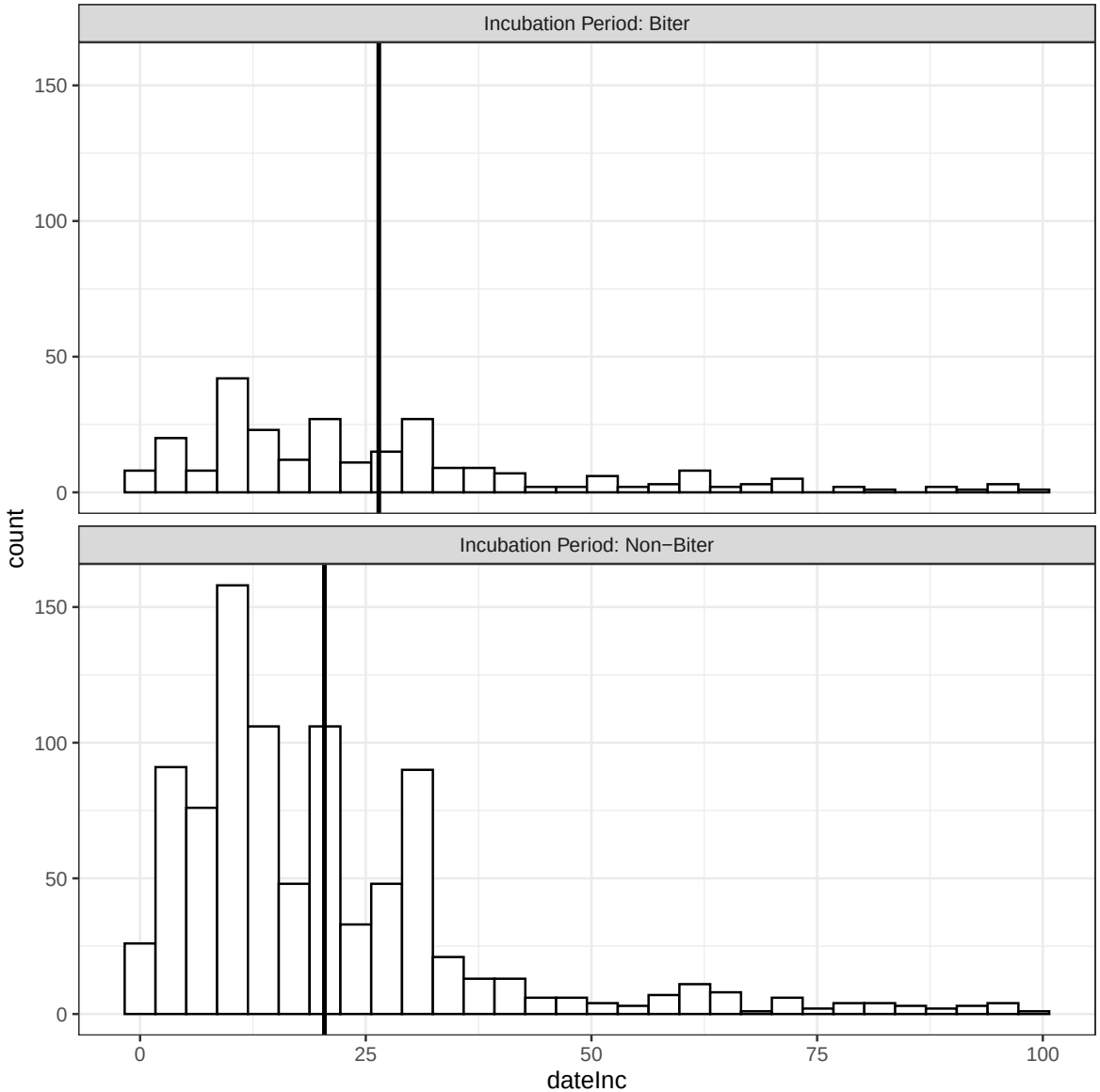
Serial interval anomaly



What if individuals aren't homogeneous?

Observed intervals

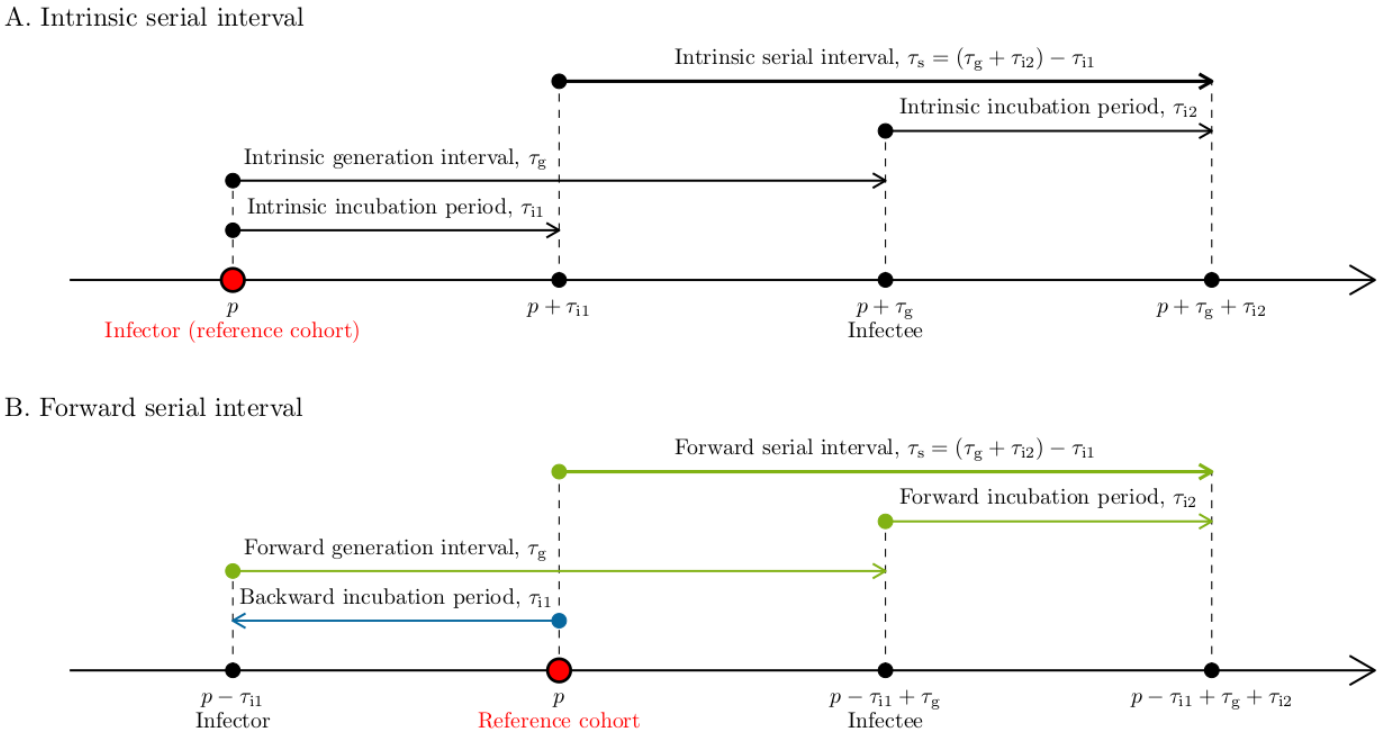



Incubation Period: Biter
Incubation Period: Non−Biter
count
dateInc
0
50
100
150
0
25
50
75
100

