Time distributions and coronavirus control

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SMB, Aug 2020

Outline

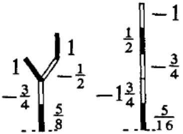
Speed and strength are dual paradigms

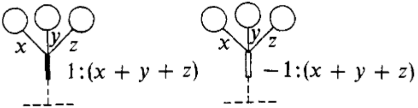
Generation intervals link speed with strength

Generation intervals are complicated

There is much to be done

Speed and strength are dual paradigms

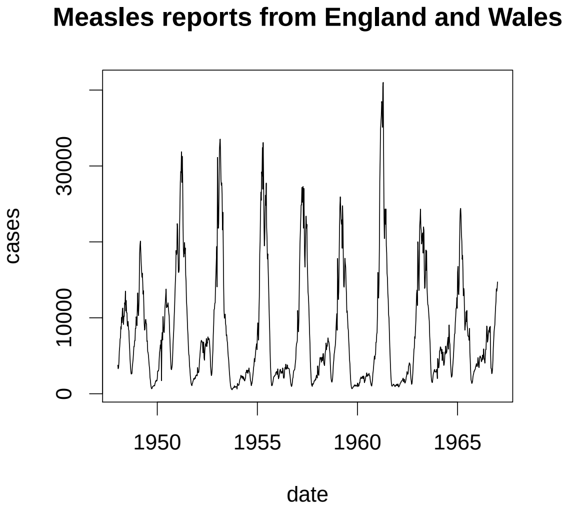




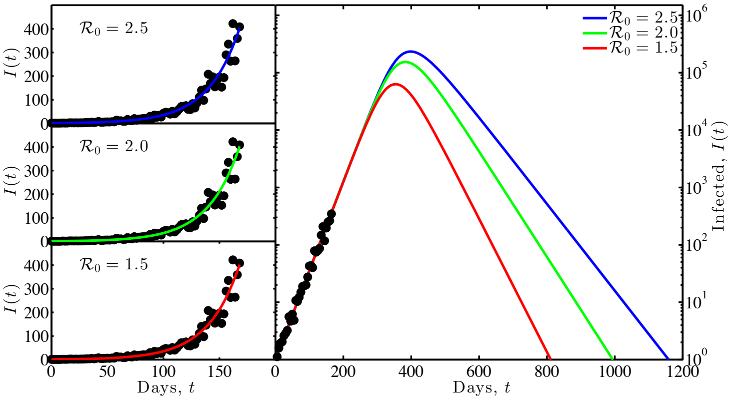
- $\mathcal{R}||r$
- h/t John Horton Conway 1937–2020
- Speed is better for some applications, and strength for others
- Or you may see different things

