

Generation intervals and outbreak fitting

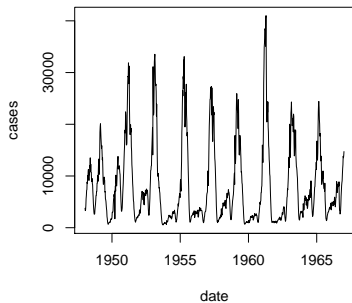
Jonathan Dushoff, McMaster University

BIRS, Nov 2018

Dynamical modeling connects scales

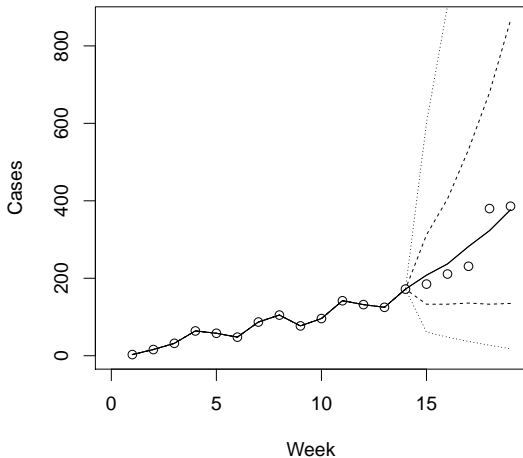


Measles reports from England and Wales



Statistics allows us to evaluate uncertainty

Sierra Leone



Outline

Compartmental models

The $r\mathcal{R}$ relationship

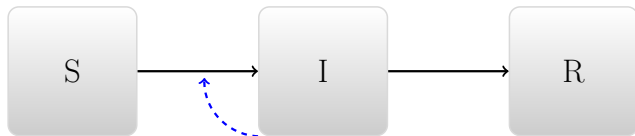
Generation intervals

Generations through time

Other kinds of generation interval

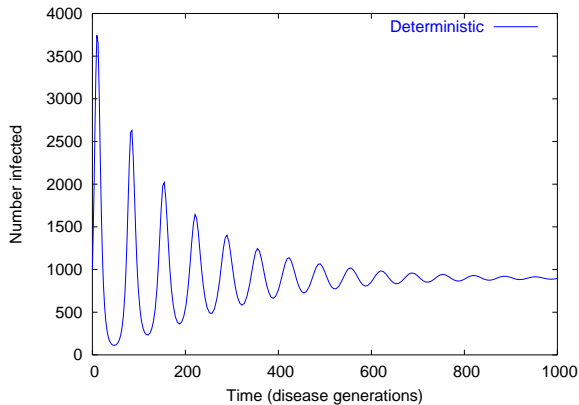
Compartmental models

Divide people into categories:

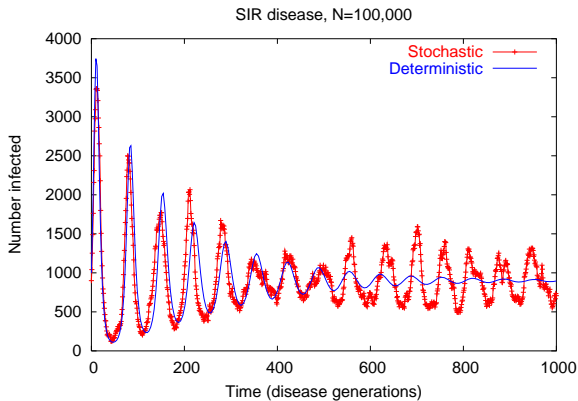


- ▶ Susceptible \rightarrow Infectious \rightarrow Recovered
- ▶ Individuals recover independently
- ▶ Individuals are infected by infectious people

