r and $\mathcal{R}$

- Initial growth rate, generation intervals and reproductive numbers in the spread of infectious disease

- ICMA-V
- University of Western Ontario

- Jonathan Dushoff
- McMaster University

Outline

r and $\mathcal{R}$

Time scales and disease risk

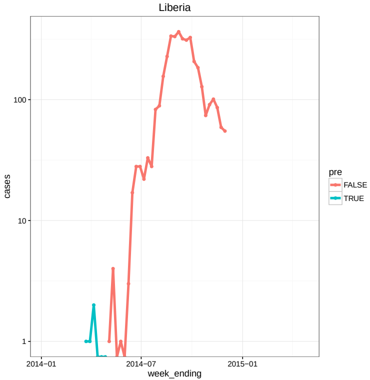
- Post-death transmission and safe burial
- Generation time and disease risk

Generation times and generating functions

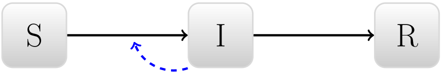
Moment approximations

Conclusion

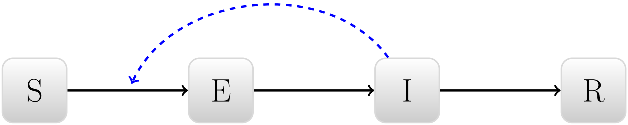
TSUB Disease modeling



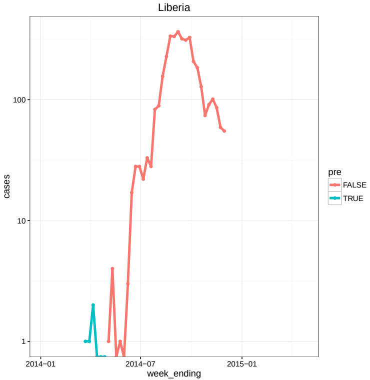
Box models of disease

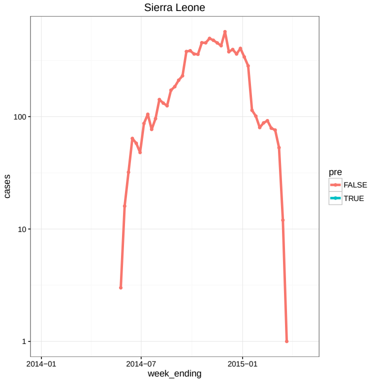


Add an exposed class



Epidemic data





r – the growth rate

- $$i(t) \approx i(0)\exp(rt)$$
- $$T_c = 1/r$$
- $$T_2 = \ln(2)/r$$

- r_0 can be observed early in the epidemic
- r can typically be measured more robustly than $\mathcal{R}$

$\mathcal{R}$ – the reproductive number

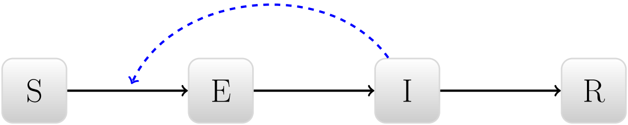
- Expected number of new cases per cases
- $\mathcal{R} = \beta DS/N$
  - Disease increases iff $\mathcal{R} > 1$
- $\mathcal{R}_0 = \beta D$
  - Disease is usually eliminated when $\mathcal{R}_0 < 1$