The link paradox

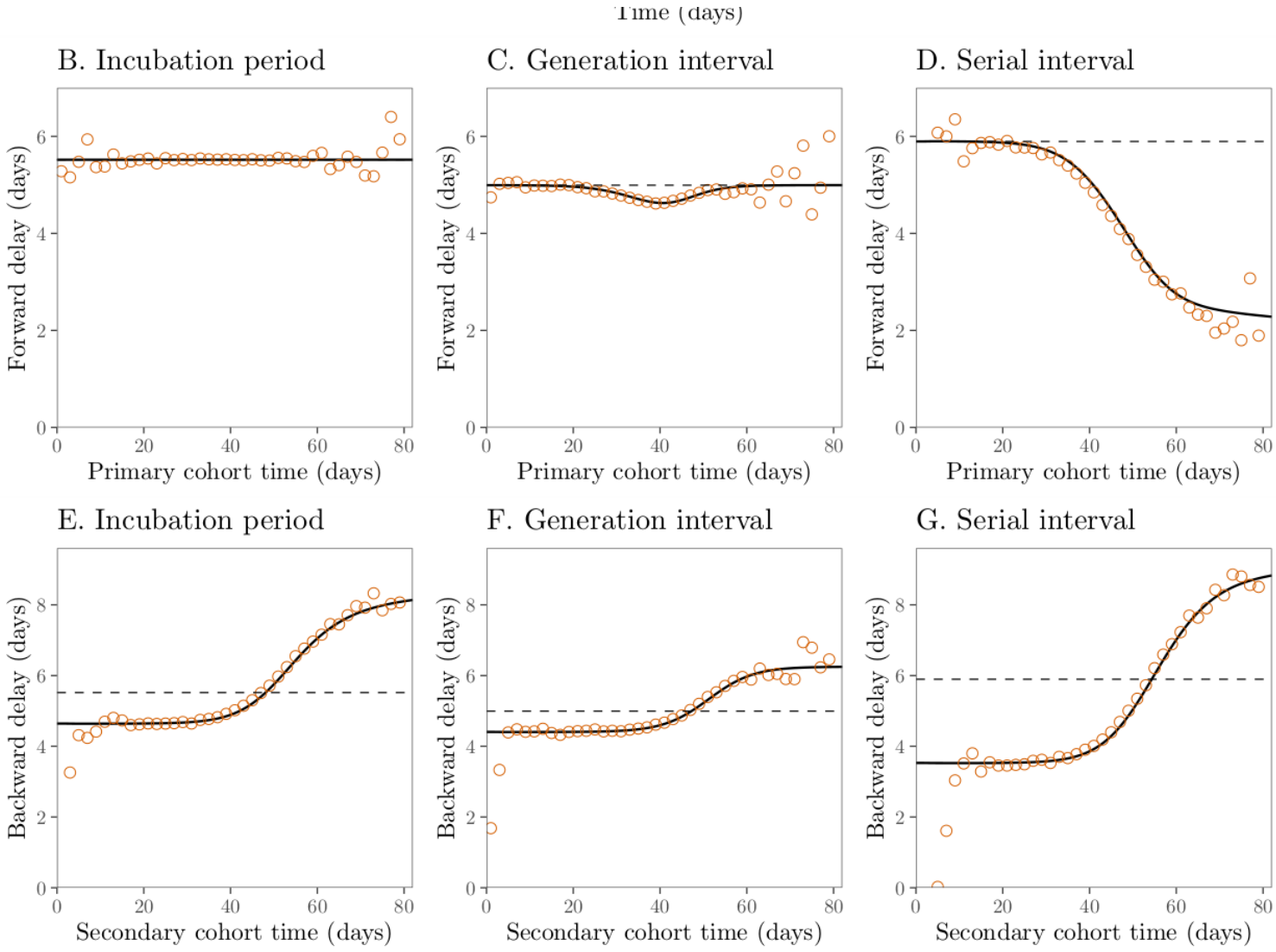
- Imagine a renewal process where symptoms in the infector cause symptoms in the infectee
  - Assume homogeneity
- This has to match the same $r\mathcal{R}$ link as the true process
- But it also can't (because the serial interval is in general broader than the generation interval)

The forward serial interval



- Dynamical effects mean that the forward serial interval is shortened!

Observed epidemiological intervals



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

Outline

Modeling disease spread

Linking strength and speed

Estimating transmission intervals
- Generations through time
- Generations in space
- Serial intervals

The speed paradigm

Real-time evaluation

The speed paradigm

- Why are people scrambling to estimate $\mathcal{R}$ and mostly ignoring r?
  - History
  - Equilibrium and herd immunity
  - Modelers gotta model

