

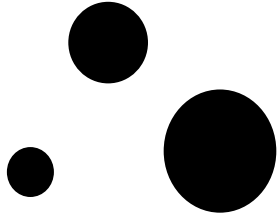
Estimating epidemiological time intervals

Hiroaki Murayama

hiromura319@gmail.com

2/05/2021

Table of contents



- Time intervals



Linton et al. + Nishiura et al.

- Doubly interval-censoring
- Types of generation time



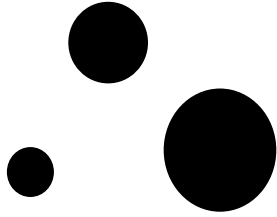
Ganyani et al.

- Generation time estimation

Key Topics

1. Doubly interval-censoring model
2. The properties of serial interval
3. The properties of three generation time
4. The estimation of generation time
5. The assumptions that are put on the model
6. One critical point to a model

Today's main papers

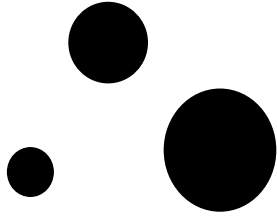


- Linton NM, Kobayashi T, Yang Y, et al. Incubation Period and Other Epidemiological Characteristics of 2019 Novel Coronavirus Infections with Right Truncation: A Statistical Analysis of Publicly Available Case Data. *J Clin Med*. 2020;9(2):538. Published 2020 Feb 17. doi:10.3390/jcm9020538
- Nishiura H, Linton NM, Akhmetzhanov AR. Serial interval of novel coronavirus (COVID-19) infections. *Int J Infect Dis*. 2020;93:284-286. doi:10.1016/j.ijid.2020.02.060
- Ganyani T, Kremer C, Chen D, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Euro Surveill*. 2020;25(17):2000257. doi:10.2807/1560-7917.ES.2020.25.17.2000257

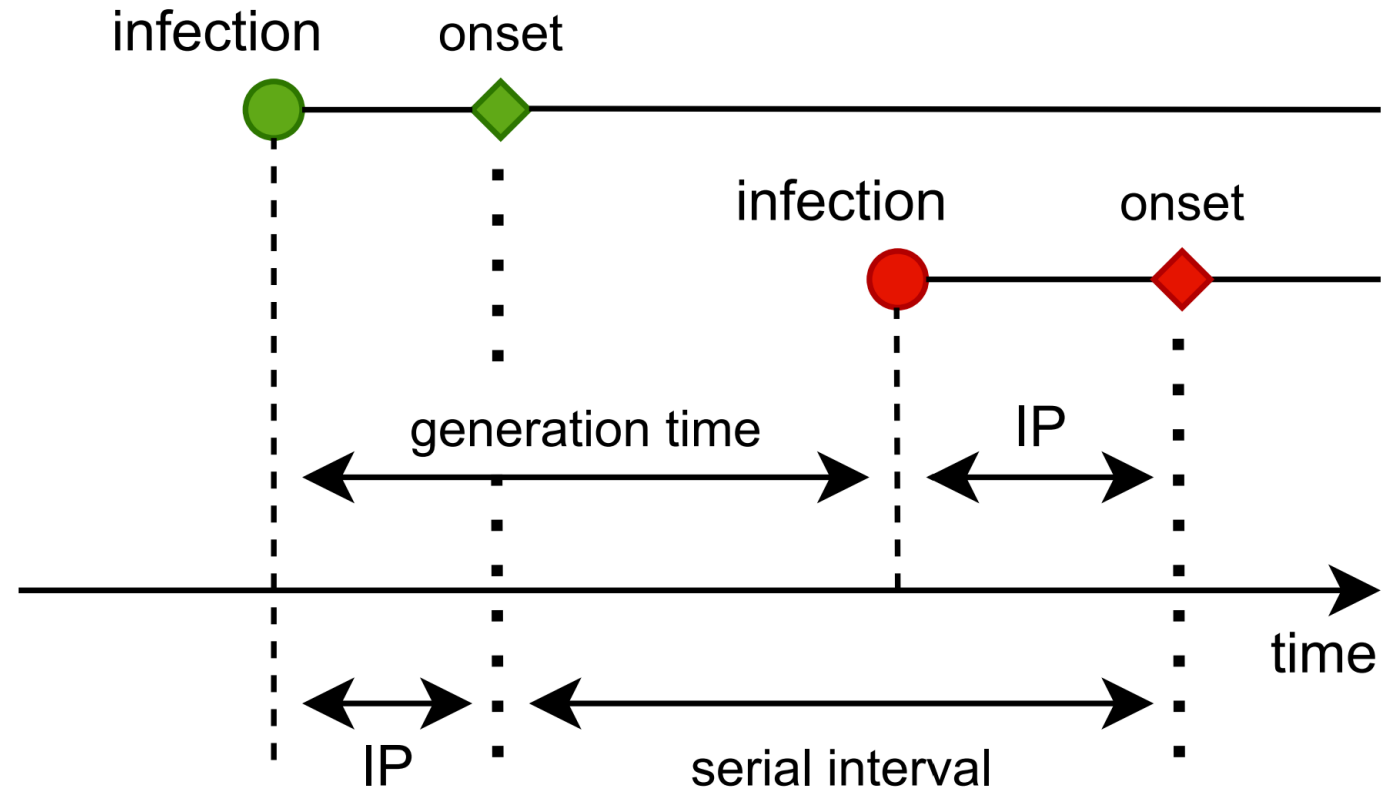


Some other articles

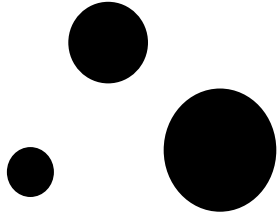
Epidemiological time interval



- Generation time
- Serial interval
- Incubation period



Why important?



Generation time

- Understand the transmissibility
- Infection times are generally unobserved

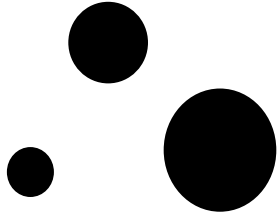
Serial interval

- Used as a proxy of generation time

Incubation period

- Useful to diagnose afferent infectious diseases
- Projecting an epidemic

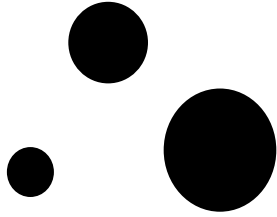
Other epidemiological time intervals



- Time-delay from onset of symptoms to hospital admission for living/deceased cases
- Time-delay from onset of symptoms to death
- Time-delay from hospital admission to death

Critical to capture the temporal
dynamics of an epidemic and
underpin CFR

Today's main papers

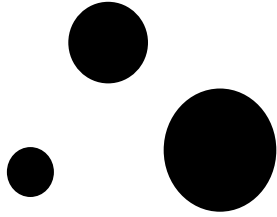


- Linton NM, Kobayashi T, Yang Y, et al. Incubation Period and Other Epidemiological Characteristics of 2019 Novel Coronavirus Infections with Right Truncation: A Statistical Analysis of Publicly Available Case Data. *J Clin Med*. 2020;9(2):538. Published 2020 Feb 17. doi:10.3390/jcm9020538
- Nishiura H, Linton NM, Akhmetzhanov AR. Serial interval of novel coronavirus (COVID-19) infections. *Int J Infect Dis*. 2020;93:284-286. doi:10.1016/j.ijid.2020.02.060
- Ganyani T, Kremer C, Chen D, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Euro Surveill*. 2020;25(17):2000257. doi:10.2807/1560-7917.ES.2020.25.17.2000257

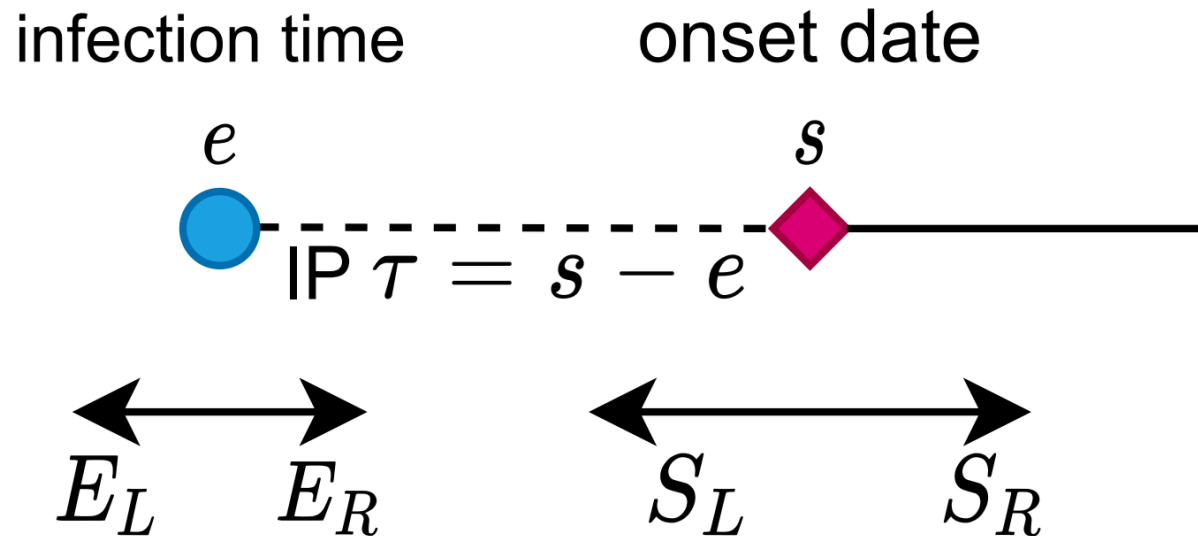


Some other articles

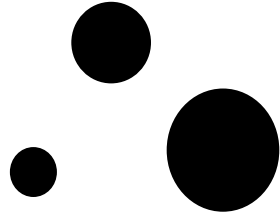
Doubly interval-censored data



- Doubly interval-censoring (e.g. incubation period)



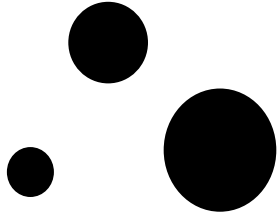
Doubly interval censored data



e.g. data for IP
(Linton et al.)