Outline

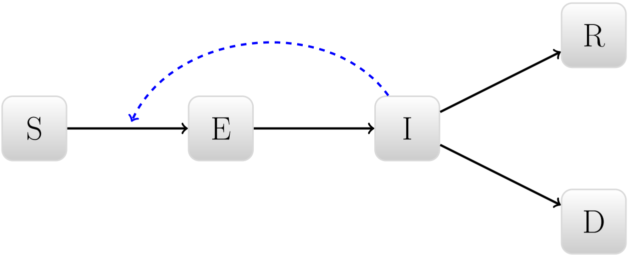
Post-death transmission and safe burial

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

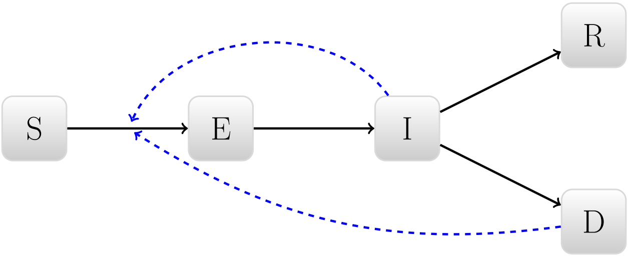
Standard disease model



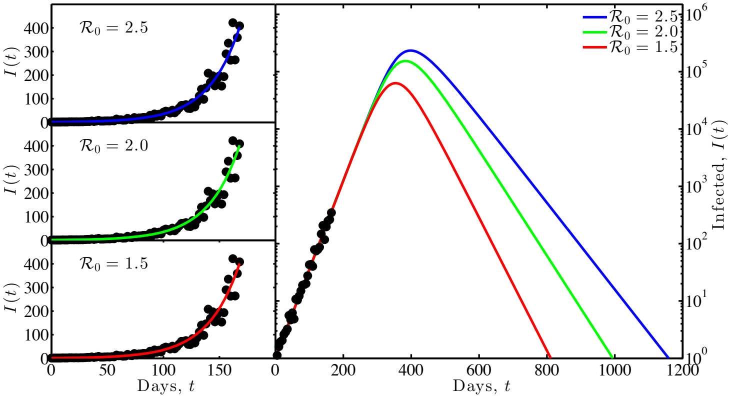
Disease model including post-death transmission



Disease model including post-death transmission



Scenarios



$\mathcal{R}_0 = 2.5$
$\mathcal{R}_0 = 2.0$
$\mathcal{R}_0 = 1.5$
$I(t)$
Days, t
Infected, $I(t)$

Conclusions

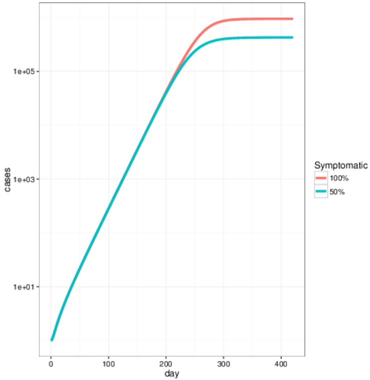
- Different parameters can produce indistinguishable early dynamics
- More after-death transmission implies
  - Higher $\mathcal{R}_0$
  - Larger epidemics
  - Larger importance of safe burials

Generation time and disease risk

- Which is more dangerous, a fast disease, or a slow disease?
  - How are we measuring speed?
  - How are we measuring danger?
  - *What are we conditioning on?*

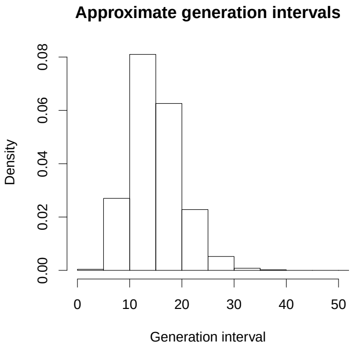
Exponential growth

- The characteristic time scale for Ebola *spread* during the outbreak period was $C \approx 1\,\mathrm{month}$
- In other words, incidence was following $i(t) = i(0)\exp(t/C)$
- Faster $C \implies$ more danger

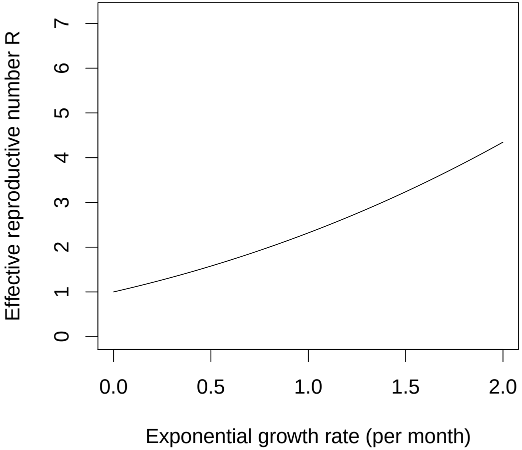


Life cycle

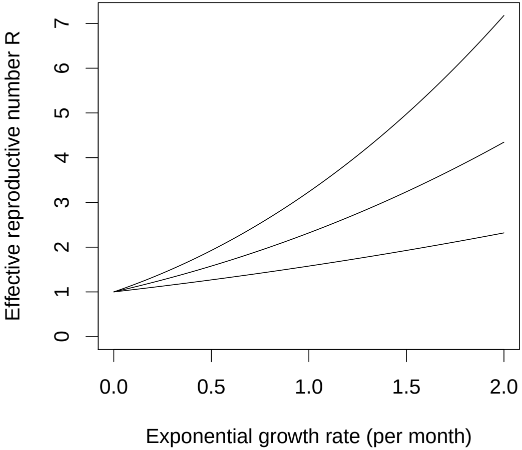
- C is the characteristic time for Ebola *growth* . . .
- G is the generation distribution
  - Interval between "index" infection and resulting infection
- What does G tell us about how dangerous the epidemic is?
  - It depends on what else we know!