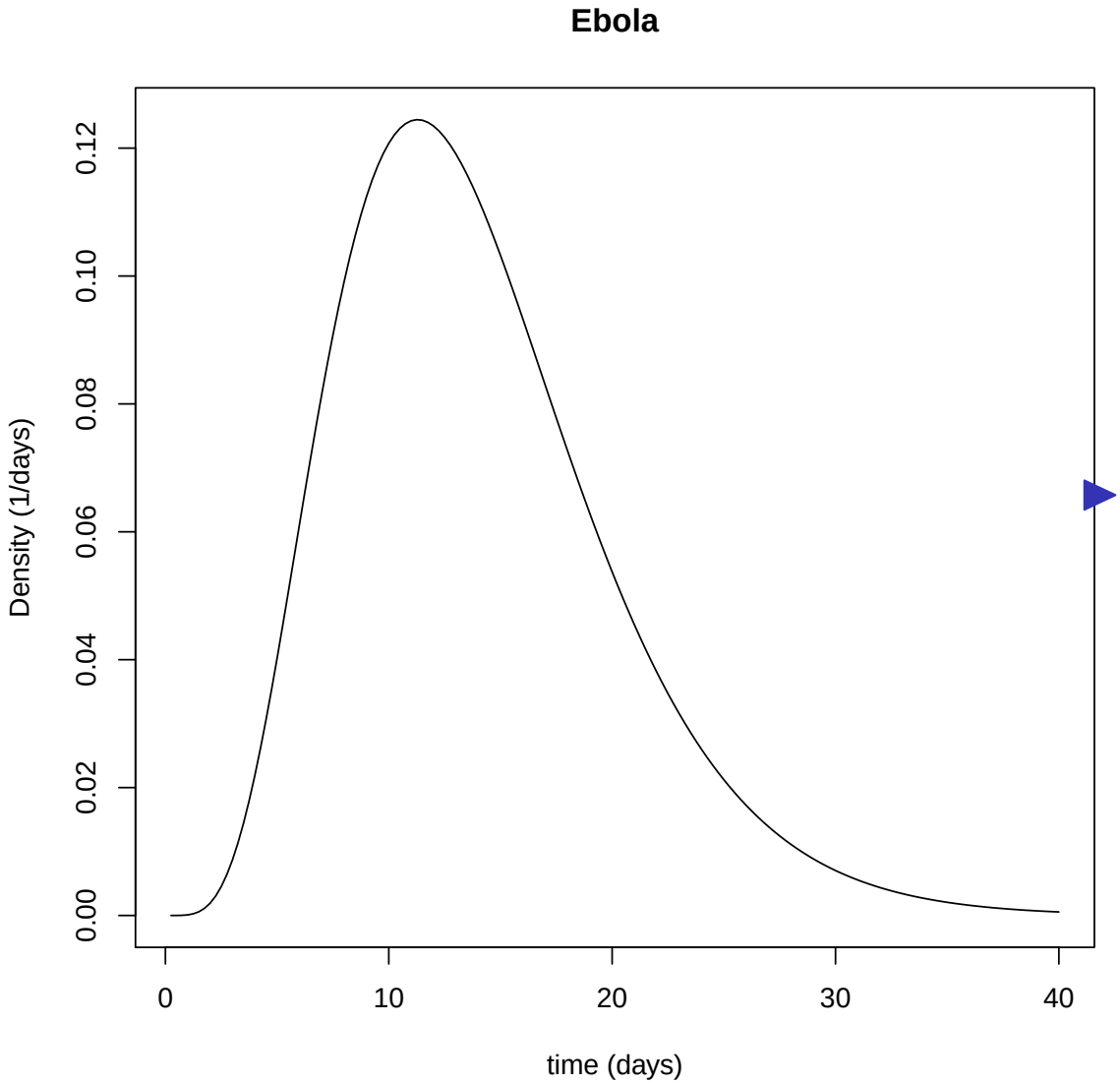
The strength paradigm

- $\mathcal{R} > 1$ is a threshold
- If we can reduce transmission by a constant *factor* of $\theta > \mathcal{R}$, disease can be controlled
- In general, we can define θ as a (harmonic) mean of the reduction factor over the course of an infection
  - weighted by the *intrinsic* generation interval
- Epidemic is controlled if $\theta > \mathcal{R}$
- More direct information about long term (tells us about final size, equilibrium)

The speed paradigm

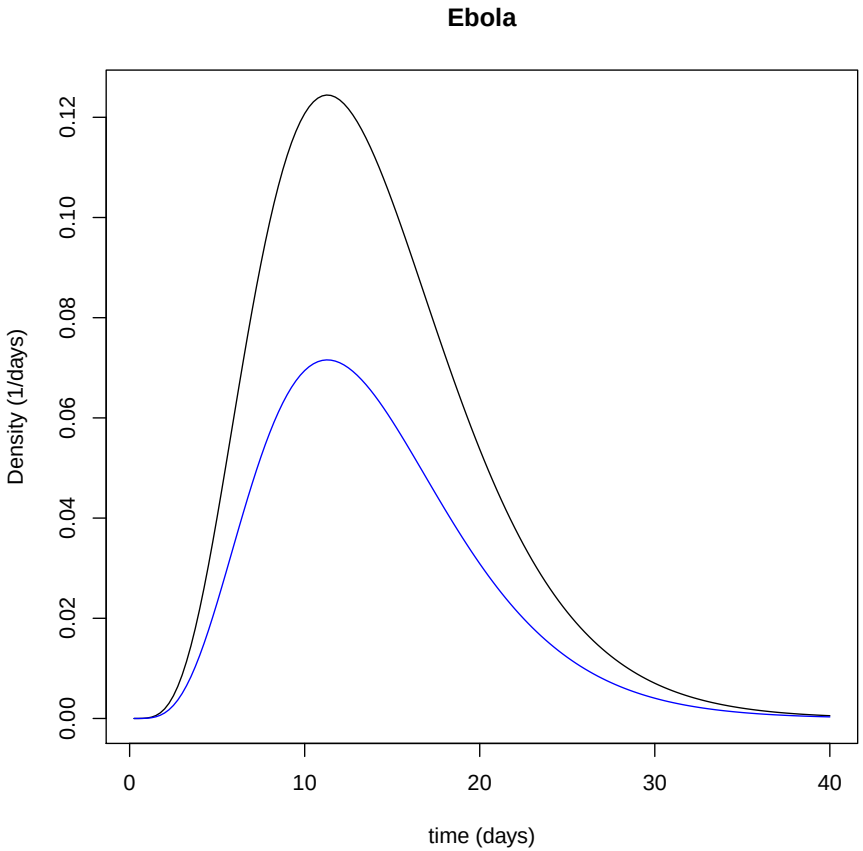
- $r > 0$ is a threshold
- If we can reduce transmission at a constant *hazard rate* of $\phi > r$, disease can be controlled
- In general, we can define ϕ as a (very weird) mean of the reduction factor over the course of an infection
  - weighted by the *backward* generation interval
- Epidemic is controlled if $\phi > r$
- More direct information about short term (tells us about, um, speed)

Epidemic strength (present)



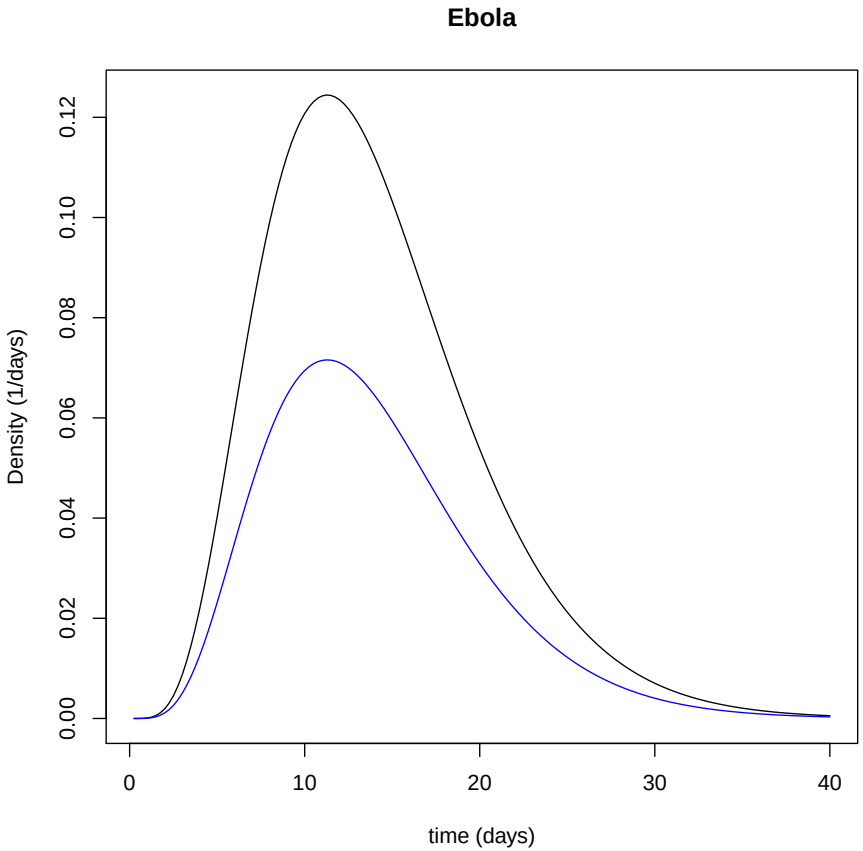
- $\mathcal{R}$, the epidemic strength, is the area under the curve.