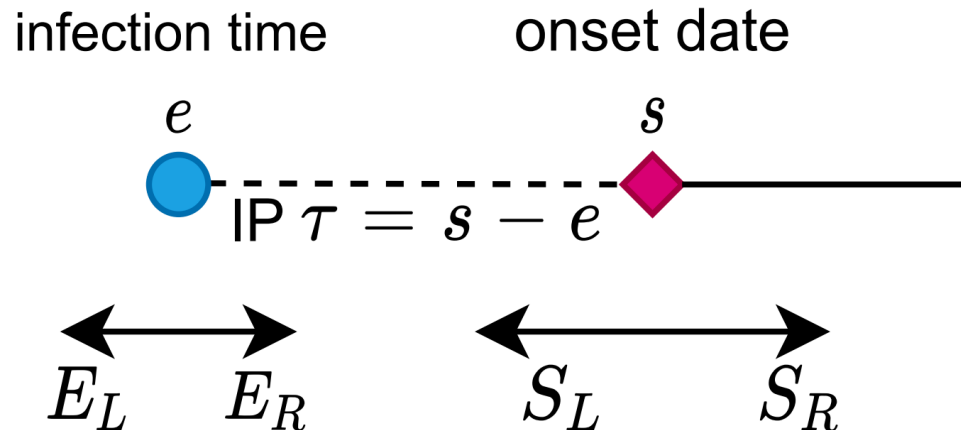
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
2	ID	ExposureL	ExposureR	ExposureT	Onset	DateCaseFi	DateHospit	DateReport	Source									
3	NW001	2019/12/29	2020/1/4	Travel to V	2020/1/3	NA	2020/1/11	2020/1/19	http://wsjkw.gd.gov.cn/zwyw_yqxx/content/post_2876057.html									
4	NW002	NA	2020/1/6	Travel to V	2020/1/3	2020/1/10	2020/1/10	2020/1/16	https://www.mhlw.go.jp/stf/newpage_08906.html									
5	NW003	NA	2020/1/8	Lives-worl	2020/1/5	NA	2020/1/8	2020/1/13	https://www.who.int/csr/don/14-january-2020-novel-coronavirus-thailand-ex-china/en/									
6	NW004	NA	2020/1/13	Lives-worl	NA	2020/1/13	2020/1/13	2020/1/17	https://pr.moph.go.th?url=pr/detail/2/04/137232/									
7	NW006	2020/1/14	2020/1/14	Contact w	2020/1/18	2020/1/20	NA	2020/1/25	https://news.sina.com.cn/2020-01-26/doc-iihnzhha4680951.shtml									
8	NW007	NA	2020/1/19	Lives-worl	2020/1/18	2020/1/18	2020/1/19	2020/1/20	https://www.who.int/csr/don/21-january-2020-novel-coronavirus-republic-of-korea-ex-china/en/									
9	NW008	2020/1/7	NA	Travel to V	2020/1/13	NA	NA	2020/1/20	http://www.bjnews.com.cn/news/2020/01/20/677095.html									
10	NW009	2020/1/9	NA	Travel to V	2020/1/14	NA	NA	2020/1/20	http://www.bjnews.com.cn/news/2020/01/20/677095.html									
11	NW010	NA	NA	Lives-worl	2020/1/13	NA	NA	2020/1/20	http://www.bjnews.com.cn/news/2020/01/20/677095.html									
12	NW011	NA	2020/1/12	Lives-worl	2020/1/15	2020/1/15	NA	2020/1/20	https://www.weibo.com/2372649470/lqogQhgfa									
13	NW012	2020/1/8	2020/1/11	Travel to V	NA	NA	2020/1/16	2020/1/21	http://www.bjd.com.cn/a/202001/21/WS5e263c86e4b0e6e58393ac88.html									
14	NW013	NA	2020/1/3	Lives-worl	2020/1/4	2020/1/4	2020/1/17	2020/1/21	http://www.zjw.gov.cn/art/2020/1/21/art_1202101_41786033.html									
15	NW014	NA	2020/1/20	Lives-worl	NA	NA	2020/1/20	2020/1/21	https://www.cdc.gov.tw/En/Bulletin/Detail/pVg_jRVvtHhp94C6GShRkQ?typeid=158									
16	NW016	NA	NA	Travel to V	2020/1/14	NA	2020/1/14	2020/1/21	https://news.sina.com.cn/c/2020-01-25/doc-iihnzakh6270149.shtml									
17	NW017	NA	2020/1/7	Lives-worl	2019/12/29	NA	2020/1/20	2020/1/21	https://www.who.int/csr/don/21-january-2020-novel-coronavirus-republic-of-korea-ex-china/en/									
18	NW018	NA	2020/1/15	Travel to V	2020/1/15	2020/1/15	2020/1/15	2020/1/21	http://www.cs.com.cn/xwzx/hg/202001/t20200122_6019311.html									
19	NW019	NA	2020/1/11	Lives-worl	2020/1/15	NA	NA	2020/1/20	http://wsjkj.zhuhai.gov.cn/zwgk/tzgg/content/post_2461447.html									
20	NW020	NA	2020/1/11	Lives-worl	NA	NA	2020/1/18	2020/1/20	http://wsjkj.zhuhai.gov.cn/zwgk/tzgg/content/post_2461447.html									
21	NW022	NA	2020/1/15	Travel to V	2020/1/15	2020/1/19	2020/1/19	2020/1/21	https://www.nejm.org/doi/full/10.1056/NEJMoa2001191									
22	NW024	2019/12/17	2020/1/15	Travel to V	2020/1/15	2020/1/16	2020/1/17	2020/1/21	https://m.weibo.cn/status/4463321081961974									
23	NW025	2020/1/10	2020/1/11	Travel to V	2020/1/14	2020/1/20	2020/1/20	2020/1/21	http://wjw.beijing.gov.cn/xwzx_20031/wnxw/202001/t20200121_1620353.html									
24	NW026	2020/1/3	2020/1/4	Travel to V	2020/1/9	2020/1/14	2020/1/20	2020/1/21	http://wjw.beijing.gov.cn/xwzx_20031/wnxw/202001/t20200121_1620353.html									
25	NW027	2020/1/8	2020/1/16	Travel to V	2020/1/16	2020/1/20	2020/1/20	2020/1/21	http://wjw.beijing.gov.cn/xwzx_20031/wnxw/202001/t20200121_1620353.html									
26	NW028	2020/1/12	2020/1/17	Travel to V	2020/1/19	2020/1/20	2020/1/20	2020/1/21	http://wjw.beijing.gov.cn/xwzx_20031/wnxw/202001/t20200121_1620353.html									
27	NW029	2020/1/13	2020/1/17	Travel to V	NA	2020/1/20	2020/1/20	2020/1/21	http://wjw.beijing.gov.cn/xwzx_20031/wnxw/202001/t20200121_1620353.html									
28	NW032	2019/12/20	2020/1/9	Travel to V	2020/1/10	2020/1/10	2020/1/10	2020/1/21	http://m.thepaper.cn/newsDetail_forward_5594388									
29	NW033	NA	2020/1/2	Lives-worl	NA	2020/1/10	2020/1/10	2020/1/21	http://m.thepaper.cn/newsDetail_forward_5594388									
30	NW038	NA	2020/1/17	Lives-worl	2020/1/11	2020/1/17	2020/1/17	2020/1/22	http://www.bjnews.com.cn/news/2020/01/22/677946.html									
31	NW039	2020/1/13	2020/1/13	Lives-worl	2020/1/14	2020/1/14	2020/1/19	2020/1/22	http://www.bjnews.com.cn/news/2020/01/22/677946.html									
32	NW040	NA	2020/1/18	Travel to V	2020/1/20	2020/1/20	2020/1/20	2020/1/22	https://cbgc.scol.com.cn/news/219477									
33	NW041	NA	2020/1/13	Travel to V	2020/1/20	2020/1/20	2020/1/20	2020/1/22	https://cbgc.scol.com.cn/news/219477									
34	NW042	NA	2020/1/17	Travel to V	2020/1/18	2020/1/18	2020/1/18	2020/1/22	https://cbgc.scol.com.cn/news/219477									