On Numbers and Games

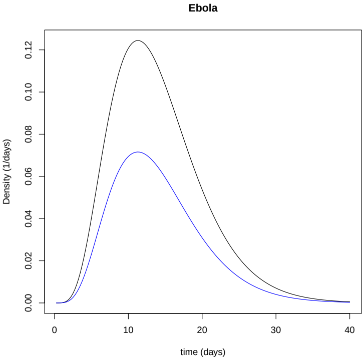
Observing strength



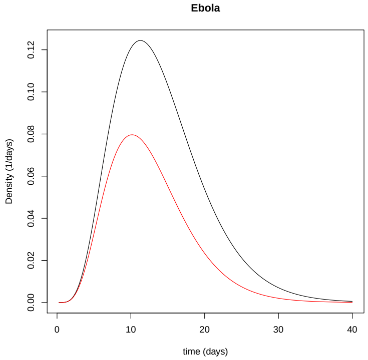
Observing speed



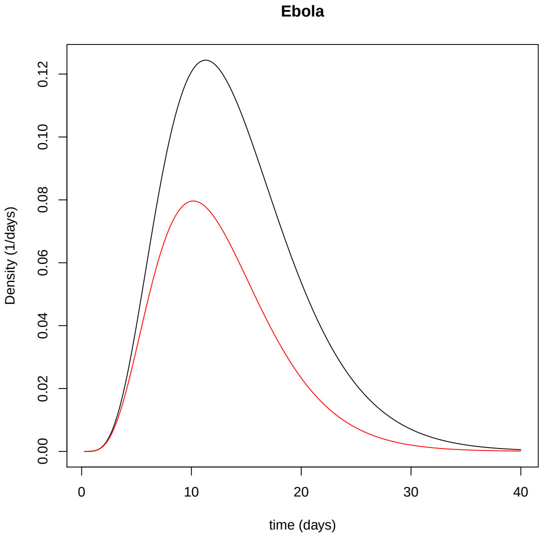
Strength-like interventions



Speed-like interventions

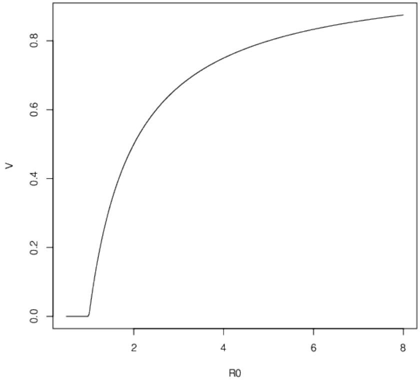


Comparison



Ebola
Density (1/days)
0.00
0.02
0.04
0.06
0.08
0.10
0.12
0
10
20
30
40
time (days)

$\mathcal{R}$ and control



The speed paradigm

- We can define the strength of an intervention so that it can be naturally compared to $\mathcal{R}$
  - Epidemic controlled when $\theta > \mathcal{R}$
- We can define the *speed* of an intervention so that it can be naturally compared to r
  - Epidemic controlled when $\phi > r$
- *https://www.biorxiv.org/content/10.1101/2020.03.02.974048v1*

Outline

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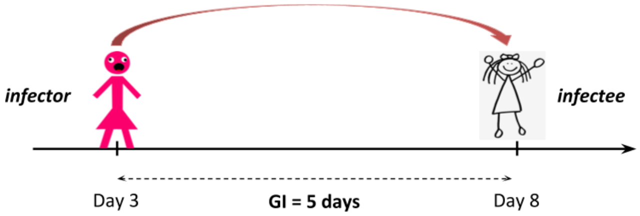
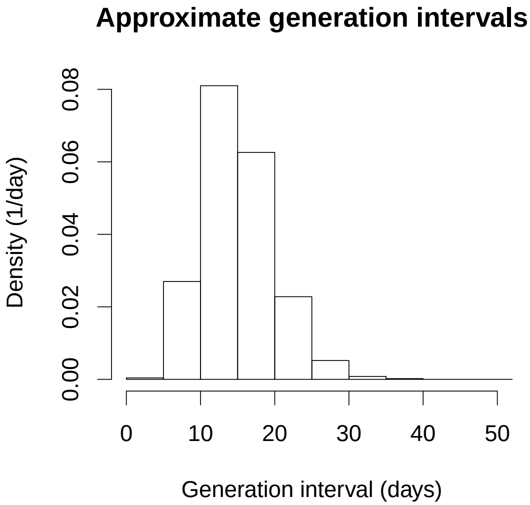
Definition

Generation Interval:

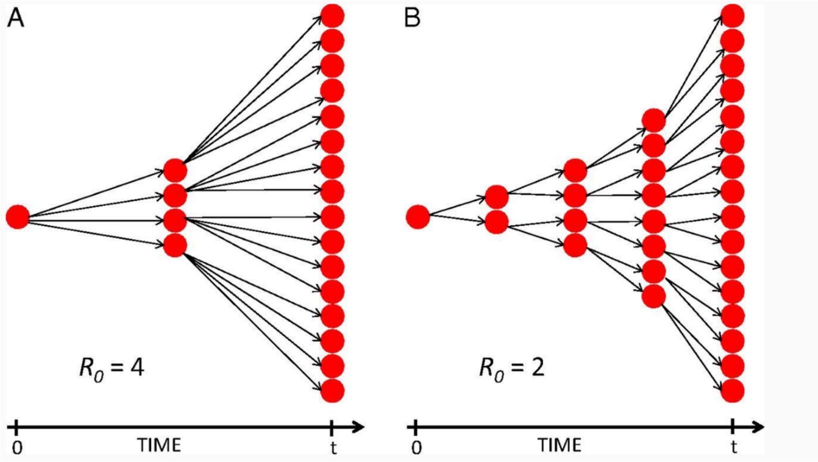
Interval between the time that an individual is infected by an infector and the time this infector was infected