Strength of intervention



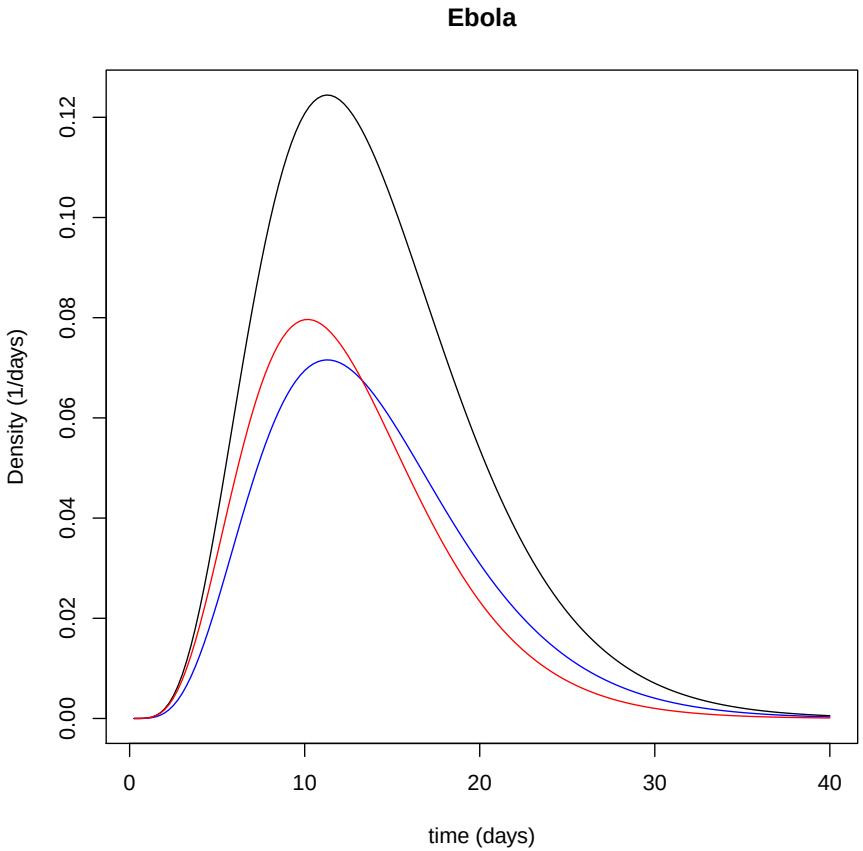
- . . . by what factor do I need to reduce this curve to eliminate the epidemic?

Strength-like interventions



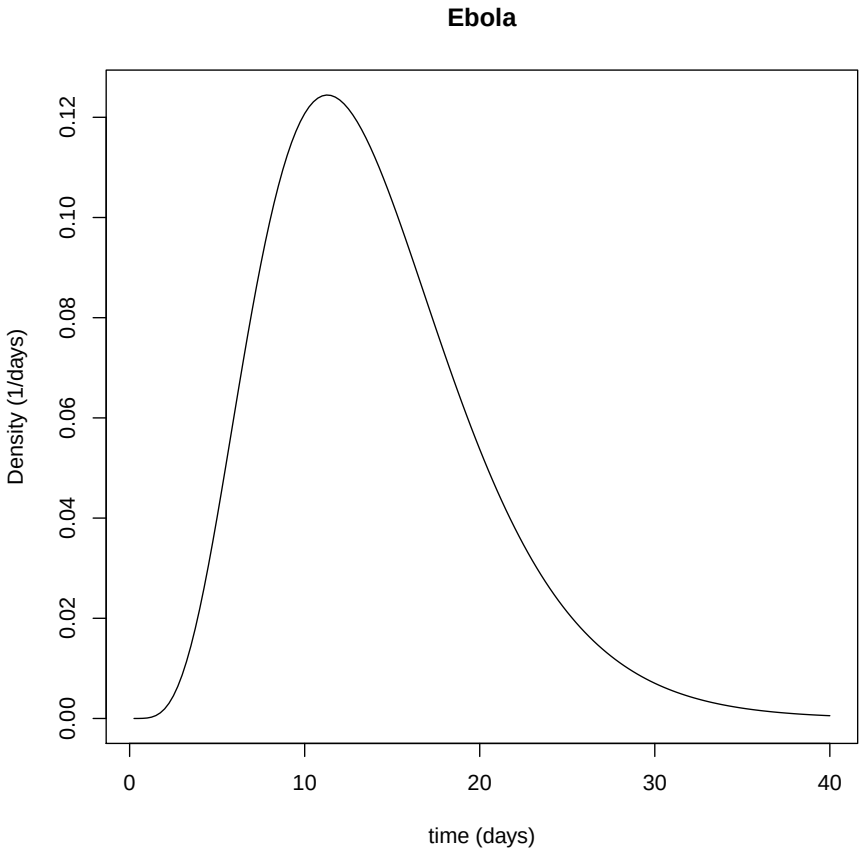
- idealized vaccination
- removes a fixed proportion of people

Speed-like interventions



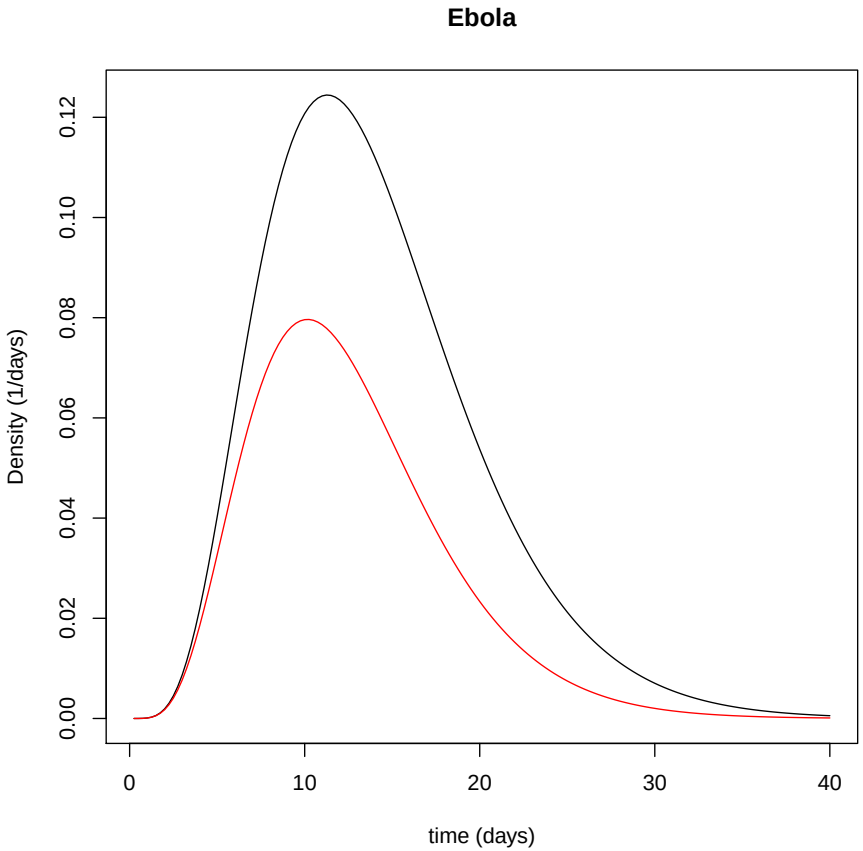
- idealized quarantine
- removes people at a fixed rate