Likelihood function

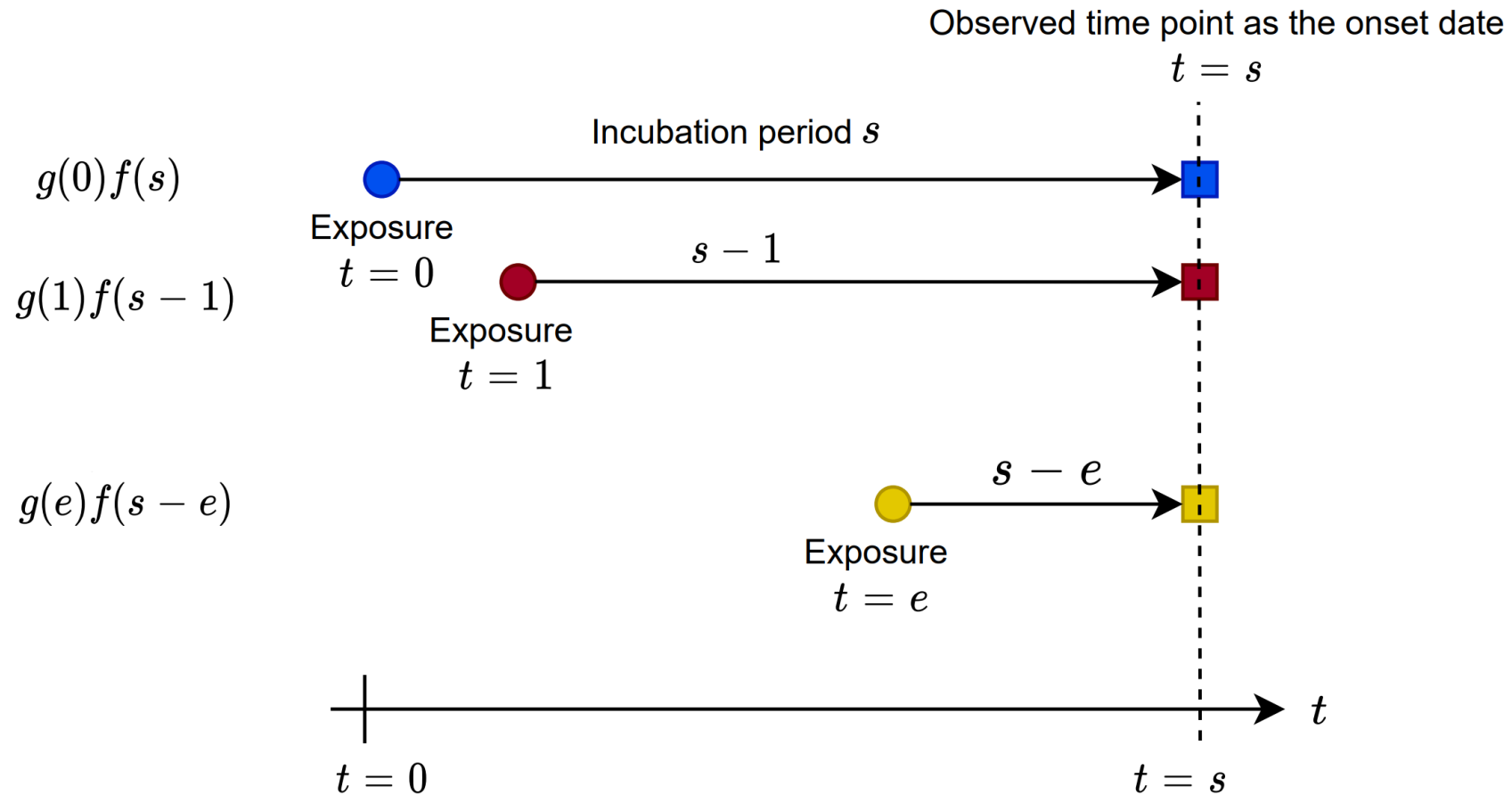
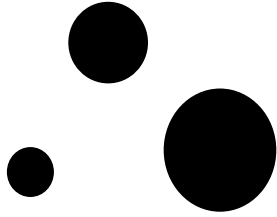


- $g(\cdot)$: pdf of exposure following uniform distribution
- $f(\cdot)$: pdf of the incubation period independent of $g(\cdot)$

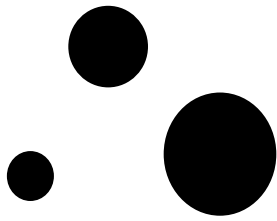
$$L(\Theta_g; \mathbf{D}) = \prod_i \int_{E_L, i}^{E_R, i} \int_{S_L, i}^{S_R, i} g(e) f(s - e) ds de$$



Discrete illustrations

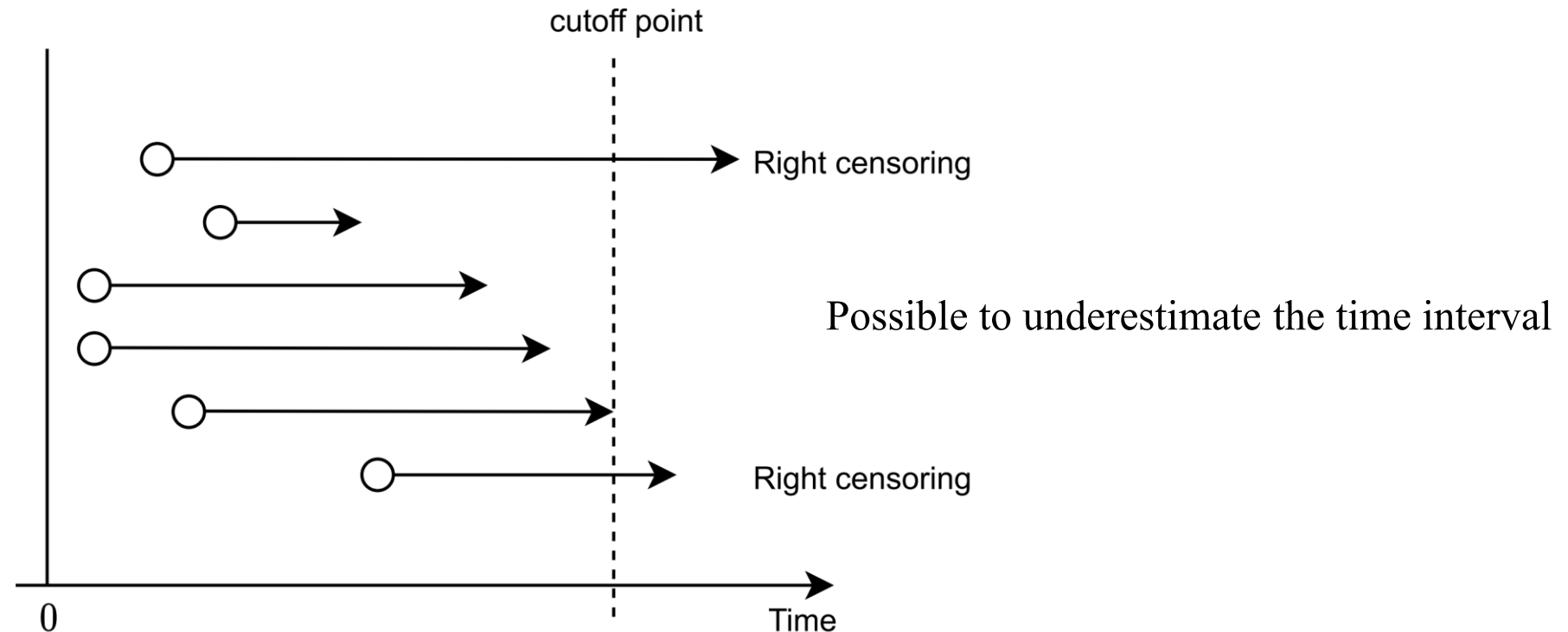


Pitfall

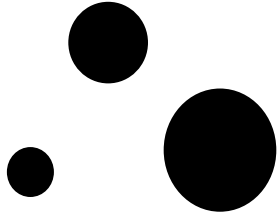


- The epidemic will continue to grow beyond the data collection cutoff point.

➡ Selection bias, i.e. right truncation (censoring) as to incubation period and serial interval



How to deal with the selection bias



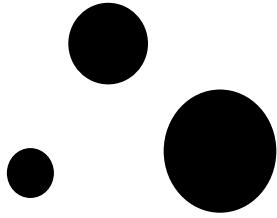
$$L(\Theta|\mathbf{D}) = \prod_i \int_{E_{L,i}}^{E_{R,i}} \int_{S_{L,i}}^{S_{R,i}} g(e) f'(s-e, e) ds de$$

Adjust for the right truncation

$$\begin{aligned} f'(s-e, e) &= \frac{f(s-e)}{\int_0^{T-e} \frac{\frac{d}{du}(1-S(u))}{1-S(u)} F(T-e-u) du} \\ &= \frac{f(s-e)}{\int_0^{T-e} \frac{r \exp(-ru)}{1-\exp(-ru)} F(T-e-u) du} \end{aligned}$$

- $S(\cdot)$: survival function
- $F(\cdot)$: cdf of the incubation period
- T : the latest time of observation

Fine point 1.