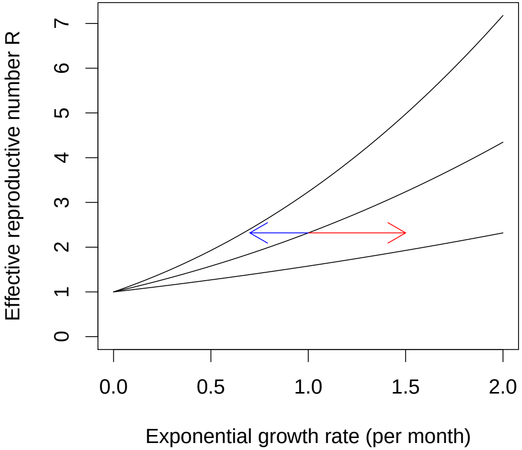
Conditional effect of generation time



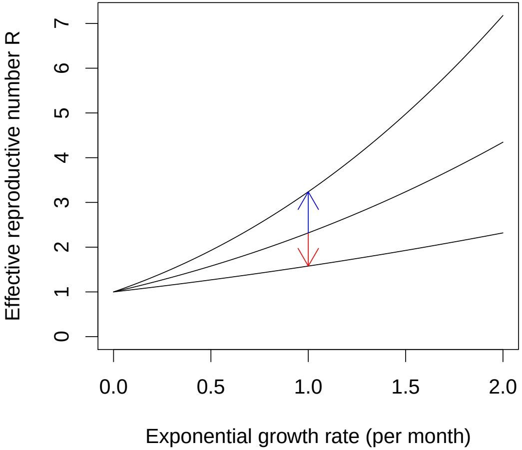
Conditional effect of generation time



Conditional effect of generation time



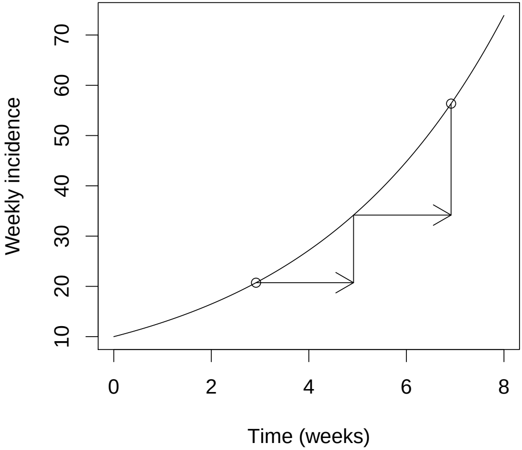
Conditional effect of generation time



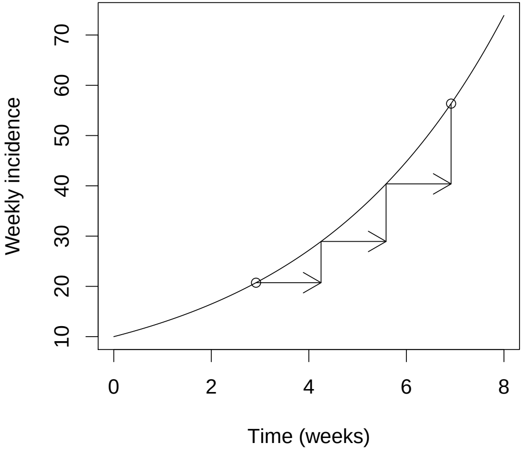
Conditional effect of generation time

- *Given* the reproductive number $\mathcal{R}$
  - faster generation time G means faster spread time C
  - More danger
- *Given* the spread time C
  - faster generation time G means *smaller* $\mathcal{R}$
  - Less danger

Generations and $\mathcal{R}$



Generations and $\mathcal{R}$



$\mathcal{R}$ vs. C

- We typically think $\mathcal{R}$ is more important
- Higher $\mathcal{R}$:
  - Higher final attack rate if nothing changes
  - Broader intervention required
- Faster C (higher r):
  - Less time for behaviour change
  - Faster intervention required