Epidemic speed



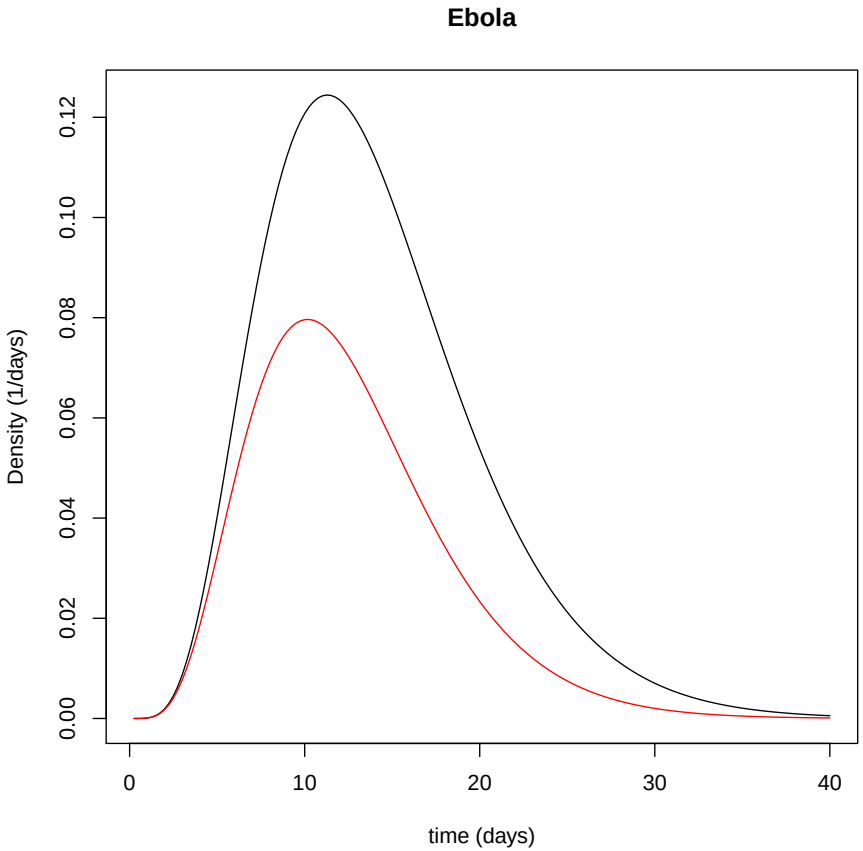
- r, the epidemic speed, is the "discount" rate required to balance the tendency to grow

Epidemic speed



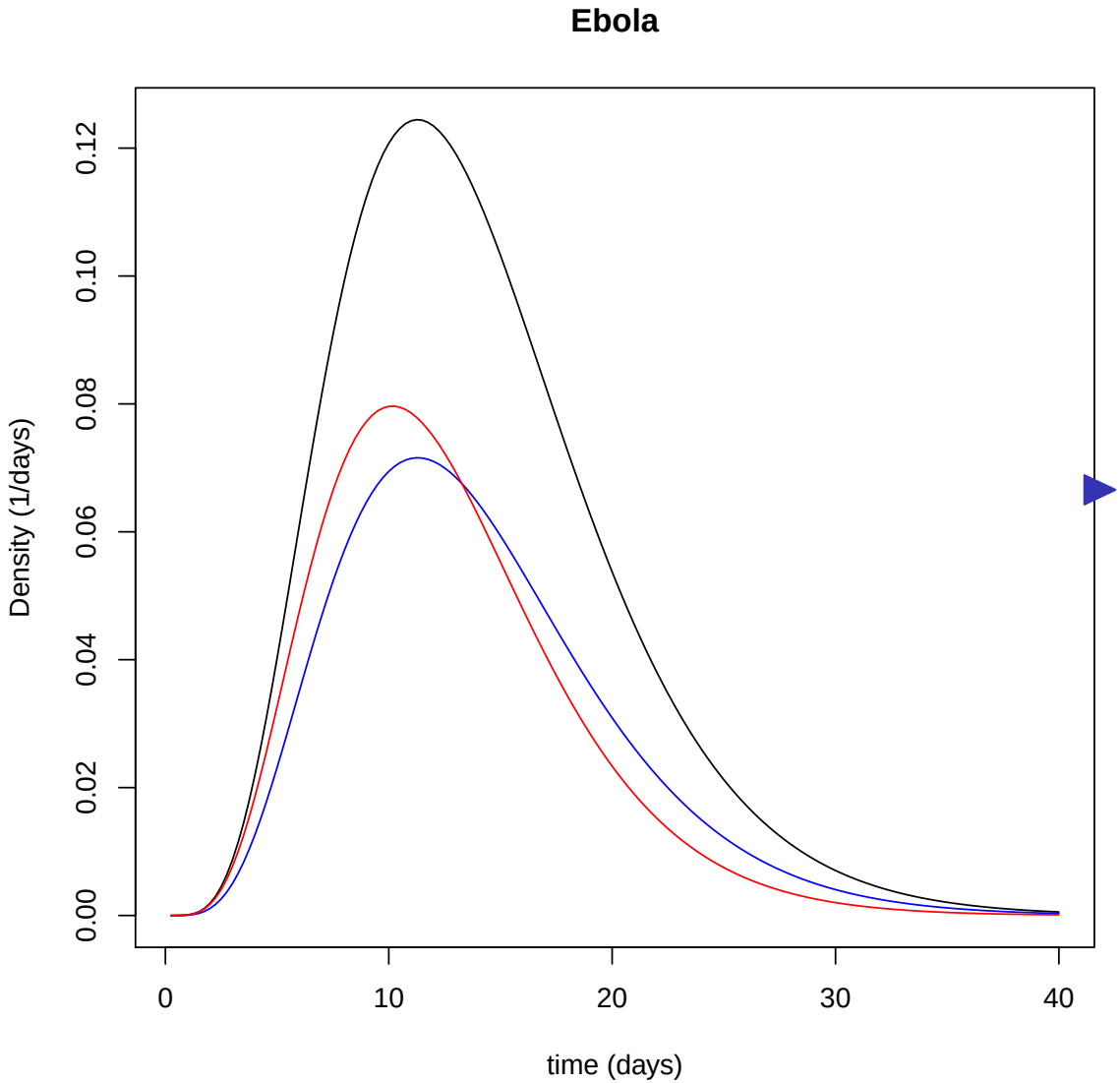
- $k(\tau) = \exp(r\tau)b(\tau)$, where $b(\tau)$ is the initial backward generation interval

Speed of intervention



- . . . how *quickly* do I need to reduce this curve to eliminate the epidemic?

Different interventions (present)



- Sometimes it's easier to estimate strength, sometimes speed

Measuring the intervention

Measuring the intervention

- We imagine an intervention that takesj
- Assume the intervention takes
  - $k(\tau) \to \hat{k}(\tau)$
- Instantaneous strength of intervention is $L(\tau) = k(\tau)/\hat{k}(\tau)$
- Instantaneous speed of intervention is $h(\tau) = \frac{dL(\tau)}{L(\tau)d\tau}$

The strength paradigm

- $k(\tau) = \mathcal{R}g(\tau)$
  - g is the intrinsic generation interval
  - $\mathcal{R}$ is the strength of the epidemic
- If $L(\tau) \equiv L$, then $\theta = L$ is the strength of the intervention
- In general, θ is a (harmonic) mean of L
  - weighted by $g(\tau)$, but not affected by $\mathcal{R}$.
- Epidemic is controlled if $\theta > \mathcal{R}$