Generation intervals



Linking



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

Estimating $\mathcal{R}$

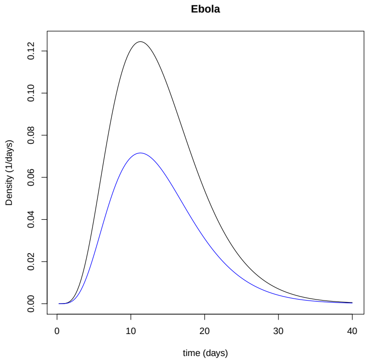
- Differential equation approach: $\mathcal{R} = 1 + r\bar{G}$
- Discrete generation approach: $\mathcal{R} = \exp(rG)$

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
- *doi: 10.1137/18M1186411*

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



Euler-Lotka equation

- If we neglect changes in S, we expect exponential growth
- $1 = \int k(\tau) \exp(-r\tau)\, d\tau$
  - i.e., the total of *discounted* contributions is 1
- $1/\mathcal{R} = \int g(\tau) \exp(-r\tau)\, d\tau$
- This beautiful equation underlies both the filtered mean approach (below) and the concept of speed of interventions

Filtered mean approach

- **Define** $\hat{G}$ so that
$$\mathcal{R} = \exp(r\hat{G})$$
- Then:
  - $$1/\mathcal{R} = \int g(\tau)\exp(-r\tau)\,d\tau$$
  - $$\exp(-r\hat{G}) = \langle \exp(-r\tau) \rangle_g .$$
  - A filtered mean:
    - The discounted value of $\hat{G}$ is the expectation of the discounted values across the distribution
- Intuitively useful, but usually not practical
  - $\hat{G}$ can depend strongly on r, which is not what you want

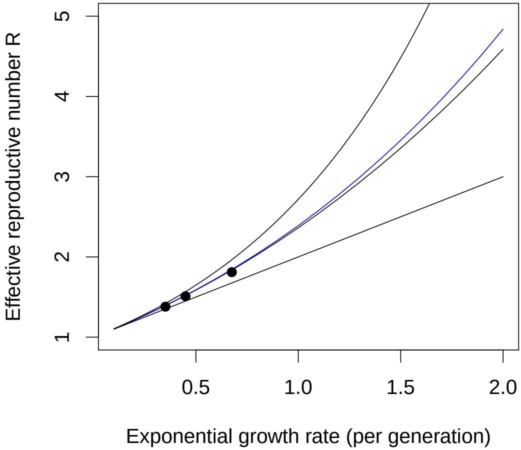
Gamma approximation

- When g is gamma distributed, the $r\mathcal{R}$ link is given by a compound-interest approximation to the exponential:
- $\mathcal{R} \approx (1 + r\kappa\bar{G})^{1/\kappa}$
- $\kappa = \sigma_G^2/\mu_G^2$ – the squared coefficient of variation
- Matches the ODE formula ($\kappa = 1$), and the discrete-time formula $\kappa \to 0$
- Why does more dispersion reduce $\mathcal{R}$?

Effective dispersion

- **Define** $\hat{\kappa}$ so that $\mathcal{R}(1 + r\hat{\kappa}\bar{G})^{1/\hat{\kappa}}$
- This is a dispersion in the sense that it increases as variation in the generation interval increases
- Hard to think about, but *usually* practical
- $\hat{\kappa}$ often relatively insensitive to r.
- *doi: 10.1016/j.epidem.2018.12.002*