Differential equation implementation



Individual-based implementation



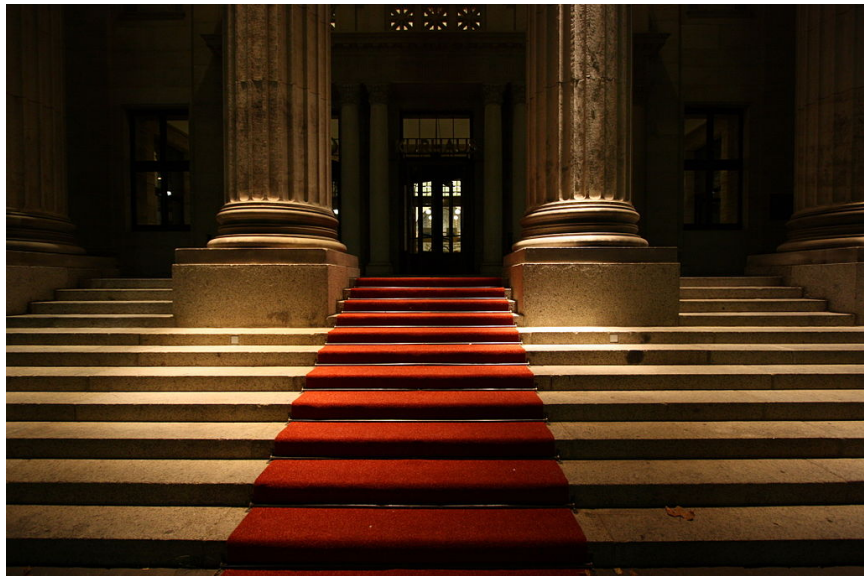
Lessons

- ▶ Tendency to oscillate
- ▶ Thresholds
- ▶ Exponential growth

Big \mathcal{R}

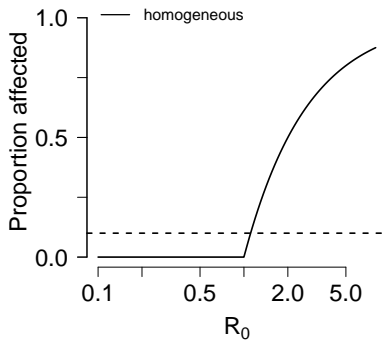
- ▶ \mathcal{R} is the number of people who would be infected by an infectious individual *in a fully susceptible population*.
- ▶ $\mathcal{R} = \beta/\gamma = \beta D = (cp)D$
 - ▶ c : Contact Rate
 - ▶ p : Probability of transmission (infectivity)
 - ▶ D : Average duration of infection
- ▶ A disease can invade a population if and only if $\mathcal{R} > 1$.
- ▶ Often focus on initial period (may also say \mathcal{R}_0)

Big \mathcal{R}



Yellow fever in Panama

endemic equilibrium



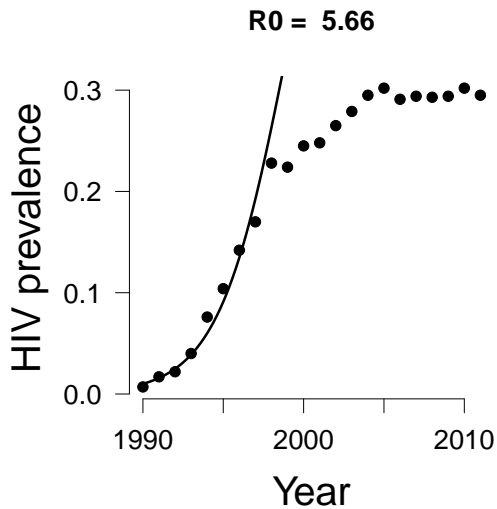
Exponential growth

- ▶ Diseases have a tendency to grow exponentially at first
 - ▶ I infect three people, they each infect 3 people ...
 - ▶ How fast does disease grow?
 - ▶ How quickly do we need to respond?

little r

- ▶ We measure epidemic *speed* using little r :
 - ▶ *Units*: [1/time]
 - ▶ Disease increases like e^{rt}
- ▶ Time scale is $C = 1/r$
 - ▶ Ebola, $C \approx 1\text{month}$
 - ▶ HIV in SSA, $C \approx 18\text{month}$
- ▶ Often focus on initial period (may also say r_0)

little r



Limitations

- ▶ Many conclusions from this framework make strong assumptions:
 - ▶ **Spatial homogeneity:** everywhere is the same
 - ▶ **Individual homogeneity:** everyone is the same
 - ▶ and everyone is everywhere
 - ▶ **Temporal homogeneity:**
 - ▶ It doesn't matter how long I've been infected, I'm either infected or not

Outline

Compartmental models

The $r\mathcal{R}$ relationship

Generation intervals

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Other kinds of generation interval

The $r\mathcal{R}$ relationship

- ▶ We're very interested in the relationship between little r and \mathcal{R} .
- ▶ We might have good estimates of r only
 - ▶ e.g., West African Ebola outbreak, HIV in Africa
- ▶ Or we might have good estimates of \mathcal{R} only
 - ▶ Measles, influenza

Example: Post-death transmission and safe burial

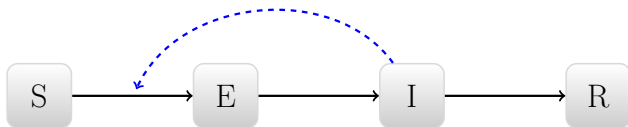
- ▶ How much Ebola spread occurs before vs. after death
- ▶ Highly context dependent
 - ▶ Funeral practices, disease knowledge
- ▶ *Weitz and Dushoff Scientific Reports 5:8751.*