- Survival function $S(t)$ is non-increasing function over time taking on the value 1 at $t=0$.
- $S(t)$ indicates the probability that an observed case will survive to time t or beyond.
- Cumulative distribution function $F(t)$ is defined as $1-S(t)$.

$$S(t) \stackrel{\text{def}}{=} P[T \geq t] = 1 - F(t) \quad (T \text{ denotes a survival time})$$

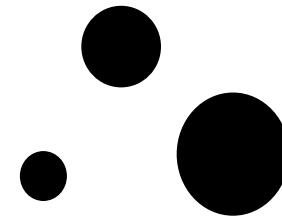
$$f(t) = \frac{dF(t)}{dt}$$

$$\lambda(t) = \lim_{h \rightarrow 0} \frac{P[t \leq T \leq t+h | T \geq t]}{h} = \frac{f(t)}{S(t)}$$

Assuming the exponential
growth of the outbreak...

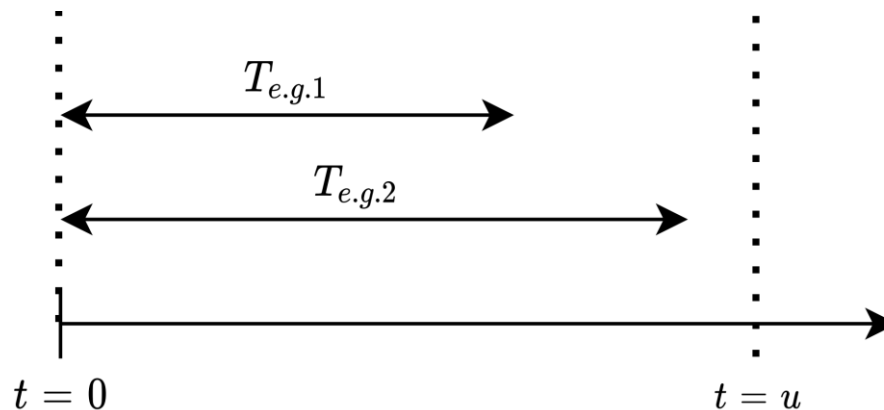
$$\begin{aligned} \frac{dS(t)}{dt} &= -rS(t) \\ S(t) &= e^{-rt} \end{aligned}$$

Fine point 2.

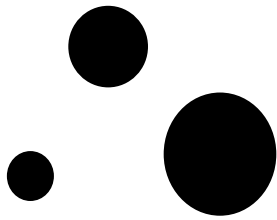


- To address the right truncated data, let us introduce the probability p to observe an event at time u conditional on $T \leq u$

$$p \propto \frac{f(u)}{1 - S(u)}$$



Fine point 3.



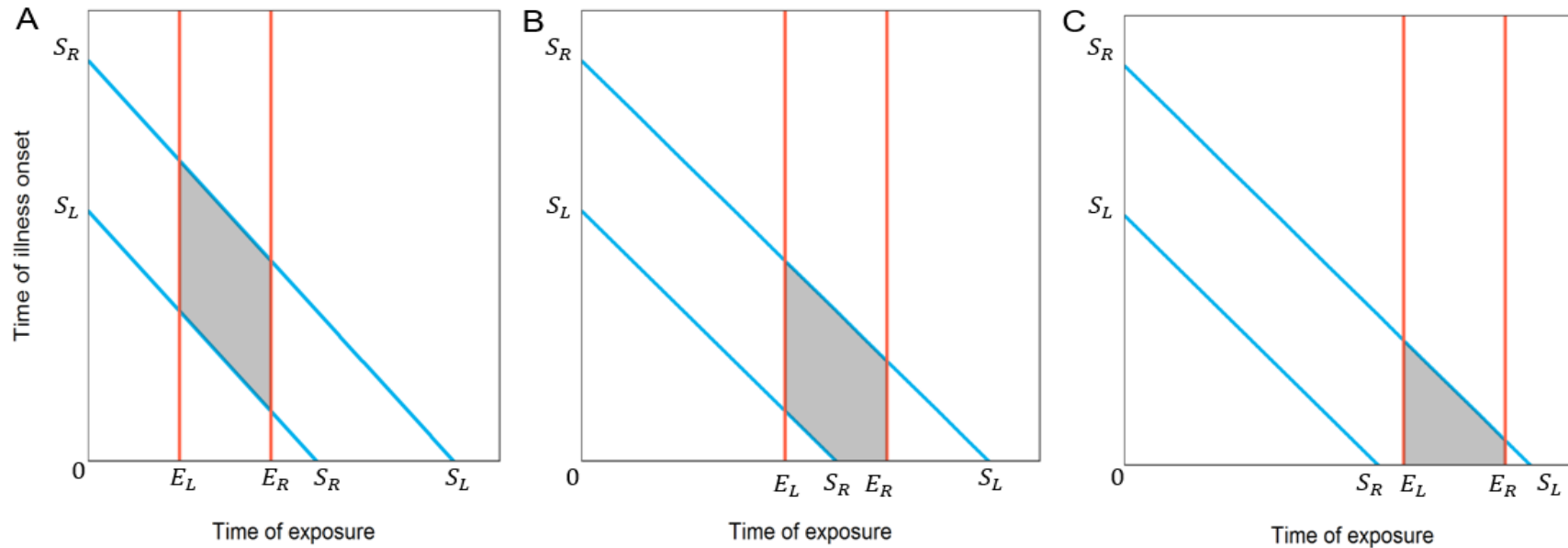
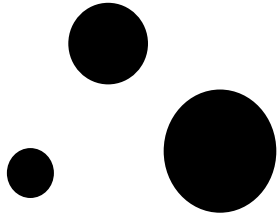
- Let us consider a truncated distribution to estimate time intervals using the right-truncated observations

$$h(x|\alpha \leq x \leq \beta) = \frac{h(x)}{H(\beta) - H(\alpha)} \quad h(x|x \leq \beta) = \frac{h(x)}{H(\beta)}$$

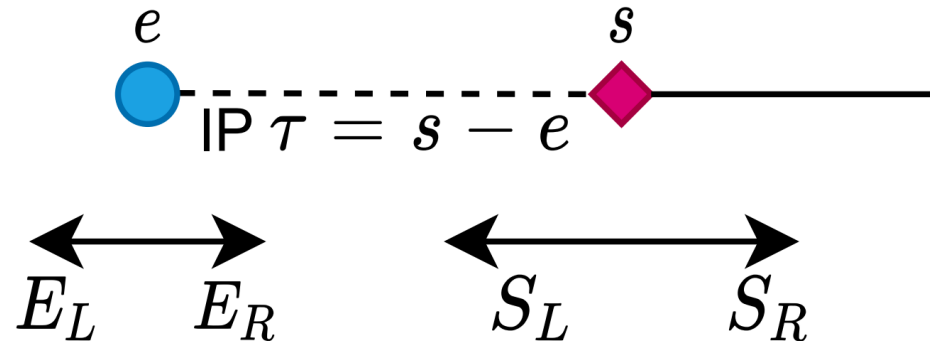
- Note that the adjusted formula (1) is formed as a truncated distribution taking account of the right truncation in the denominator.

$$\begin{aligned}
 f'(s-e, e) &= \frac{f(s-e)}{\int_0^{T-e} \frac{\frac{d}{du}(1-S(u))}{1-S(u)} F(T-e-u) du} \\
 &= \frac{f(s-e)}{\int_0^{T-e} \underbrace{\frac{r \exp(-ru)}{1 - \exp(-ru)}}_{\text{the probability of observations}} \underbrace{F(T-e-u)}_{\text{shorter length of IP}} du} \quad (1) \\
 &= \frac{f(s-e)}{F^*(T-e)}
 \end{aligned}$$