Ebola example

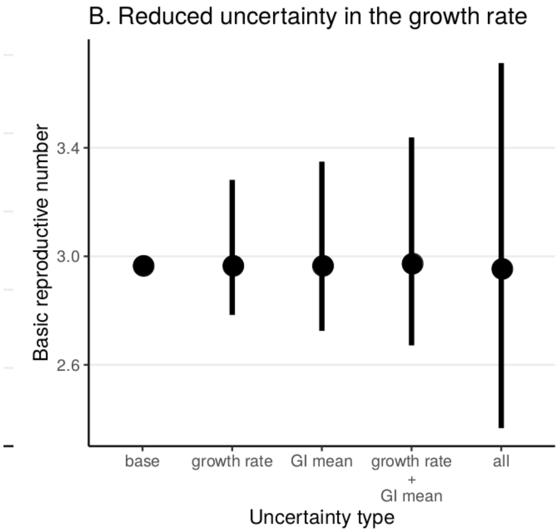


Comparing estimates

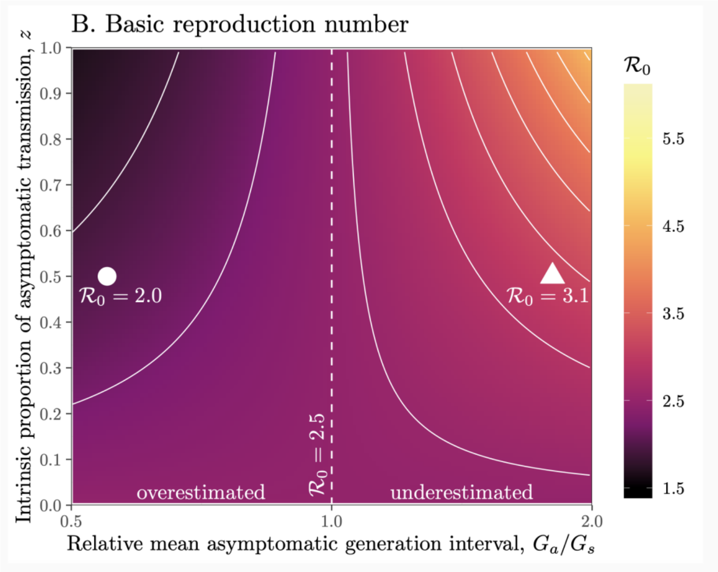
- Early-outbreak estimates of $\mathcal{R}$ from exponential growth are effectively using the compount-interest approximation
- Typically, studies explicitly use gamma distributions
  - e.g., fixed generation, SEIR with equal delays, SIR, a gamma fit ...
- But it doesn't matter: studies can be compared based on their inferences or assumptions about r, $\bar{G}$ and $\hat{\kappa}$

doi: 10.1098/rsif.2020.0144

Propagating error for coronavirus



Asymptomatic transmission



doi: 10.1016/j.epidem.2020.100392

Transmission routes, speed and strength

- What if more SARS-CoV-2 is presymptomatic?
- G may be faster than we think
- $\mathcal{R}$ may be *lower* than we think
- Early estimates of r and the required *speed* of intervention are not affected
- How about estimates of the *achieved* speed of intervention?

Outline

Generation intervals are complicated

- 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?

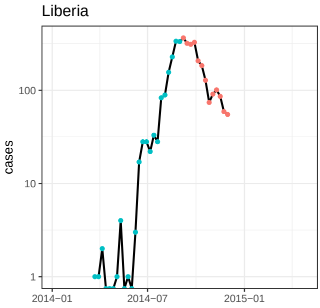
- Contact-tracing intervals look systematically different, depending on when you observe them.
- Observed in:
  - Real data, detailed simulations, simple model
- Also differ from intrinsic (infector centered) estimates