Standard disease model

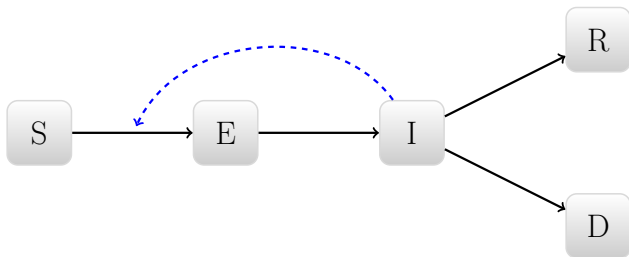


Add a latent period

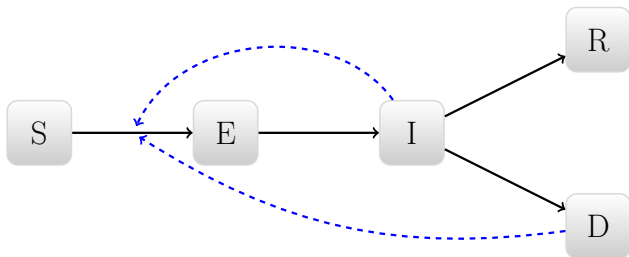


- ▶ (i.e., a lag between infection and infectiousness)

Add post-death transmission



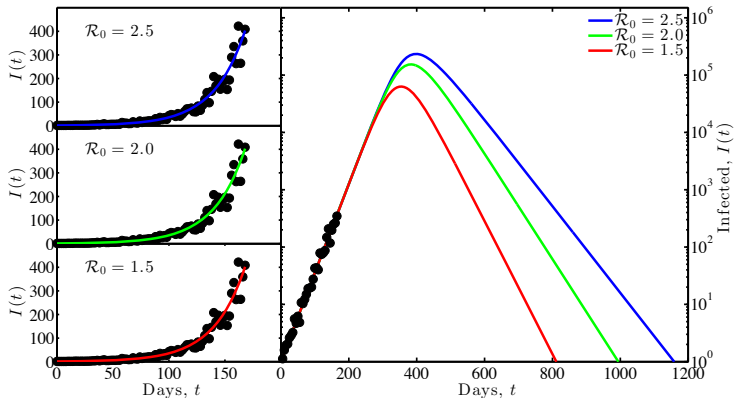
Add post-death transmission



What happens if we account for burial transmission?

- ▶ We've made the disease transmitting process slower, so obviously Ebola is *less* dangerous than we thought
- ▶ We've added another source of transmission, so obviously Ebola is *more* dangerous than we thought
- ▶ What we learn depends on what we know!

What do we know?



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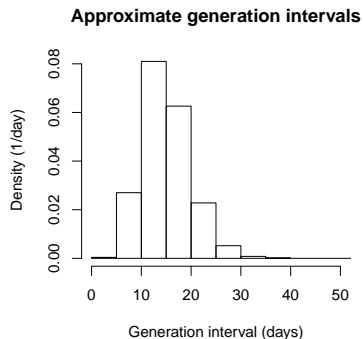
Generation intervals

Generations through time

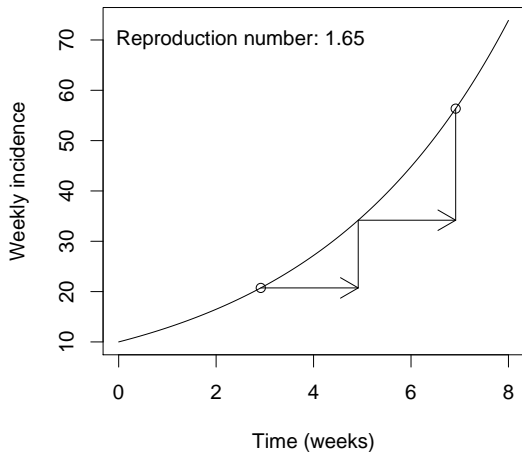
Other kinds of generation interval

Generation intervals

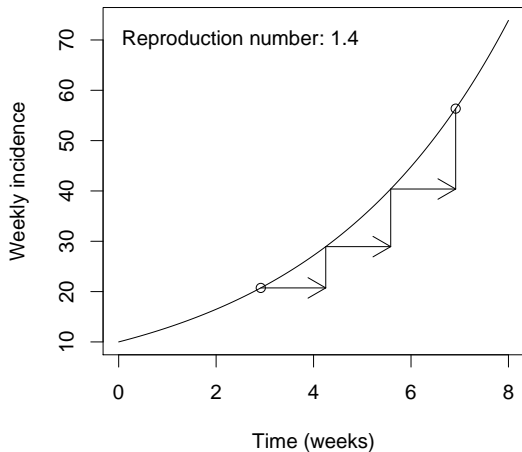
- ▶ The generation distribution measures the time between generations of the disease
 - ▶ Interval between “index” infection and resulting infection
- ▶ Generation intervals provide the link between \mathcal{R} and r



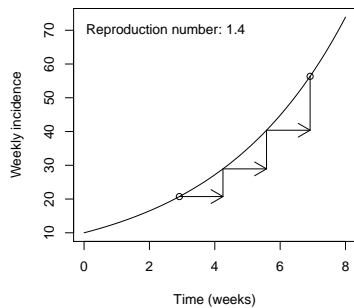
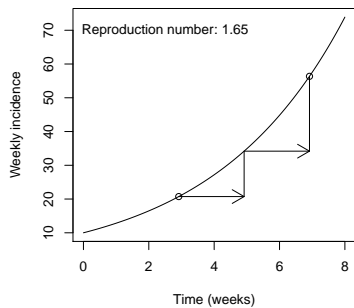
Generations and \mathcal{R}