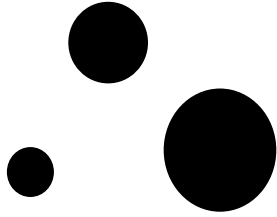
Exposure and onset fall as to IP



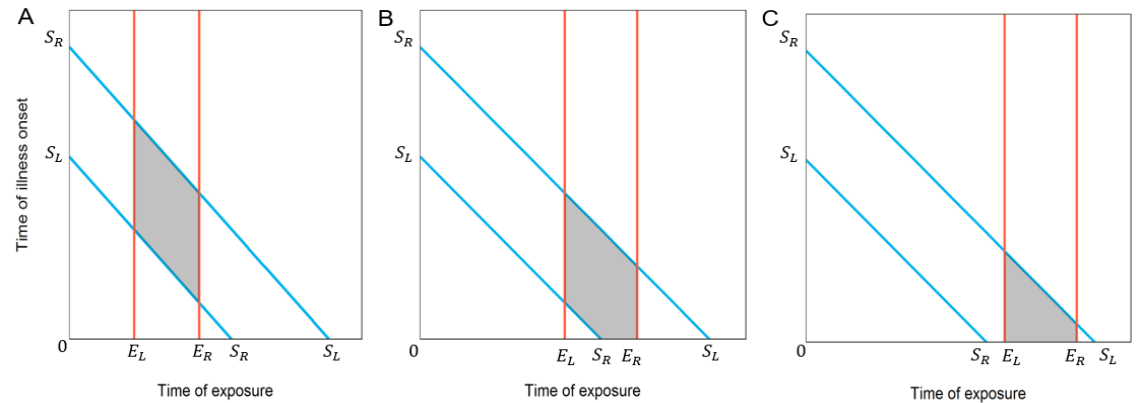
Linton et al. 2020



General form of the likelihood



$$\begin{aligned}\tau_i &= \int_{E_{L,i}}^{E_{R,i}} \int_{S_{L,i}}^{S_{R,i}} g(e) f'(s - e, e) ds de \\ &= \int_{E_{L,i}}^{E_{R,i}} de g(e) \int_{S_{L,i}}^{S_{R,i}} f'(s', e) ds' \quad (s' = s - e)\end{aligned}$$



Linton et al. 2020

(A) $S_{L,i} \geq E_{R,i}$

$$\begin{aligned}\tau_i &= \int_{E_{L,i}}^{E_{R,i}} de g(e) \int_{S_{L,i}}^{S_{R,i}} f'(s', e) ds' \\ &= \int_{E_{L,i}}^{E_{R,i}} g(e) (F'(S_{R,i} - e, e) - F'(S_{L,i} - e, e)) de\end{aligned}$$

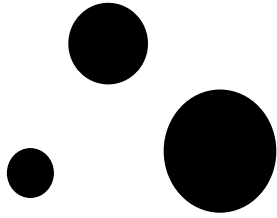
(B) $E_{R,i} \geq S_{L,i} \geq E_{L,i}$

$$\begin{aligned}\tau_i &= \int_{E_{L,i}}^{S_{L,i}} g(e) (F'(S_{R,i} - e, e) - F'(S_{L,i} - e, e)) de \\ &\quad + \int_{S_{L,i}}^{E_{R,i}} g(e) F'(S_{R,i} - e, e) de\end{aligned}$$

(C) $E_{L,i} \geq S_{L,i}$

$$\tau_i = \int_{E_{L,i}}^{E_{R,i}} g(e) F'(S_{R,i} - e, e) de$$

Method to infer parameter estimates

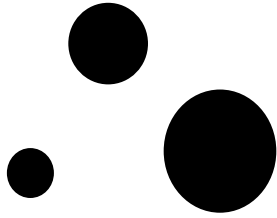


- Bayesian method and MLE
- Verify the Bayesian estimates were in line with pointwise estimates (MLE)

Implementation

- Data processing: R version 3.6.2
- Computing MLE: Julia version 1.3
- Computing MCMC (NUTS): CmdStan version 2.22.1

Set the priors



$$e_i = E_{L,i} + (E_{R,i} - E_{L,i})\tilde{e}_i$$

$$s_i = \hat{S}_{L,i} + (S_{R,i} - \hat{S}_{L,i})\tilde{s}_i$$

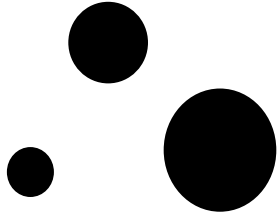
$$\hat{S}_{L,i} = e_i \text{ if } e_i > S_{L,i}, \text{ and } \hat{S}_{L,i} = S_{L,i}, \text{ otherwise}$$

$$\tilde{e}_i \sim \text{Norm}(\text{mean}=0.5, \text{SD}=0.5), \tilde{s}_i \sim \text{Norm}(\text{mean}=0.5, \text{SD}=0.5)$$

- Priors of parameters of time interval distributions were chosen as the Stan developer community generally recommends(*).
- Lognormal: $\log(\text{mean}) \sim \text{Norm}(0, 1)$, $\log(\text{SD}) \sim \text{Norm}(0, 1)$
- Weibull: $\log(\text{mean}) \sim \text{Norm}(0, 1)$, $\log(\text{SD}) \sim \text{Norm}(0, 1)$
- Gamma: $\text{shape} \sim \text{Norm}(3, 5)(> 0)$, $\text{scale}^{-1} \sim \text{Cauchy}(0, 5.0)$

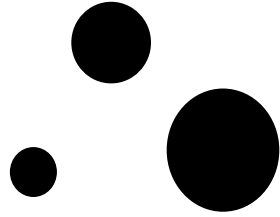
(*) <https://github.com/stan-dev/stan/wiki/Prior-Choice-Recommendations>

Three distributions for fitting



- Lognormal dist.
 - Weibull dist.
 - Gamma dist.
- Select the best-fit model
- Information criterion: Widely applicable information criterion (WAIC) (*)
 - Generally, structural models, e.g. Bayesian network, neural network, hidden Markov model, deep learning, etc., cannot apply AIC.
 - Structural model: models in which latent variables, hierarchical structures, or module structures contain
- (*) <http://watanabe-www.math.dis.titech.ac.jp/users/swatanab/waic2011.html>
- (*) <http://watanabe-www.math.dis.titech.ac.jp/users/swatanab/waic2011cont.html>
- (*) <http://watanabe-www.math.dis.titech.ac.jp/users/swatanab/joho-gakushu6.html>

Results (Linton et al.)



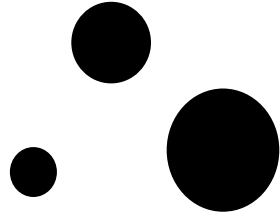
Accounting for right-truncation

Table 1. Incubation period and other time-delay distributions for COVID-19 outbreak cases reported in January 2020.

	Incubation Period Excluding WR (Days)	Incubation Period Including WR (Days)	Onset to Hospital Admission, Living (Days)	Onset to Hospital Admission, Deceased (Days)	Onset to Death (Days)	Hospital Admission to Death (Days)
Number of cases	52 cases	158 cases	155 cases	34 cases	34 cases	39 cases
			Lognormal			
Mean	5.0 (4.2, 6.0)	5.6 (5.0, 6.3)	3.9 (2.9, 5.3)	6.2 (5.0, 7.8)	14.5 (12.5, 17.0)	8.6 (6.8, 10.8)
SD	3.0 (2.1, 4.5)	2.8 (2.2, 3.6)	9.1 (5.2, 16.3)	4.3 (2.9, 6.6)	6.7 (4.9, 9.4)	6.7 (4.5, 10.3)
5%	1.7 (1.2, 2.3)	2.3 (1.9, 2.7)	0.2 (0.1, 0.3)	1.9 (1.2, 2.5)	6.5 (4.9, 7.9)	2.2 (1.5, 3.0)
Median	4.3 (3.5, 5.1)	5.0 (4.4, 5.6)	1.5 (1.2, 1.9)	5.1 (4.1, 6.3)	13.2 (11.3, 15.3)	6.7 (5.3, 8.3)
95%	10.6 (8.5, 14.1)	10.8 (9.3, 12.9)	14.0 (10.3, 20.1)	13.9 (10.8, 19.6)	26.8 (22.3, 34.5)	20.5 (15.7, 28.7)
99%	15.4 (11.7, 22.5)	14.9 (12.3, 18.7)	35.0 (23.2, 56.9)	21.1 (15.3, 32.8)	36.0 (28.6, 49.8)	32.6 (23.3, 50.1)
WAIC	257.2	859.6	693.5	183.9	221.9	240.1
Weight	1.00	1.00	0.00	0.33	1.00	0.02
			Weibull			
Mean	5.4 (4.3, 6.6)	5.8 (5.2, 6.5)	3.4 (2.7, 4.2)	6.5 (5.2, 8.0)	15.1 (12.7, 17.8)	8.9 (7.3, 10.4)
SD	3.6 (2.8, 4.7)	2.8 (2.3, 3.5)	4.4 (3.3, 6.0)	4.0 (3.1, 5.4)	7.6 (6.1, 9.7)	5.4 (4.2, 7.3)
5%	0.9 (0.5, 1.4)	2.1 (1.5, 2.6)	0.1 (0.0, 0.1)	1.9 (1.2, 2.5)	4.2 (2.5, 6.0)	1.7 (0.9, 2.7)
Median	4.7 (3.6, 5.8)	5.3 (4.7, 6.0)	1.8 (1.4, 2.3)	5.1 (4.1, 6.3)	14.3 (11.8, 17.1)	8.0 (6.2, 9.8)
95%	12.0 (9.8, 15.6)	11.0 (9.6, 12.9)	11.7 (9.3, 15.6)	13.9 (10.8, 19.6)	28.6 (24.5, 34.9)	18.8 (15.5, 24.4)
99%	15.9 (12.8, 21.5)	14.2 (12.1, 17.0)	20.3 (15.3, 29.2)	21.1 (15.3, 32.8)	35.0 (29.5, 44.4)	24.2 (19.5, 33.0)
WAIC	273.8	871.8	662.4	185.5	231.3	236.1
Weight	0.00	0.00	0.00	0.29	0.00	0.96
			Gamma			
Mean	5.3 (4.3, 6.6)	6.0 (5.3, 6.7)	3.3 (2.7, 4.0)	6.5 (5.2, 8.0)	15.0 (12.8, 17.5)	8.8 (7.2, 10.8)
SD	3.2 (2.4, 4.3)	3.1 (2.7, 3.7)	4.2 (3.3, 5.4)	4.0 (2.9, 5.6)	6.9 (5.2, 9.1)	5.7 (4.3, 7.8)
5%	1.4 (0.7, 2.0)	1.5 (1.1, 2.0)	0.0 (0.0, 0.1)	1.6 (0.8, 2.4)	5.8 (3.9, 7.6)	1.9 (1.0, 2.9)
Median	4.7 (3.8, 5.7)	5.6 (4.9, 6.4)	1.7 (1.2, 2.2)	5.6 (4.5, 6.9)	13.9 (11.8, 17.1)	7.6 (6.0, 9.3)
95%	11.3 (9.2, 14.5)	11.7 (10.3, 13.4)	11.6 (9.4, 14.7)	13.8 (11.1, 18.6)	27.4 (23.2, 34.1)	19.9 (15.7, 25.7)
99%	15.2 (12.0, 20.2)	14.5 (12.6, 16.9)	19.4 (15.4, 25.1)	18.6 (14.6, 26.2)	34.9 (28.8, 44.8)	26.8 (21.1, 36.5)
WAIC	265.8	895.9	656.6	183.4	225.1	236.3
Weight	0.00	0.00	1.00	0.38	0.00	0.02