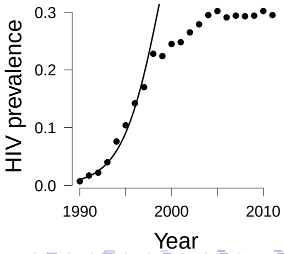
Types of interval

- 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

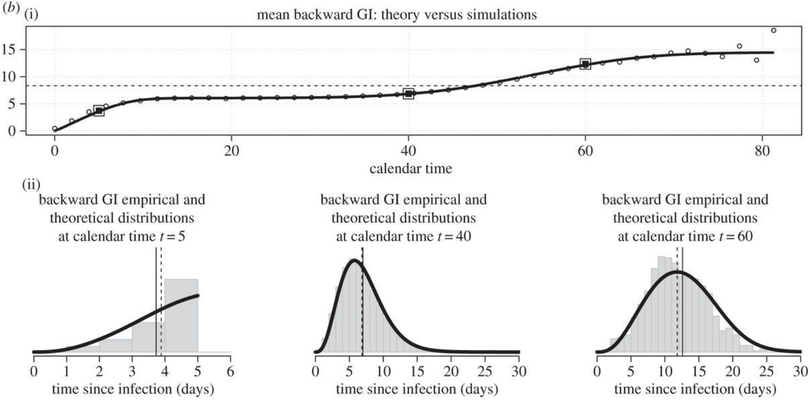
Growing epidemics

- 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





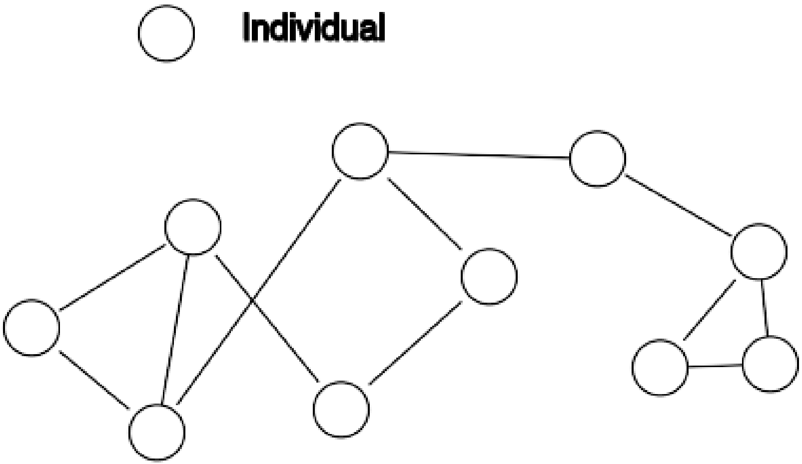
Backward intervals



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

Generations in space

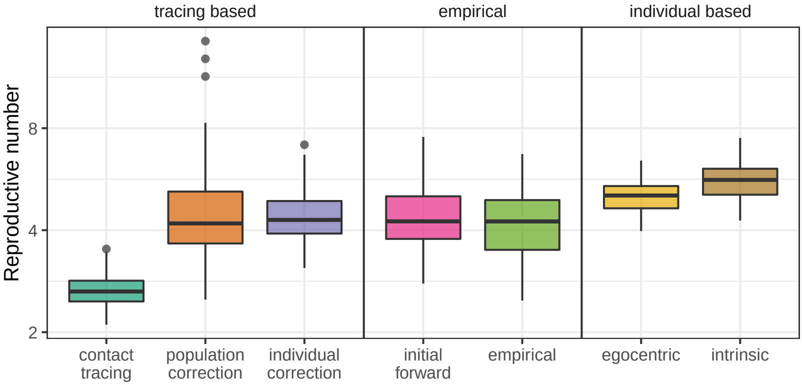
- How do local interactions affect realized generation intervals?



Surprising results

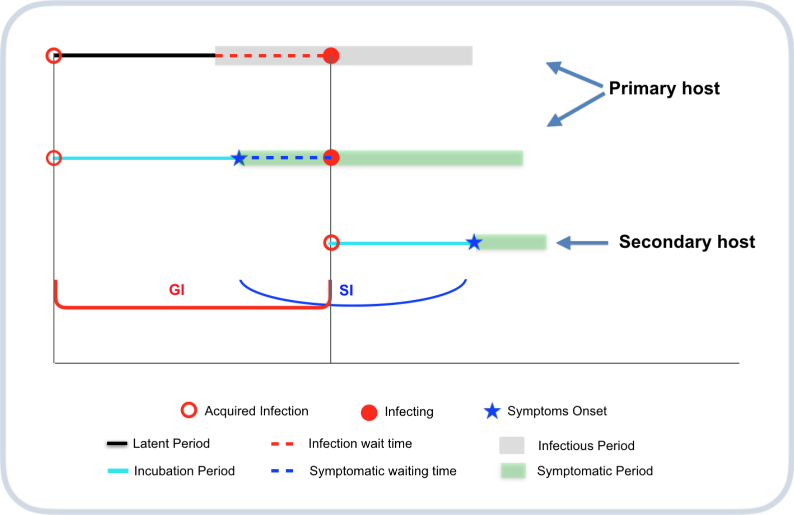
- We tend to think that heterogeneity leads to underestimates of $\mathcal{R}$, which can be dangerous.
- $\mathcal{R}$ on networks generally *smaller* than values estimated using r.
    - *Trapman et al., 2016. JRS Interface*
      DOI: 10.1098/rsif.2016.0288