Generations and \mathcal{R}



Generations and \mathcal{R}



Conditional effect of generation time

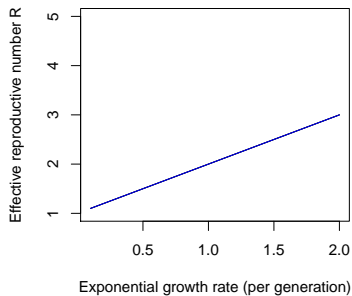
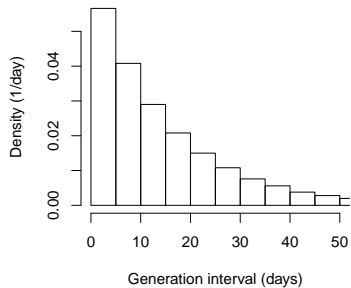
- ▶ *Given* the reproductive number \mathcal{R}
 - ▶ faster generation time G means higher r
 - ▶ More danger
- ▶ *Given* r
 - ▶ faster generation time G means *smaller* \mathcal{R}
 - ▶ Less danger

Linking framework

- ▶ Epidemic speed (r) is a *product*:
 - ▶ (something to do with) generation speed
 - ▶ \times (something to do with) epidemic strength
- ▶ Epidemic strength is therefore (approximately) a *quotient*
 - ▶ Epidemic speed
 - ▶ \div (something to do with) generation speed

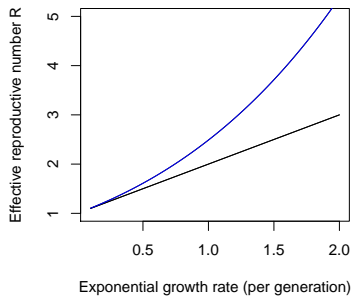
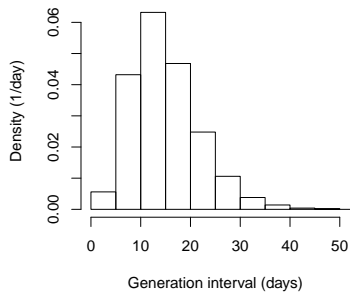
Approximations

Approximate generation intervals



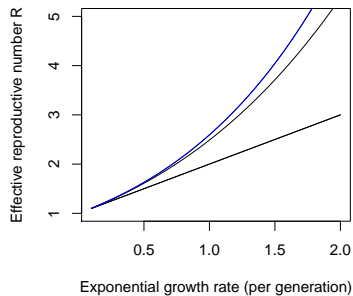
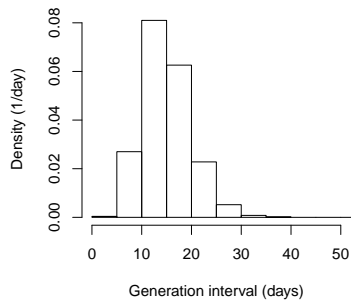
Moment approximation

Approximate generation intervals



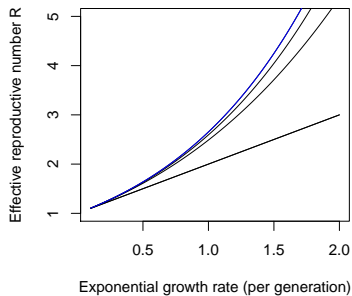
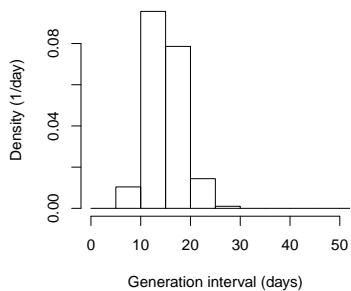
Moment approximation

Approximate generation intervals



Moment approximation

Approximate generation intervals



Compound-interest interpretation

- ▶ Define $\mathcal{R} \approx (1 + r\kappa\bar{G})^{1/\kappa} \equiv X(r\bar{G}; 1/\kappa)$
- ▶ X is the compound-interest approximation to the exponential
 - ▶ Linear when $\kappa = 1$ (i.e., when g is exponential)
 - ▶ Approaches exponential as $\kappa \rightarrow 0$
- ▶ Key quantity is $r\bar{G}$: the relative length of the generation interval compared to the characteristic time scale of spread

Qualitative response

- ▶ For a given value of \bar{G} , smaller values of κ mean:
 - ▶ less variation in generation interval
 - ▶ less compounding of growth
 - ▶ greater \mathcal{R} required for a given r

Intuition

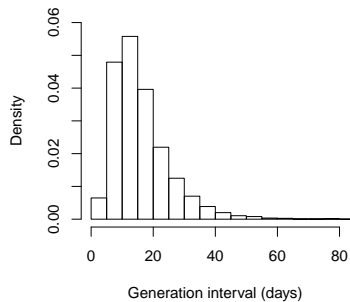
- ▶ Longer generation times mean less speed
 - ▶ \implies more strength, when speed is fixed
- ▶ What about more variation?
 - ▶ More action (both before and after the mean time)
 - ▶ But what happens early is more important in a growing system
- ▶ More variation means more speed
 - ▶ \implies less strength, when speed is fixed