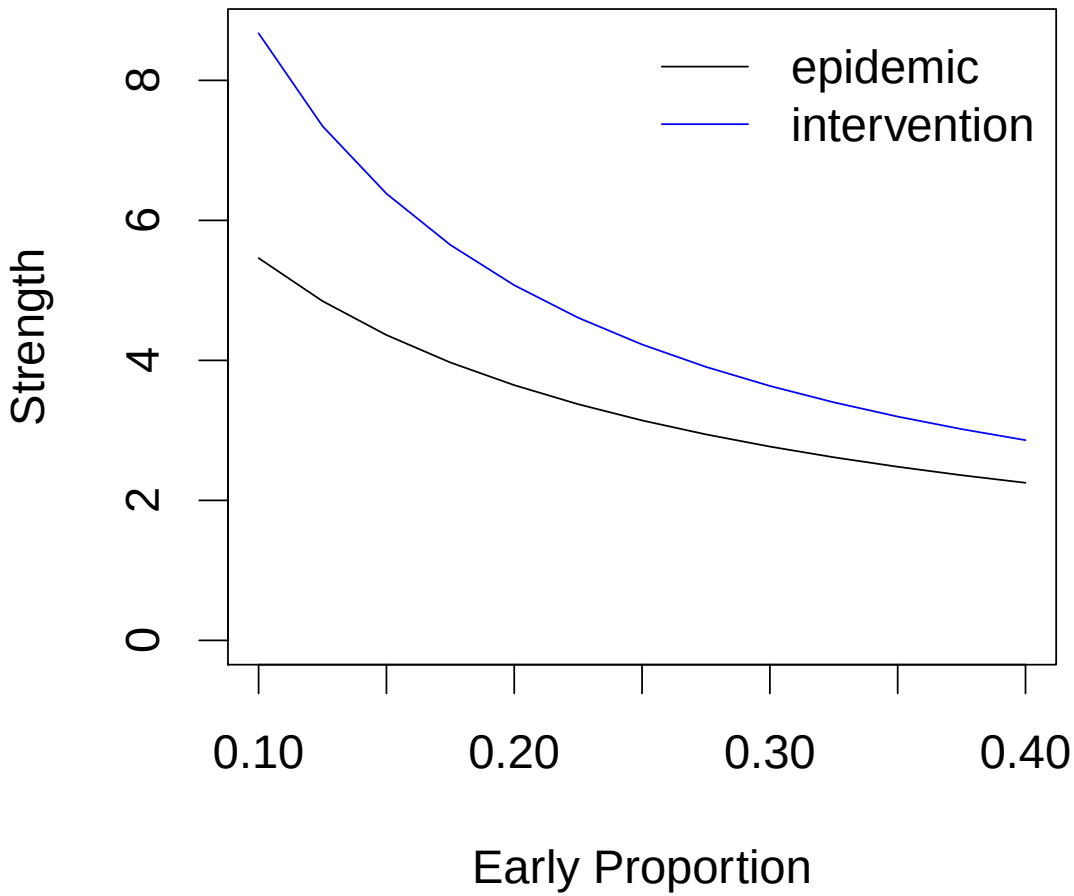
The speed paradigm

- $k(\tau) = \exp(r\tau)b(\tau)$,
  - r is the speed of the epidemic
  - b is the initial backward generation interval
- If $h(\tau) \equiv h$, then $\phi = h$ is the speed of the intervention
- In general, ϕ is a (weird) mean of h
  - weighted by $b(\tau)$, but not affected by r.
- Epidemic is controlled if $\phi > r$

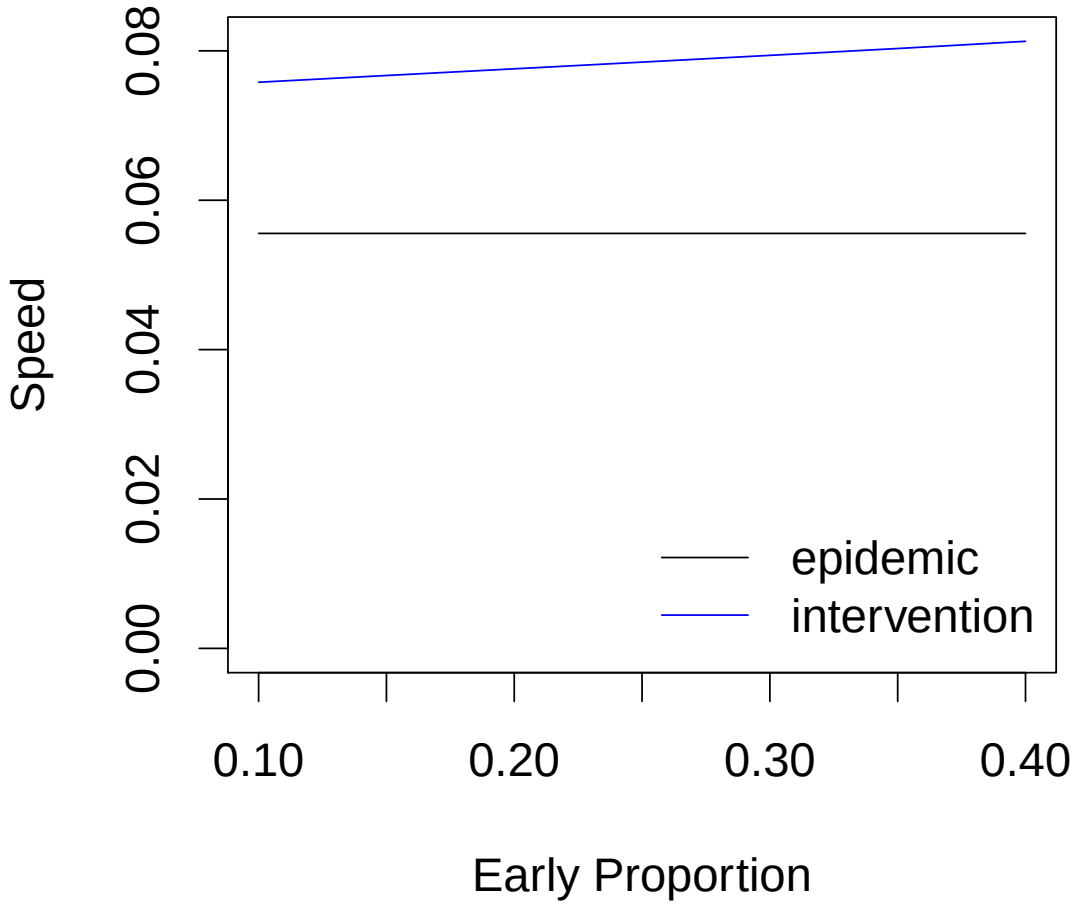
HIV

- The importance of transmission speed to HIV control is easier to understand using the speed paradigm
  - We know the speed of invasion
    - $\approx 0.7/\mathrm{yr}$
    - Characteristic scale $\approx 1.4\mathrm{yr}$
  - And can hypothesize the speed of intervention
    - Or aim to go fast enough

HIV test and treat



HIV test and treat



Coronavirus outbreak

- What do we think if the pathogen is actually quicker than we thought?
  - e.g., more pre-symptomatic transmission
- Initial speed is well known $\Longrightarrow$
- Estimate of invasion strength goes down
  - easier to control by universal changes like masking
- Does not change estimate of invasion speed
  - Puts more *weight* on what happens earlier in infection
  - Good news for event-based screening
  - Bad news for symptom-based screening