Outline

Generation intervals

- Intrinsic generation distribution:
  - How infectious a ‘typical’ infected *individual* is over the course of infection
- *forward* generation distribution:
  - the distribution of infectious times of people *infected by* the cohort infected at time t
- *backward* generation distribution:
  - the distribution of infectious times of people *who infected* the cohort infected at time t
- In the exponential phase, only the *forward* distribution should be used to estimate the intrinsic distribution

Disease model

- Many disease models behave *on average* like this:
  - $$i(t) = \int k(\tau) i(t-\tau)\, d\tau$$
- We write:
  - $$k(\tau) = \mathcal{R} g(\tau),$$
- Where:
  - $\mathcal{R}$ is the effective reproductive number
  - $g(\tau)$ (integrates to 1) is the *intrinsic* generation distribution

Euler equation

- Model
  - $$i(t) = \mathcal{R} \int g(\tau) i(t-\tau)\, d\tau$$
- Exponential phase
  - $$i(t) = i(0) \exp(t/C)$$
- Conclusion
  - $$1/\mathcal{R} = \int g(\tau) \exp(-\tau/C)\, d\tau$$

Interpretation: the "effective" generation time

- If the generation interval were absolutely fixed at a time interval of G, then
  - $$\mathcal{R} = \exp(G/C)$$
- *Define* the effective generation time so that this remains true:
  - $$\mathcal{R} = \exp(\hat{G}/C)$$

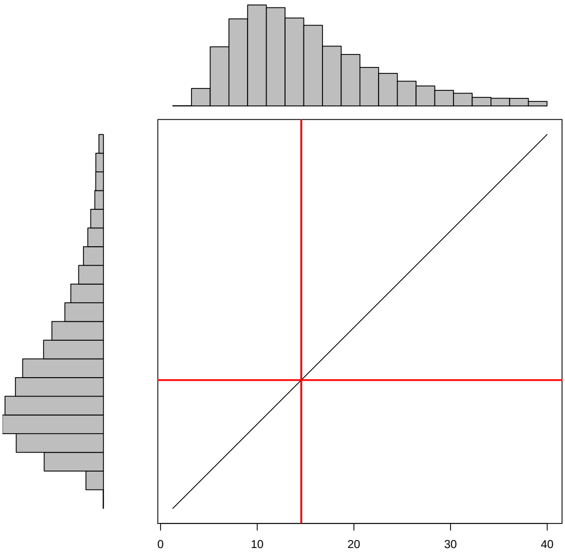
A filtered mean

- If:
  - $$\mathcal{R} = \exp(\hat{G}/C)$$
- Then
  - $$1/\mathcal{R} = \int g(\tau) \exp(-\tau/C)\, d\tau$$
- Becomes
  - $$\exp(-\hat{G}/C) = \int g(\tau) \exp(-\tau/C)\, d\tau$$
  - or,
    $$\exp(-\hat{G}/C) = \langle \exp(-\tau/C) \rangle_g$$
    ,
- This is a “filtered mean" of the distribution g.
- Equivalent to the Wallinga and Lipsitch generating function

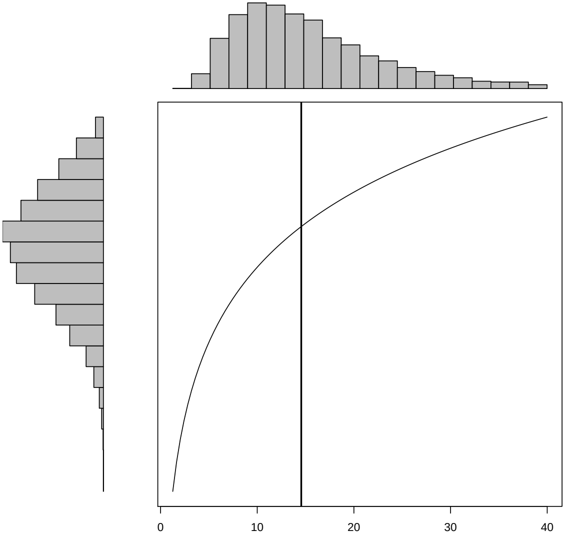
Filtered means

- Many things we know about are examples of filtered means
  - Geometric mean (log function)
  - Harmonic mean (reciprocal function)
  - Root mean square (square)
  - Heterogeneous $\mathcal{R}$ calculations