How well do approximations work

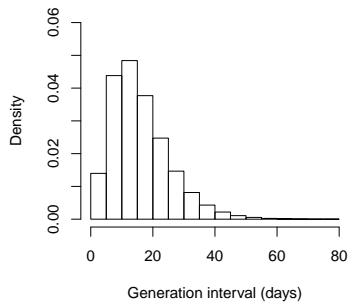
- ▶ Simulate realistic generation intervals for various diseases
- ▶ Compare approximate $r\mathcal{R}$ relationship with known exact relationship
 - ▶ Known because we are testing ourselves with simulated data

Ebola distribution

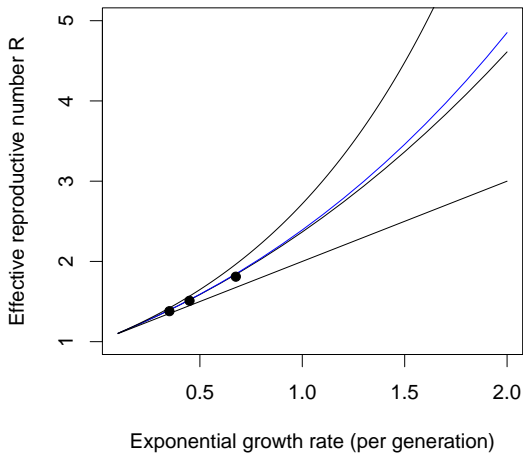
Lognormal SEIR



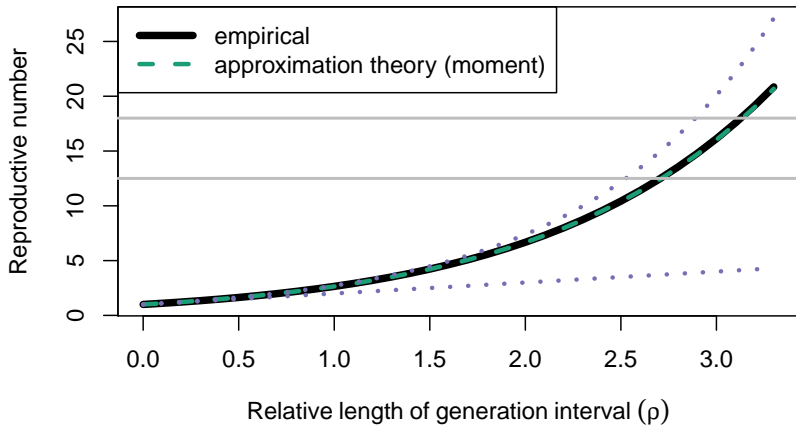
Single-gamma approximation



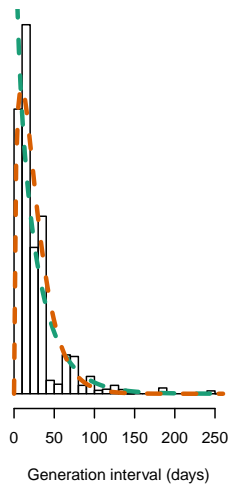
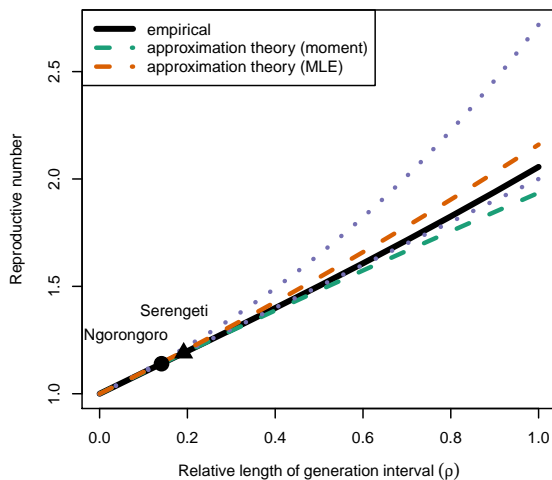
Ebola curve



Measles curve



Rabies curve



Generation intervals



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

Summary

- ▶ Generation intervals are the missing link between r and \mathcal{R}
- ▶ We need better methods for estimating them, and propagating uncertainty to other parts of the model
- ▶ Filtered means may help with intuition
- ▶ For many practical applications:
 - ▶ Estimating the mean generation interval is not enough
 - ▶ But estimating the mean and CV may be enough
 - ▶ A good basis for understanding and propagating uncertainty

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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?