Outline

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The speed paradigm

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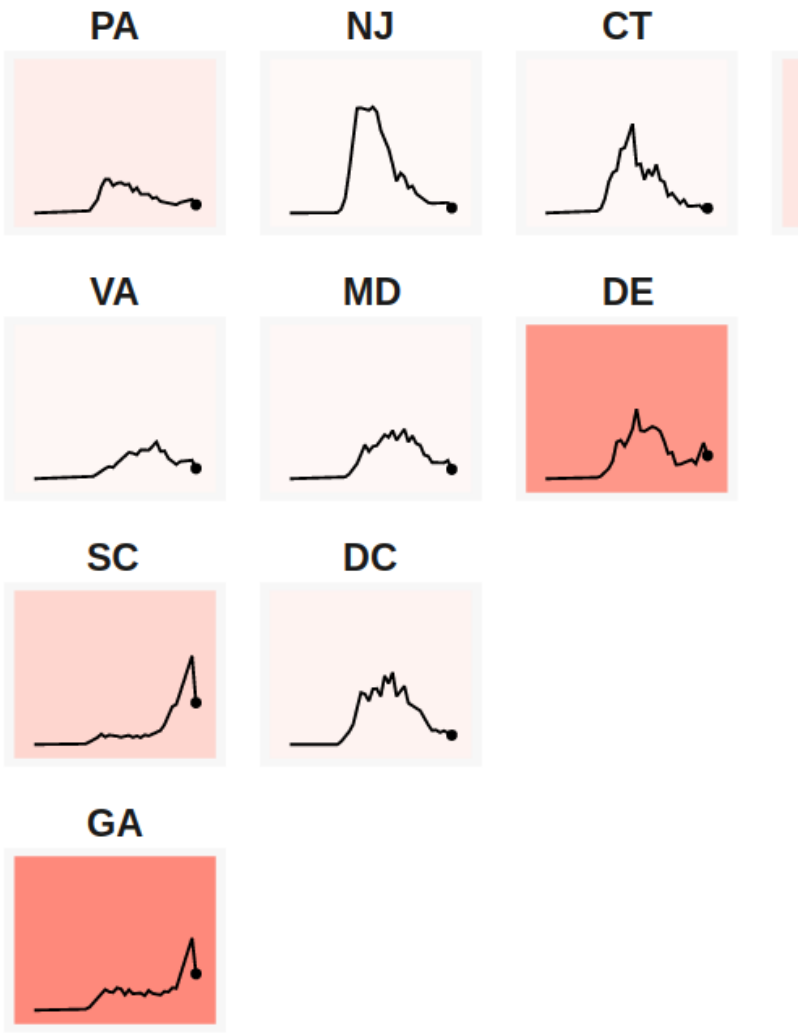
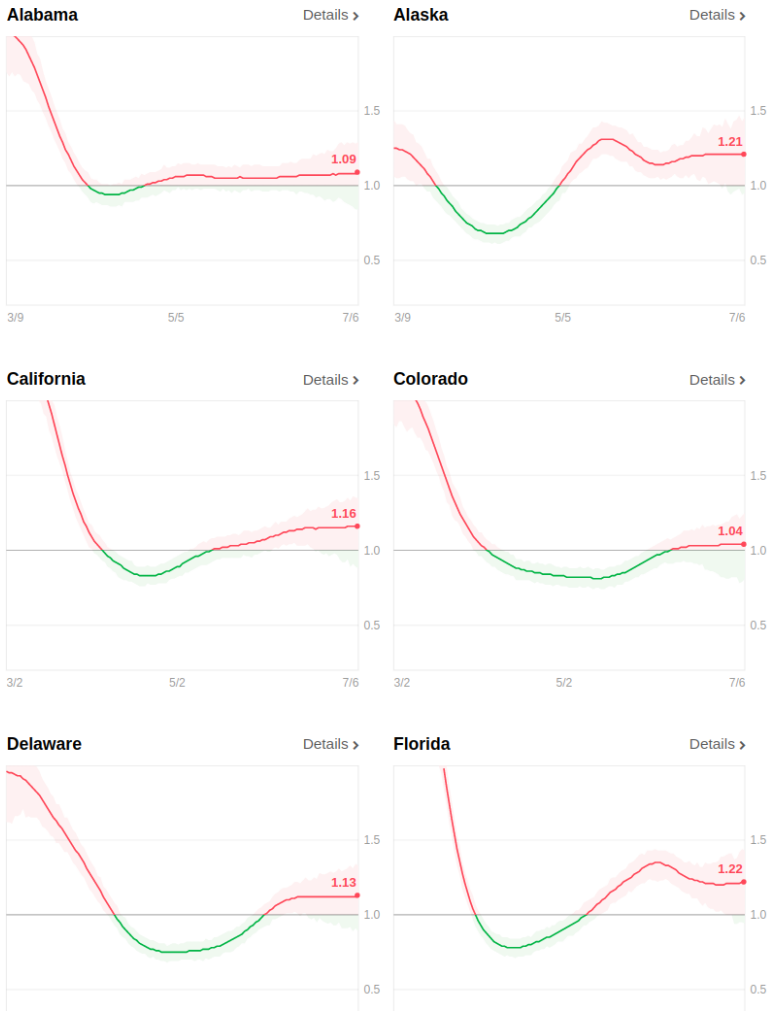
How are conditions changing through time?