WR: Wuhan residents. SD: standard deviation. WAIC: widely applicable information criterion.

Results (Linton et al.)



Not accounting for right-truncation

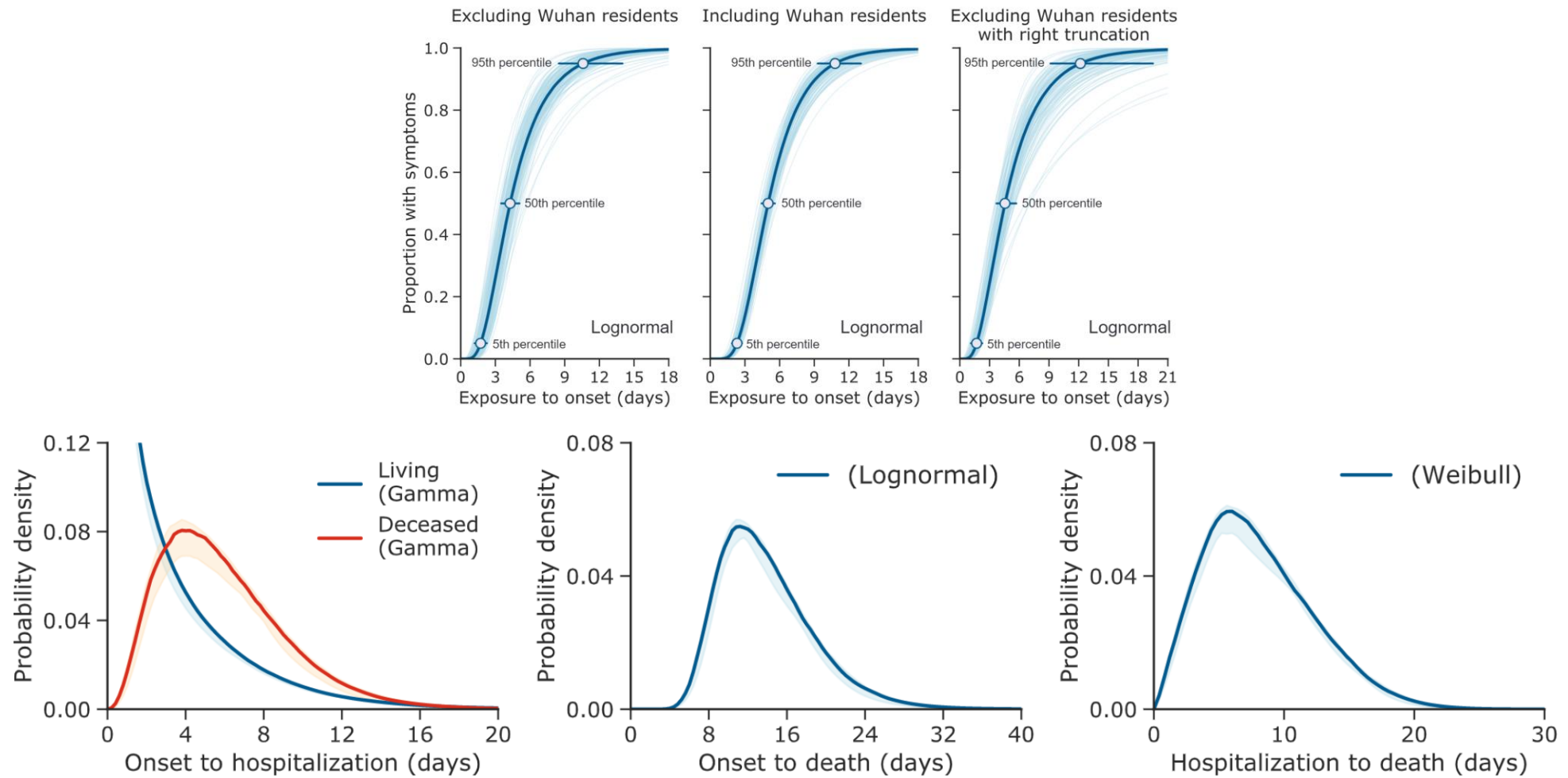
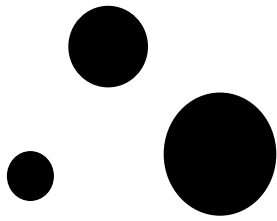
Table 2. Right-truncated incubation period and other time-delay distributions for COVID-19 outbreak cases reported in January 2020 applied to the lognormal distribution.

Lognormal	Incubation Period Excluding WR (Days)	Onset to Hospital Admission, Living (Days)	Onset to Hospital Admission, Deceased (Days)	Onset to Death (Days)	Hospital Admission to Death (Days)
Mean	5.6 (4.4, 7.4)	9.7 (5.4, 17.0)	6.6 (5.2, 8.8)	20.2 (15.1, 29.5)	13.0 (8.7, 20.9)
SD	3.9 (2.4, 6.9)	35.2 (12.9, 84.5)	4.9 (3.0, 8.6)	11.6 (6.6, 21.8)	12.7 (6.4, 26.0)
5%	1.7 (1.1, 2.3)	0.2 (0.1, 0.3)	1.9 (1.2, 2.5)	7.4 (5.6, 9.5)	2.5 (1.6, 3.6)
Median	4.6 (3.7, 5.7)	2.6 (1.9, 3.8)	5.3 (4.2, 6.8)	17.1 (13.5, 24.1)	9.1 (6.7, 13.7)
95%	12.3 (9.1, 19.8)	35.1 (20.5, 65.0)	15.0 (11.2, 23.8)	39.9 (27.9, 69.6)	33.1 (20.9, 56.7)
99%	18.6 (12.7, 34.2)	102.8 (52.8, 218.4)	23.2 (16.0, 41.6)	56.7 (37.0, 109.2)	56.7 (32.5, 125.2)

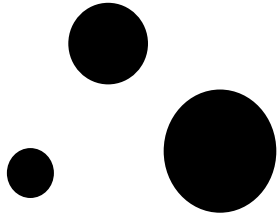
WR: Wuhan residents. SD: standard deviation.

Linton et al. 2020

Results (Linton et al.)



Results (Nishiura et al.)