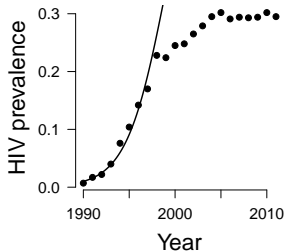
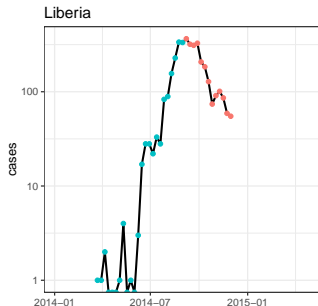
- ▶ Contact-tracing intervals look systematically different, depending on when you observe them.
- ▶ Observed in:
 - ▶ Real data, detailed simulations, simple model
- ▶ Also differ from intrinsic (infectior centered) estimates

Types of interval

- ▶ Define:
 - ▶ *Intrinsic interval*: How infectious is a patient at time τ after infection?
 - ▶ *Realized intervals*: Based on actual transmission events
 - ▶ *Forward*: When will the people infected today infect others?
 - ▶ *Backward*: When did the people who infected people today themselves become infected?
 - ▶ *Censored*: All the intervals observed up until a particular time (e.g., now)

Growing epidemics

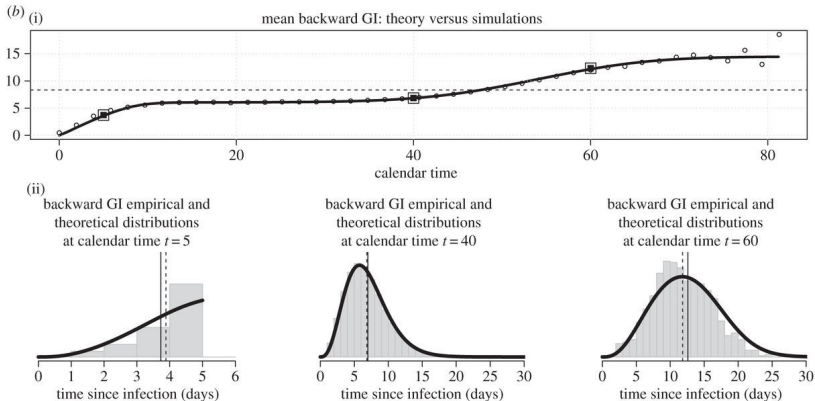
- ▶ Generation intervals look *shorter* at the beginning of an epidemic
 - ▶ A disproportionate number of people are infectious right now
 - ▶ They haven't finished all of their transmitting
 - ▶ We are biased towards observing faster events



What changes backward intervals?

- ▶ Who is likely to infect me depends on:
 - ▶ How infectious they are (intrinsic GI)
 - ▶ How many of them there are (changes in disease incidence)

Backward intervals

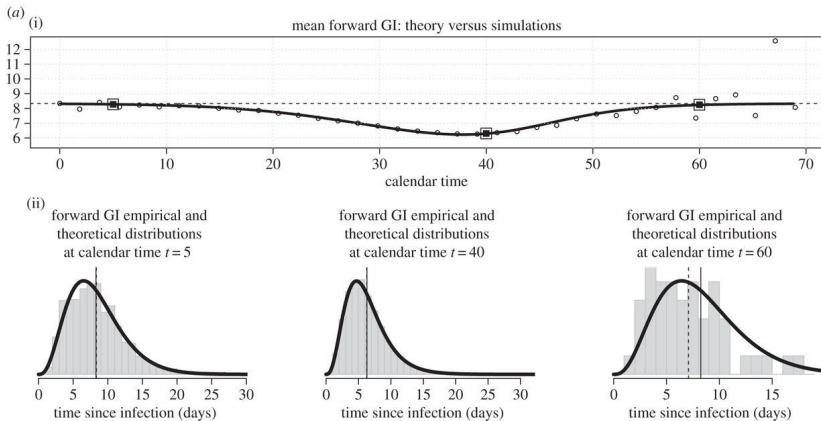


Champredon and Dushoff, 2015. DOI:10.1098/rspb.2015.2026

What changes forward intervals?

- ▶ Who I am likely to infect depends on:
 - ▶ How infectious I am (intrinsic GI)
 - ▶ How many of them there are (changes in numbers of susceptibles)

Forward intervals



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

Conclusion

- ▶ Backward intervals change if the number of infectious individuals is changing as you look back
- ▶ Forward intervals change if the number of *susceptible* individuals is changing as you look forward
- ▶ Lack of care in defining generation intervals can lead to bias
 - ▶ In particular, censored intervals look too short, lead to underestimates of \mathcal{R} .