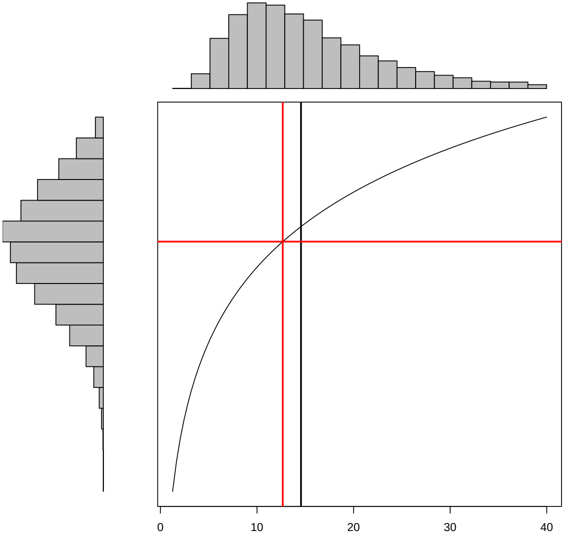
Arithmetic mean



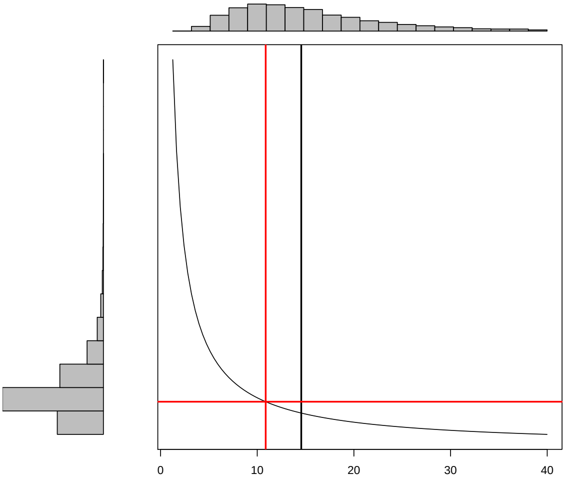
Geometric mean



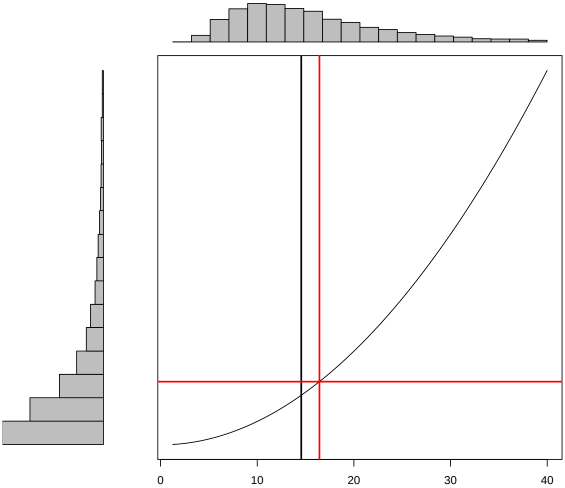
Geometric mean



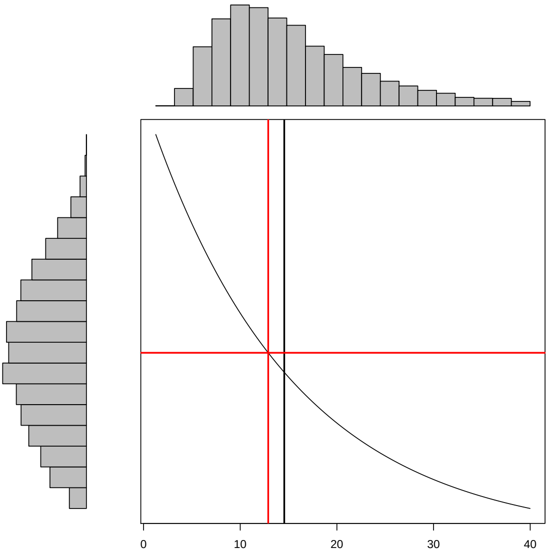
Harmonic mean



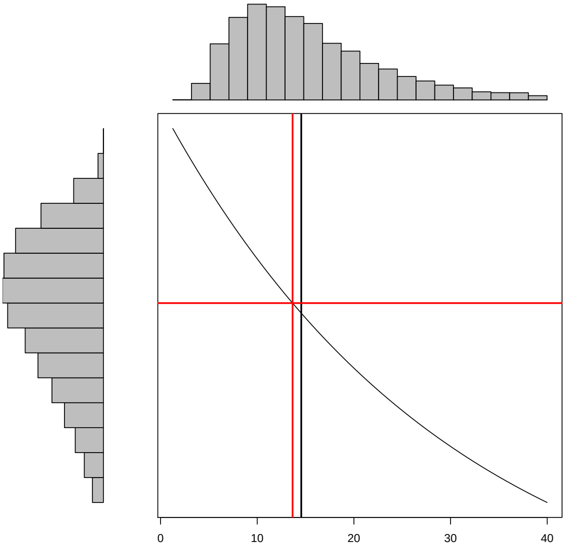
Root mean square



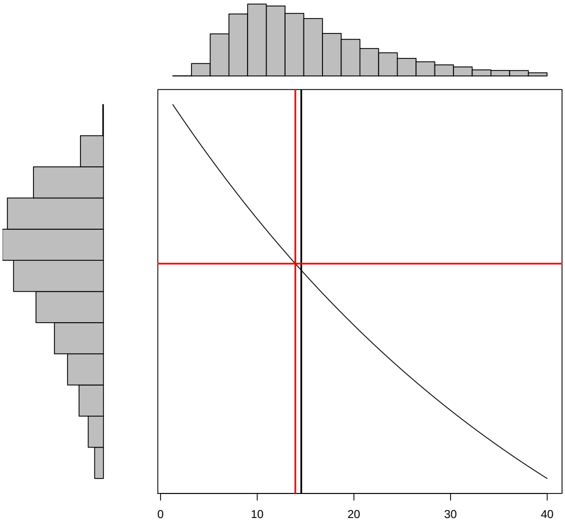
Discount, $T_c = 15d$



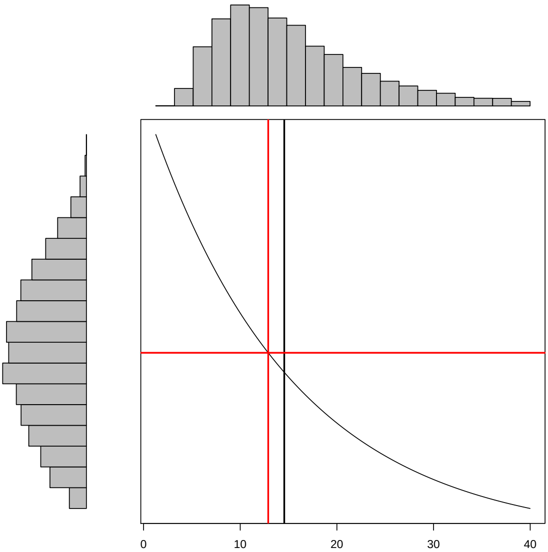
Discount, $T_c = 30d$



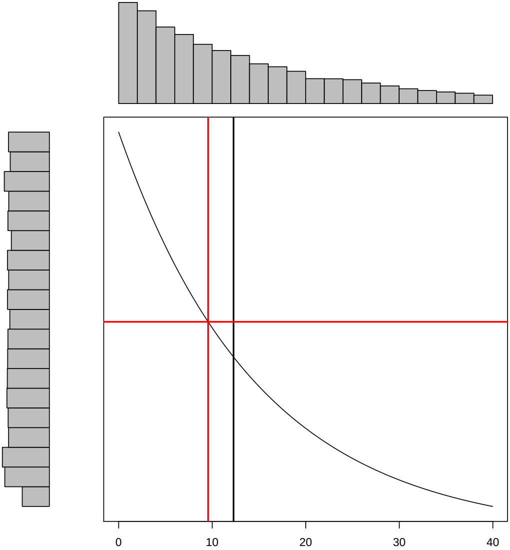
Discount, $T_c = 45d$



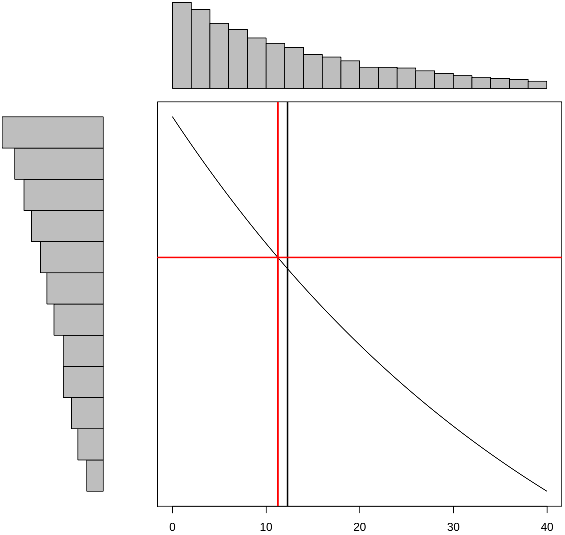
Discount, $T_c = 15d$



Exponential distribution



Discount, $T_c = 45d$



Filtered means have intuitive properties

- Shifts in distribution shift the mean about how you would expect