Accounting for right-truncation

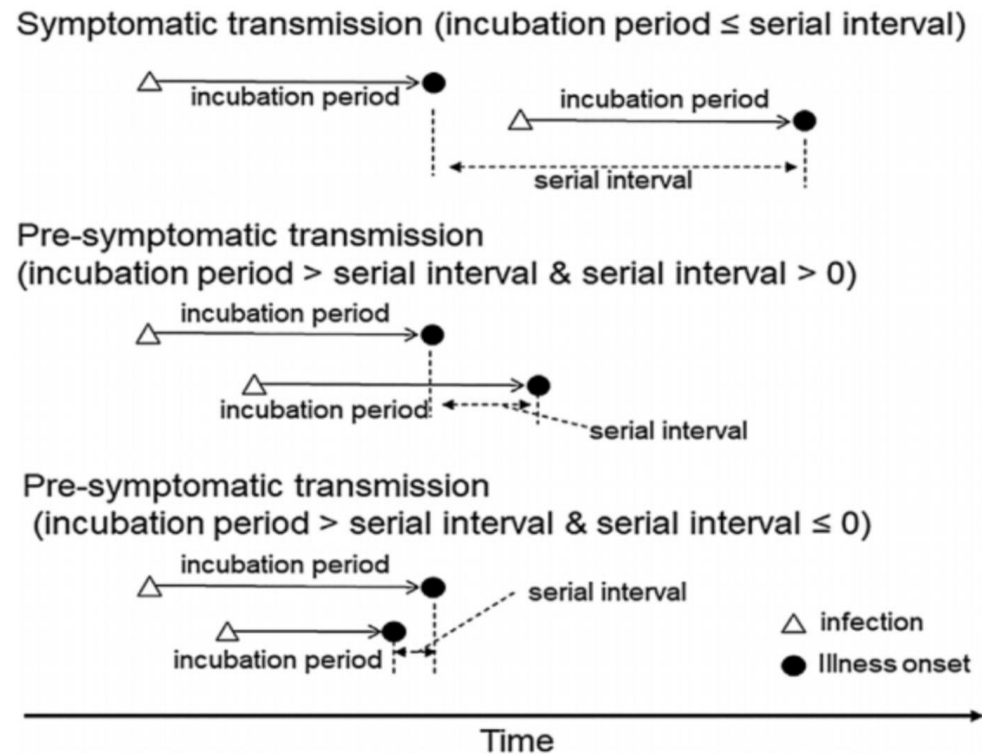
- Lognormal distribution was selected as the best-fit model (WAIC=224.0)
- The median serial interval: 4.0 days (95%CrI: 3.1, 4.9)
- Mean: 4.7 days (95%CrI: 3.7, 6.0)
- SD: 2.9 days (95%CrI: 1.9, 4.9)

Not accounting for right-truncation

- Lognormal distribution was selected as the best-fit model (WAIC=128.0)
- The median serial interval: 3.9 days (95%CrI: 3.1, 4.8)

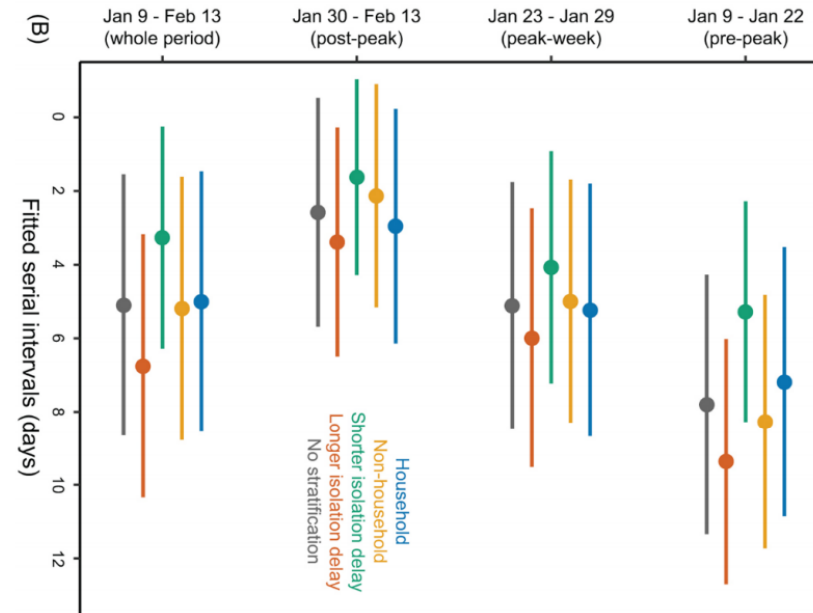
Results (Nishiura et al.)

- The estimated median serial interval (4.0 days) < the mean incubation period (5.0 days)
- Pre-symptomatic infection is likely to have taken place and may occur more frequently than symptomatic transmission.



Serial interval

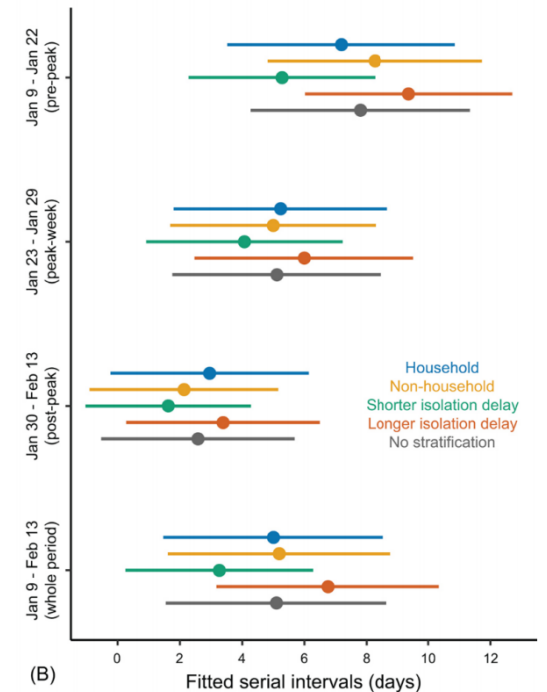
- Serial interval has been used approximately as generation time.
- Have large variance because containing two incubation periods.
- Also vulnerable to the impact of non-pharmaceutical interventions (e.g. case isolation), severity, etc. [4][11]
- According to [4], the serial interval of COVID-19 is shortened by NPIs.



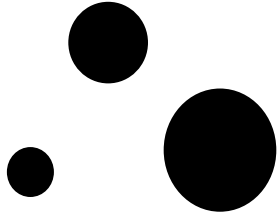
Serial interval

- Serial interval has been used approximately as generation time.
- Have large variance because containing two incubation periods.
- Also vulnerable to the impact of non-pharmaceutical interventions (e.g. case isolation), severity, etc. [4][11]
- According to [4], the serial interval of COVID-19 is shortened by NPIs.
- Potential of biased estimation of reproduction number [13]

If possible, estimate GT
to avoid the biased
estimation!



Types of generation time

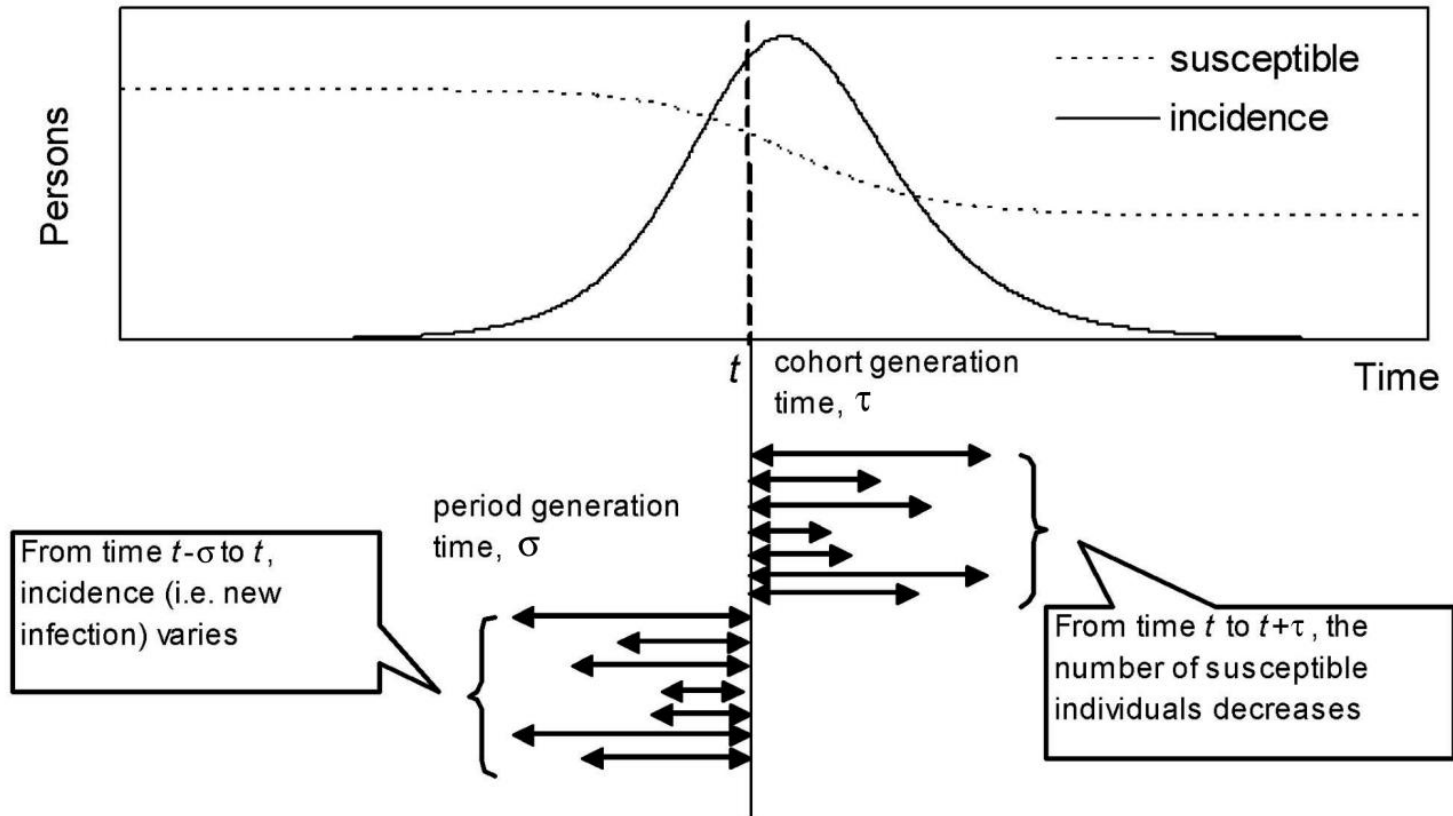
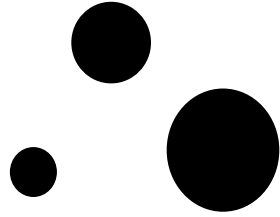


- Generation time is paramount in the estimation of reproduction number based on renewal equation.