Outbreak estimation



Park et al. `doi:10.1098/rsif.2019.0719`

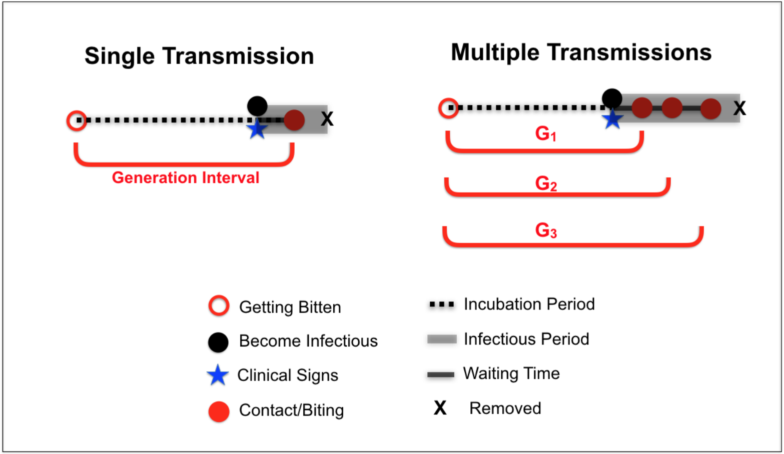
Serial intervals



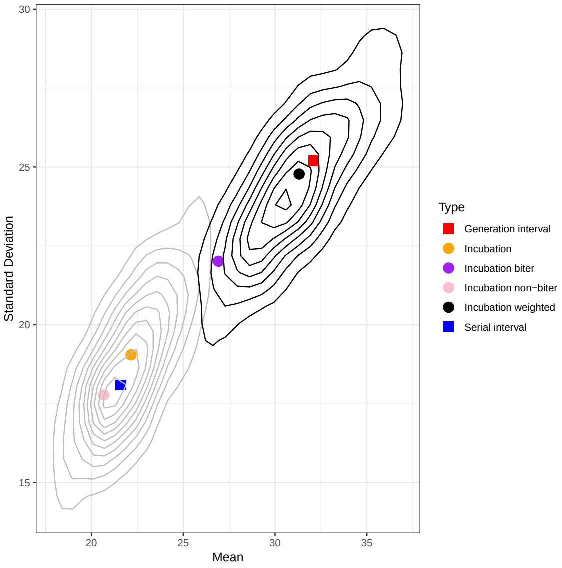
Serial intervals

- 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 even be very different
  - Even negative! You might report to the clinic with flu before me, even though I infected you

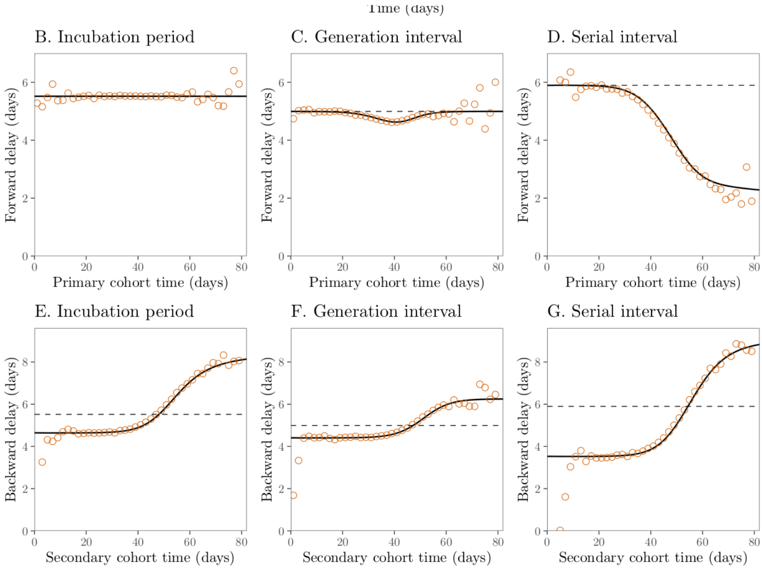
Serial intervals with no asymptomatic spread