  - More late transmission means longer $\hat{G}$
- Importance of values depends on value of the filter function
- We can predict from the filter function what the effects of increasing variance will be
- As distribution gets narrower, $\hat{G}$ approaches $\bar{G}$

The filtering function

- $\exp(-\hat{G}/C) = \langle \exp(-\tau/C) \rangle_g$,
- $\hat{G}$ is the mean of the generation distribution $g(\tau)$ ...
- Filtered by the discount function associated with the rate of exponential growth of the epidemic

Outline

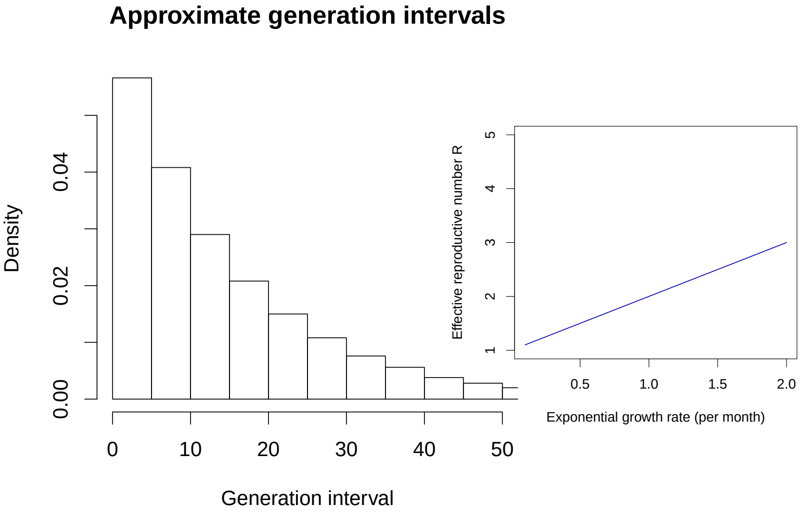
Tangled web

- The filtered mean is useful – but complicated
  - Filtering function is not scale free.