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Other kinds of generation interval

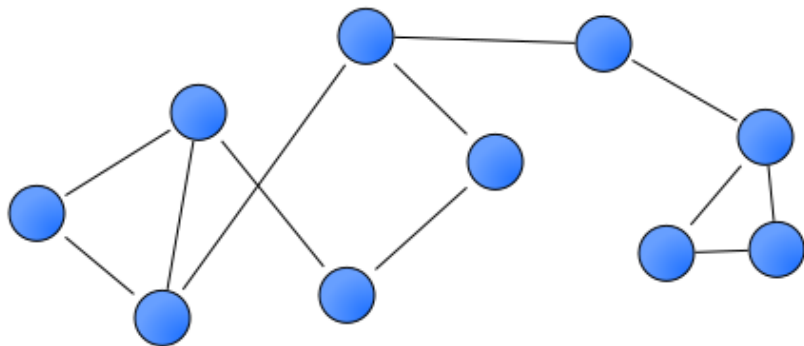


- ▶ Once you think carefully about generation intervals, they're everywhere
- ▶ Spatial heterogeneity
- ▶ Individual heterogeneity

Generations in space

- ▶ How do local interactions affect realized generation intervals?

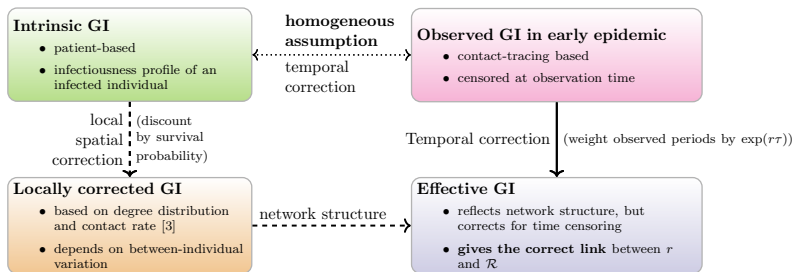
 Individual



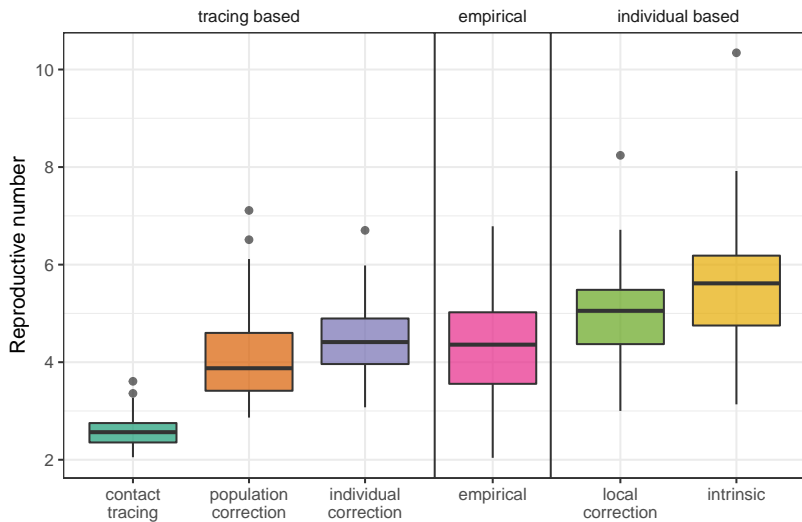
Surprising results

- ▶ \mathcal{R} on networks generally *smaller* than values estimated using r .
 - ▶ *Trapman et al., 2016. JRS Interface*
DOI:10.1098/rsif.2016.0288
- ▶ Because people don't question the intrinsic generation interval
 - ▶ Local interactions
 - ▶ \implies wasted contacts
 - ▶ \implies shorter generation intervals
 - ▶ \implies smaller estimates of \mathcal{R} .