Host heterogeneity



Serial intervals with asymptomatic spread



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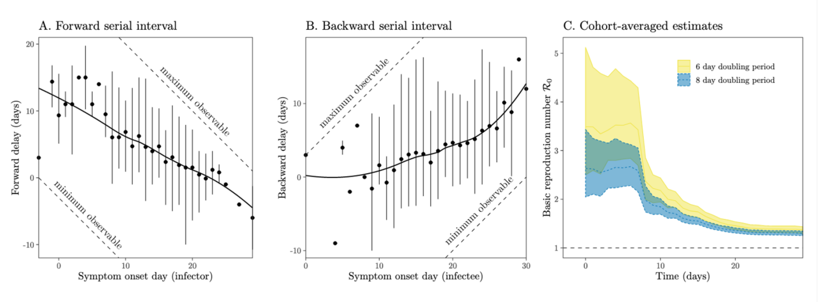
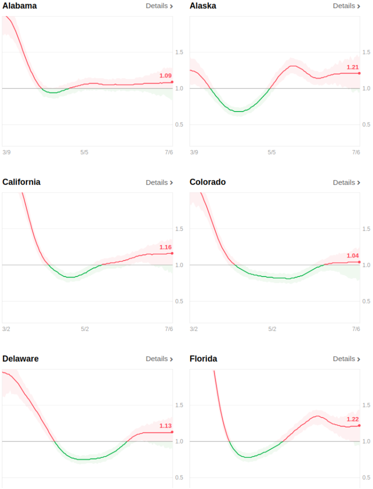


https://doi.org/10.1101/2020.06.04.20122713

Data from

https://wwwnc.cdc.gov/eid/article/26/6/20-0357_article

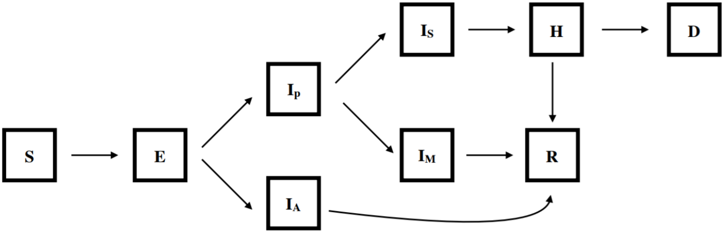
What is $\mathcal{R}_t$ doing now?



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

https://rt.live 2020 Jul 08

Mechanistic modeling



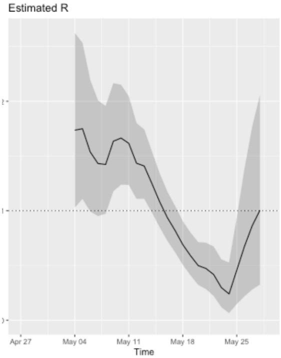
S = susceptible
E = exposed

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

H = hospitalized
R = recovered
D = dead

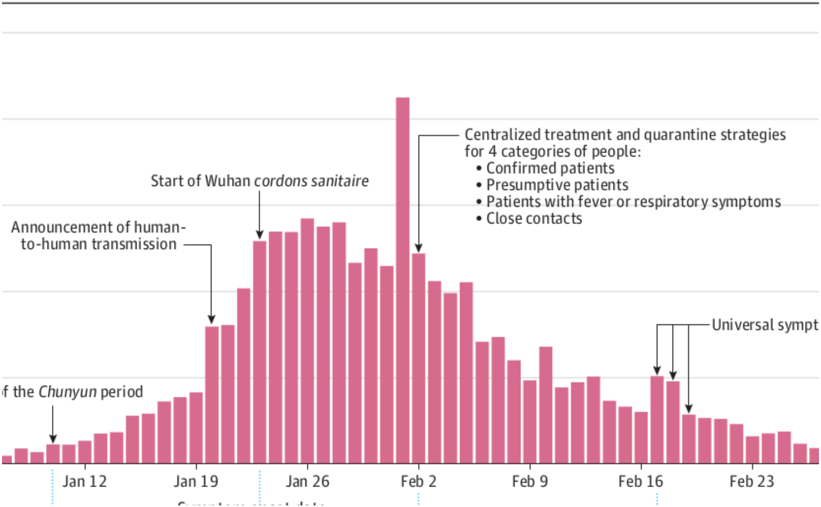
Childs et al., http://covid-measures.stanford.edu/
Macpan:https://github.com/bbolker/McMasterPandemic