- Unless the *generation interval* (not recovery time) is absolutely fixed, $\hat{G}$ will change even when g does not
- How is
  - $$\mathcal{R} = \exp(\hat{G}/C)$$
- Consistent with
  - $$\mathcal{R} = 1 + \bar{G}/C?$$

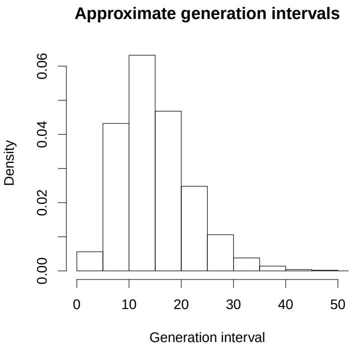
An approximation

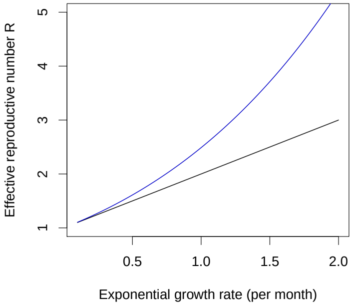
- We connect these quantities with a moment approximation
- Define $\kappa = \sigma_G^2/\mu_G^2$ – the squared coefficient of variation of the generation distribution
- $\mathcal{R} \approx (1 + \kappa\bar{G}/C)^{1/\kappa}$
  - Equal when G has a gamma distribution
  - Not clear how good an approximation it is in general
  - May be a useful qualitative guide even when it's not quantitatively accurate