Observed and estimated intervals

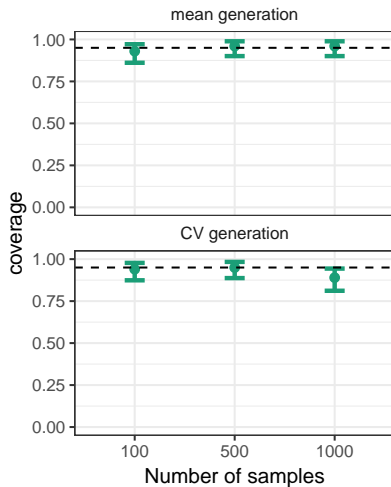


Outbreak estimation

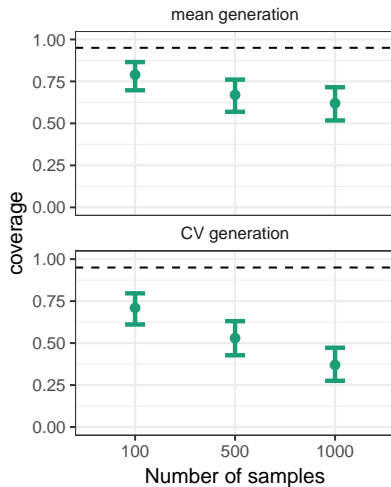


Validation

Gamma kernel

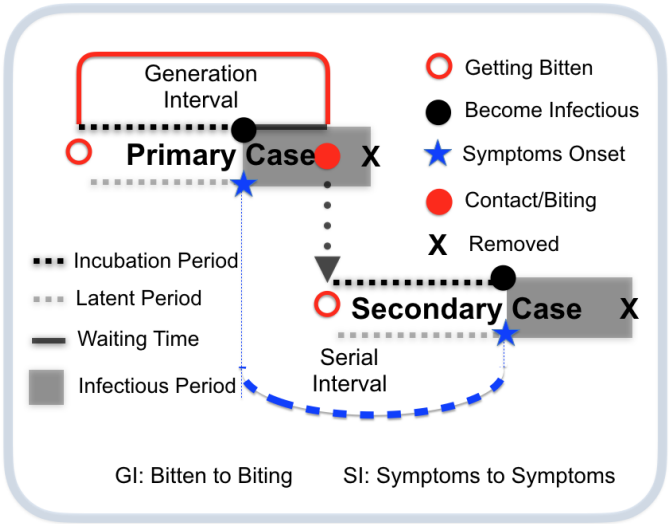


SEIR kernel



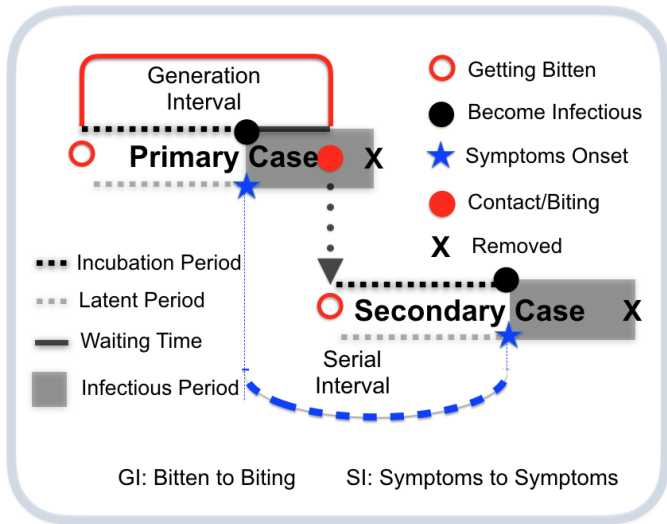
Serial intervals

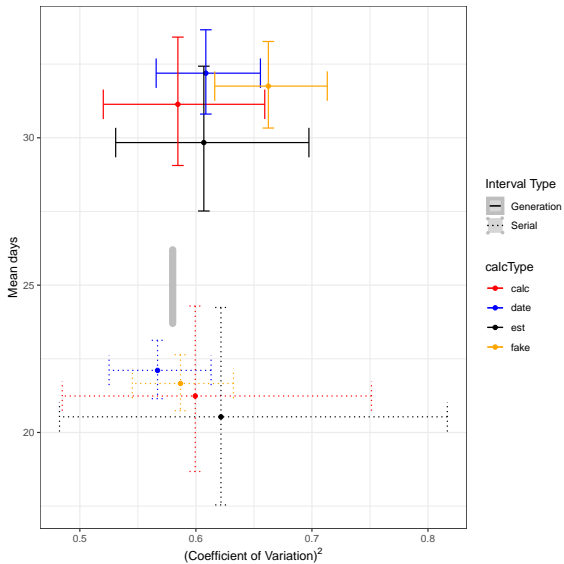
- ▶ Do serial intervals and generation intervals have the same distribution?
- ▶ It seems that they should: they describe generations of the same process
- ▶ In fact, they don't
 - ▶ Serial intervals can even be negative!
 - ▶ You might report to the clinic with flu before me, even though I infected you



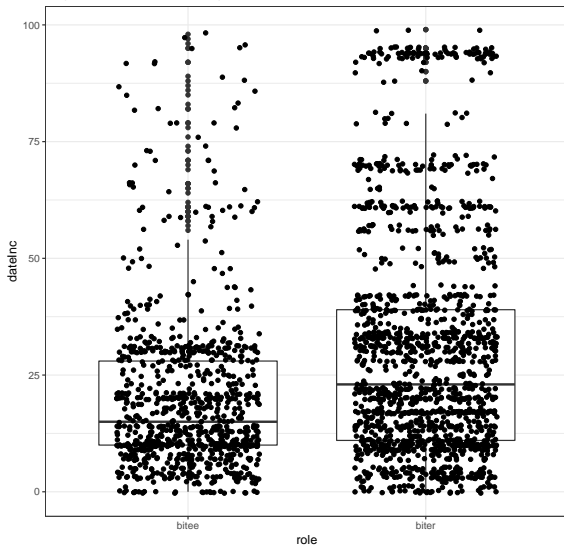
Rabies

- ▶ 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





Repeated biter incubation period



Thanks

- ▶ Organizers and BIRS
- ▶ Collaborators
- ▶ Funders: NSERC, CIHR

Linking framework

- ▶ Epidemic speed (r) is a *product*:
 - ▶ (something to do with) generation speed \times
 - ▶ (something to do with) epidemic strength
- ▶ In particular:
 - ▶ $r \approx (1/\bar{G}) \times \ell(\mathcal{R}; \kappa_g)$
 - ▶ ℓ is the inverse of X