Direct calculation



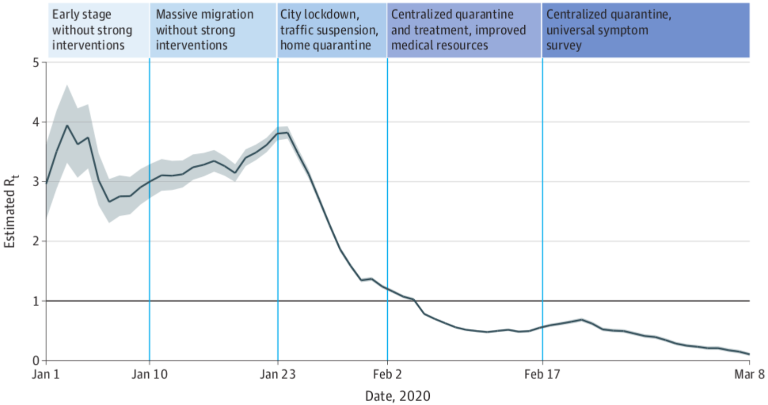
EpiEstim, https://cran.r-project.org/web/packages/EpiEstim/vignettes/demo.html
Wallinga and Teunis, https://doi.org/10.1098/rsif.2010.0679
Goldstein et al., https://doi.org/10.1073/pnas.0902958106

Wuhan control measures



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

Wuhan control measures

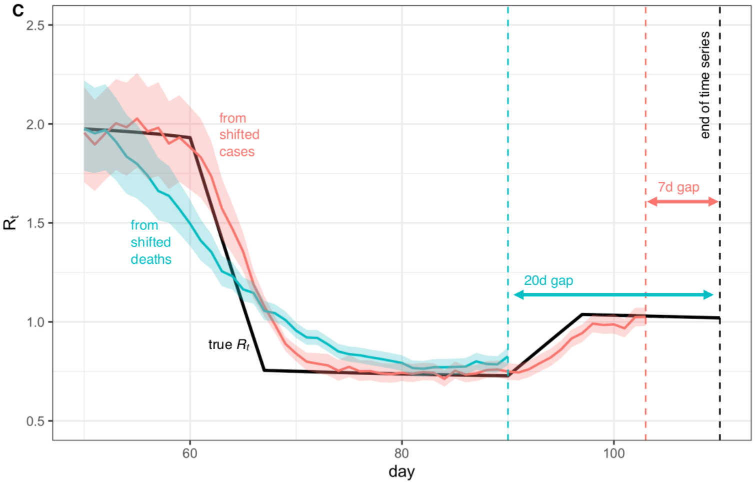


https://jamanetwork.com/journals/jama/fullarticle/2764658

Time-varying reproductive numbers

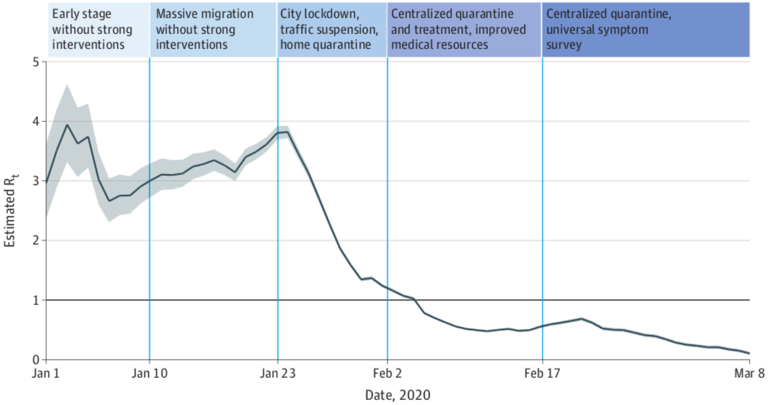
- Case reproductive number $\mathcal{R}_c$ (e.g., Wallinga and Teunis)
  - How many people will get infected by a case infected at time t?
  - $i(t) = \sum \mathcal{R}(t-\tau)g(\tau)i(t-\tau)$
- Instantaneous reproductive number $\mathcal{R}_c$ (e.g., Cori et al.)
  - What overall reproductive number predicts what I'm seeing now?
  - $i(t) = \sum \mathcal{R}(t)g(\tau)i(t-\tau)$
- Speed vs. strength
  - What if g is changing?
  - Are r-based tools available?

Developing practical methods



Gostic et al., https://doi.org/10.1101/2020.06.18.20134858

Wuhan control measures (repeat)



https://dushoff.github.io/notebook/shifts.html

How important are these subtleties?

- We don't know yet
- In some sense, it's all averaging
  - Do something sensible and track how it's changing
- Simulation-based validation

Thanks

- SMB and SMB-mathepi
- Collaborators:
  - Li, Park, Weitz, Bolker, Earn, Champredon ...
- Funders: NSERC, CIHR, PHAC, WHO