Moment approximation

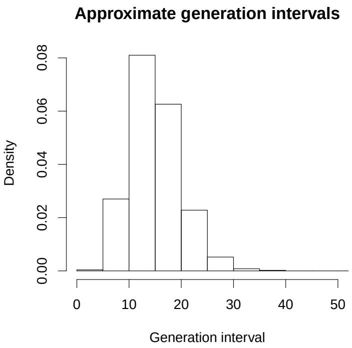


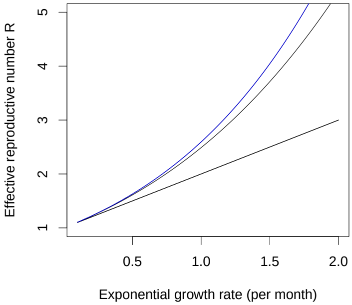
Moment approximation



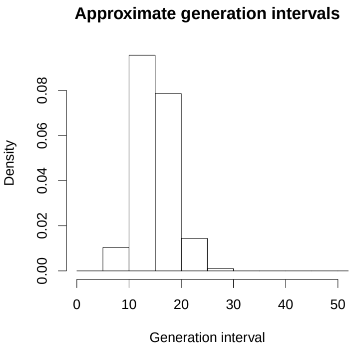


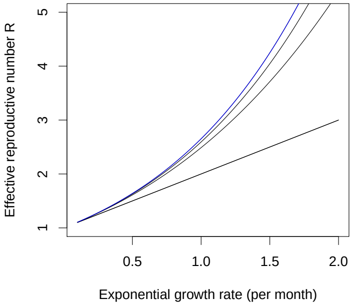
Moment approximation





Moment approximation

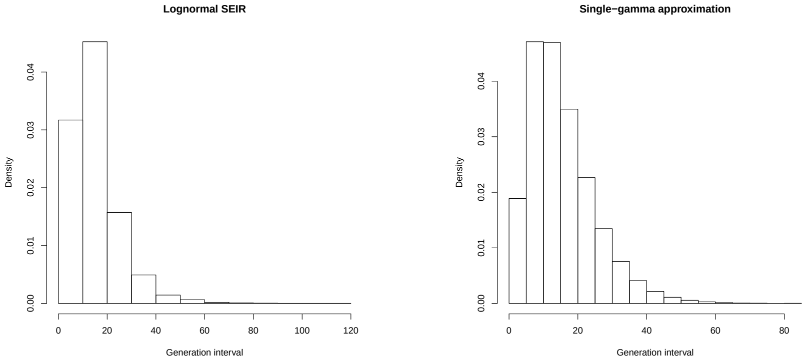




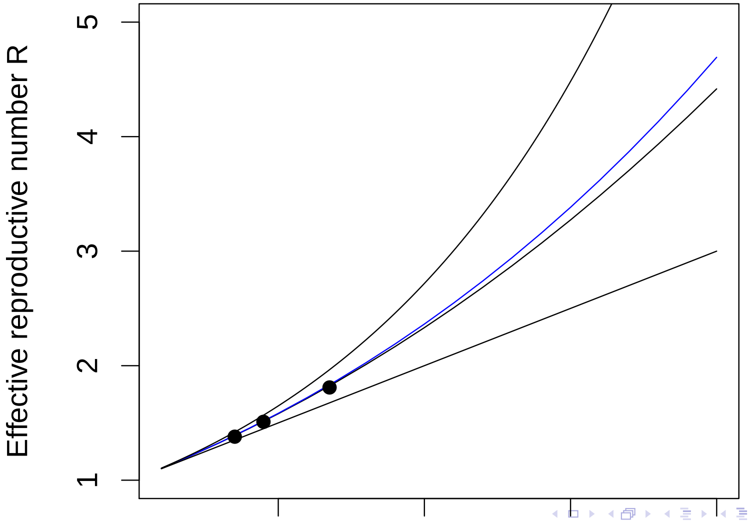
Fitting to Ebola

- Simulate generation intervals based on data and approach from WHO report
- Use both lognormals and gammas
  - WHO used gammas
  - Lognormals should be more challenging

Approximating the distribution



Approximating the curve



Outline

r and $\mathcal{R}$

Time scales and disease risk

- Post-death transmission and safe burial
- Generation time and disease risk

Generation times and generating functions

Moment approximations

Conclusion

Conclusion

- 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 can aid understanding
- Approximations may aid estimation
- For Ebola:
  - Knowing the mean generation interval is not enough
  - But knowing the mean and CV may be enough

Thanks

- Organizers
- Audience
- Collaborators: Steve Bellan, David Champredon, Joshua Weitz
- Funders: NSERC, CIHR