https://coronavirus.jhu.edu 2020 Jul 08

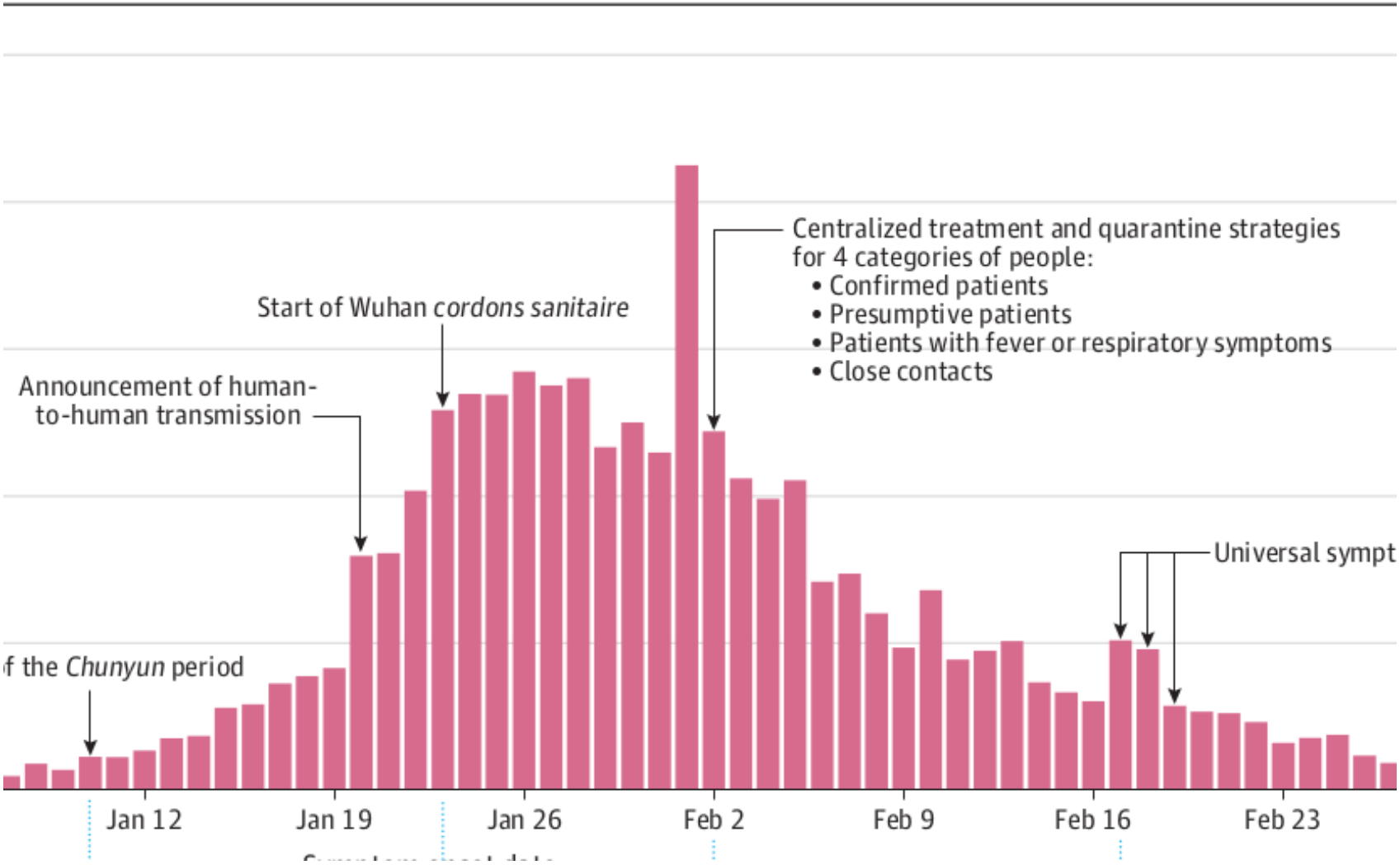


https://rt.live 2020 Jul 08

Using available data

- Time distributions are hard to measure
  - Infection date $\Longrightarrow$ Symptom onset date $\Longrightarrow$ Sample collection date $\Longrightarrow$ Test conducted $\Longrightarrow$ Test result recorded
- Deconvolution is hard

Wuhan control measures

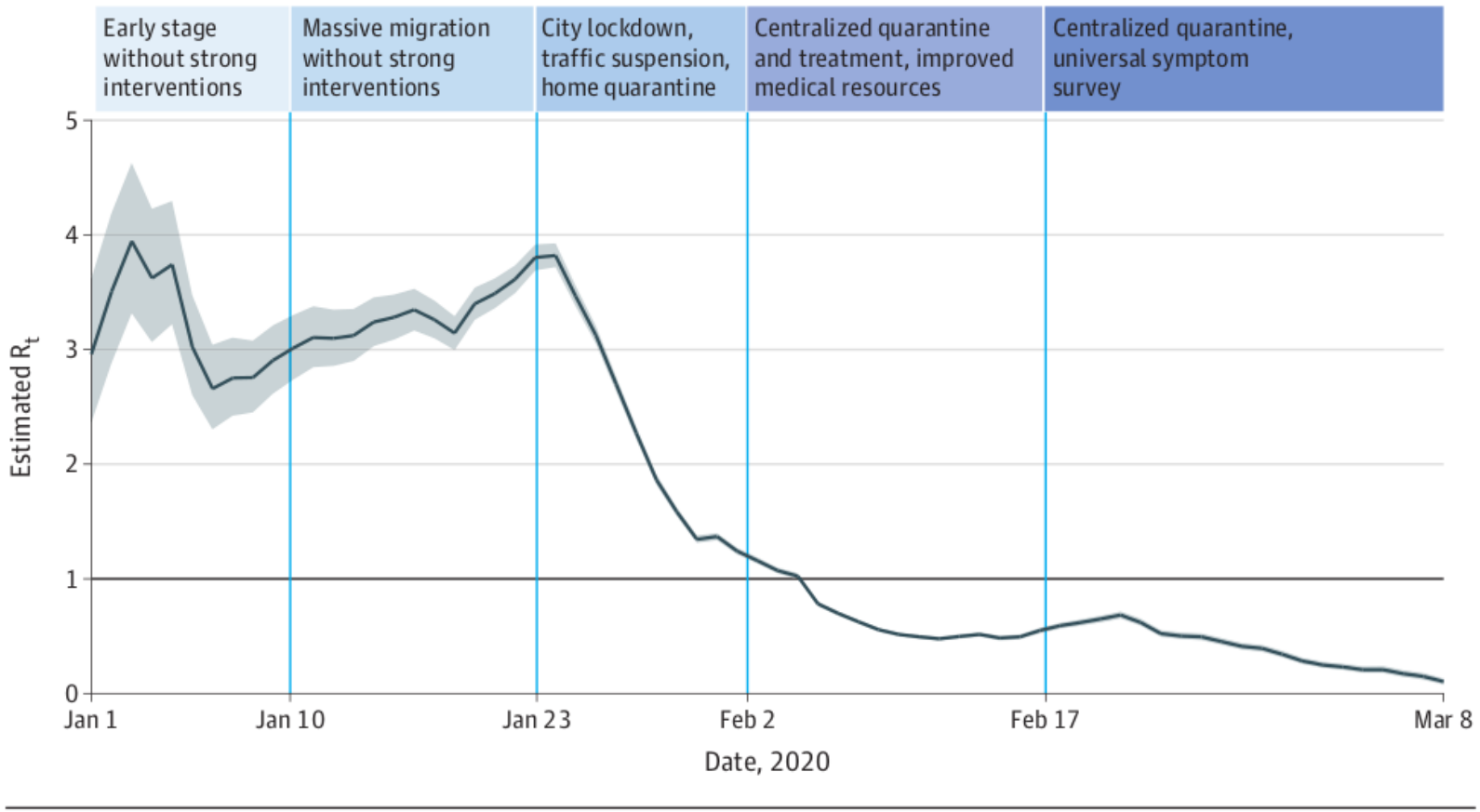


https://jamanetwork.com/journals/jama/fullarticle/2764658

Time-varying reproductive numbers

- Instantaneous $\mathcal{R}_i$ (Cori):
  - $i(t) = \int \mathcal{R}_i(t) g(\tau) i(t-\tau)\, d\tau$
  - Counterfactual: how many cases per case if conditions were frozen at time t
- Case $\mathcal{R}_c$ (Wallinga):
  - $i(t) = \int \mathcal{R}_c(t=\tau) g(\tau) i(t-\tau)\, d\tau$

Wuhan control measures



https://jamanetwork.com/journals/jama/fullarticle/2764658

Shifts

- We could best evaluate current conditions by calculating $\mathcal{R}_i$ using *incidence* data
  - Requires deconvolution
- If transmission is centered at "report" time, using $\mathcal{R}_c$ with report data may be "second-best"

Assumptions

- All current methods assume that (some version of) the generation interval does not change through time!
- This is a good match for 'strength-like' interventions (movement restrictions, masks for all)
- It's a bad match for 'speed-like' interventions (tracing, testing and isolation)

New results

- Speed-like changes cannot be distinguished from strength-like changes using incidence data
  - They can give identical results
- $\mathcal{R}_i(t)$ based on incidence data gives a good measure of effectiveness of strength-like interventions
- $r(t)$ based on incidence data gives a good measure of effectiveness of speed-like interventions
- These insights do not solve the delay and deconvolution problems

Thanks

- CAM and the organizers
- Collaborators:
  - Li, Park, Weitz, Bolker, Earn, Champredon, Gharouni, Papst, Hampson ...
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