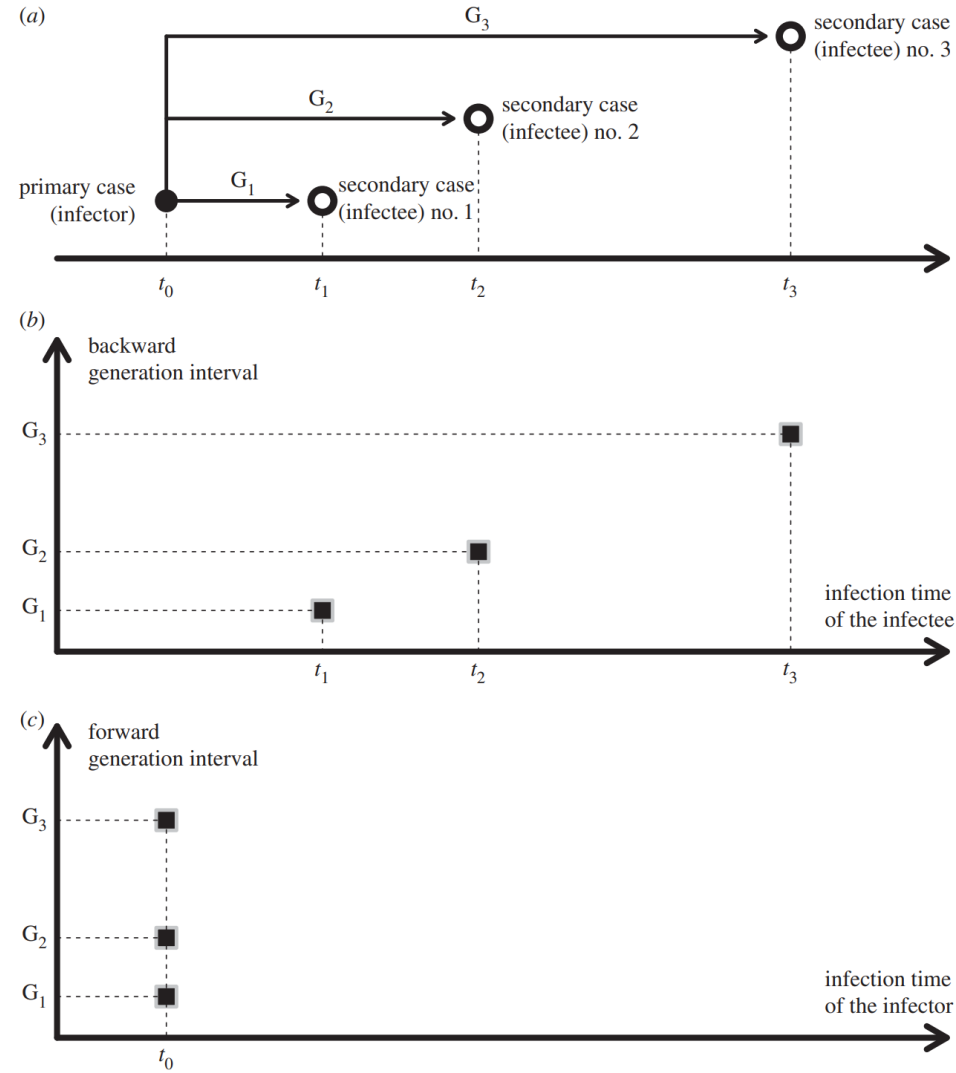
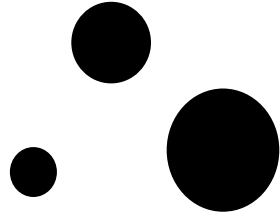
$$i(t) = R(t) \int_0^{\infty} g(t, \tau) i(t - \tau) d\tau$$

- This intrinsic generation time is different from empirical generation time.
- Two types of empirically derived estimates of generation time [5][6][7][13][14]
 - Backward generation interval (period generation time)
 - Forward generation interval (cohort generation time)

Two empirical generation times



Two empirical generation times



The formulation of three GTs

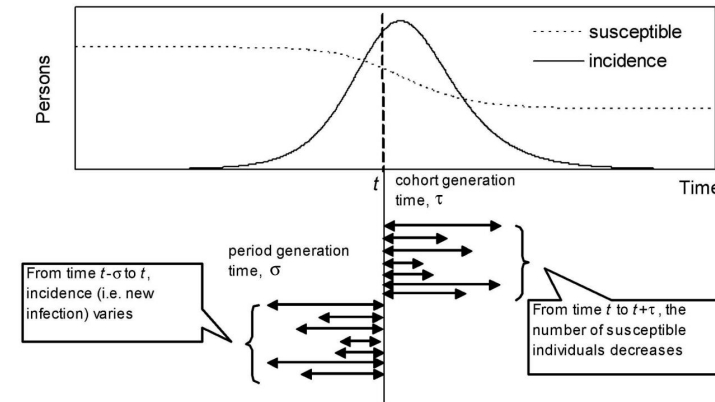
- Period generation time has the potential of selection bias [6][13].

└ length time bias

$$i(t) = R(t) \int_0^\infty g(t, \tau) i(t - \tau) d\tau$$

$$g_c(\tau) = \frac{g(\tau) i(t - \tau)}{\int_0^\infty g(\sigma) i(t - \sigma) d\sigma}$$

$$g_p(\tau) = \frac{g(\tau) S(t + \tau)}{\int_0^\infty g(\mu) i(t + \mu) d\mu}$$



Nishiura. 2010

- More details are explored in [5][6][7].

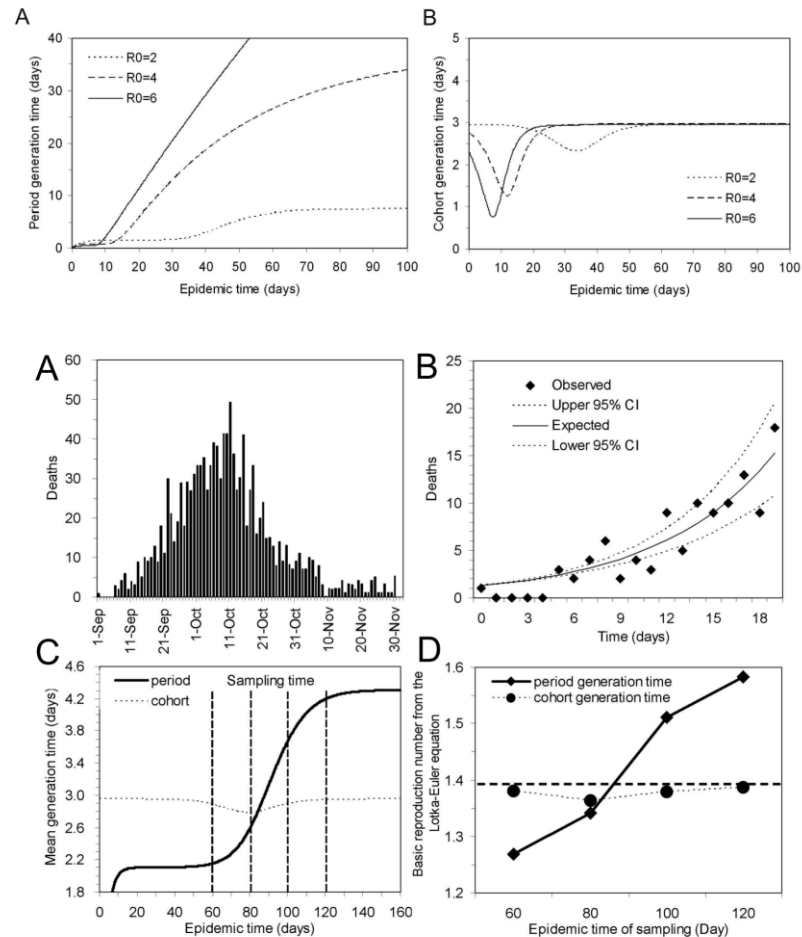
([5] mentions the model of exponential growth of incidence)

([6] constructs the Erlang SEIR model to check the trajectories of two GT)

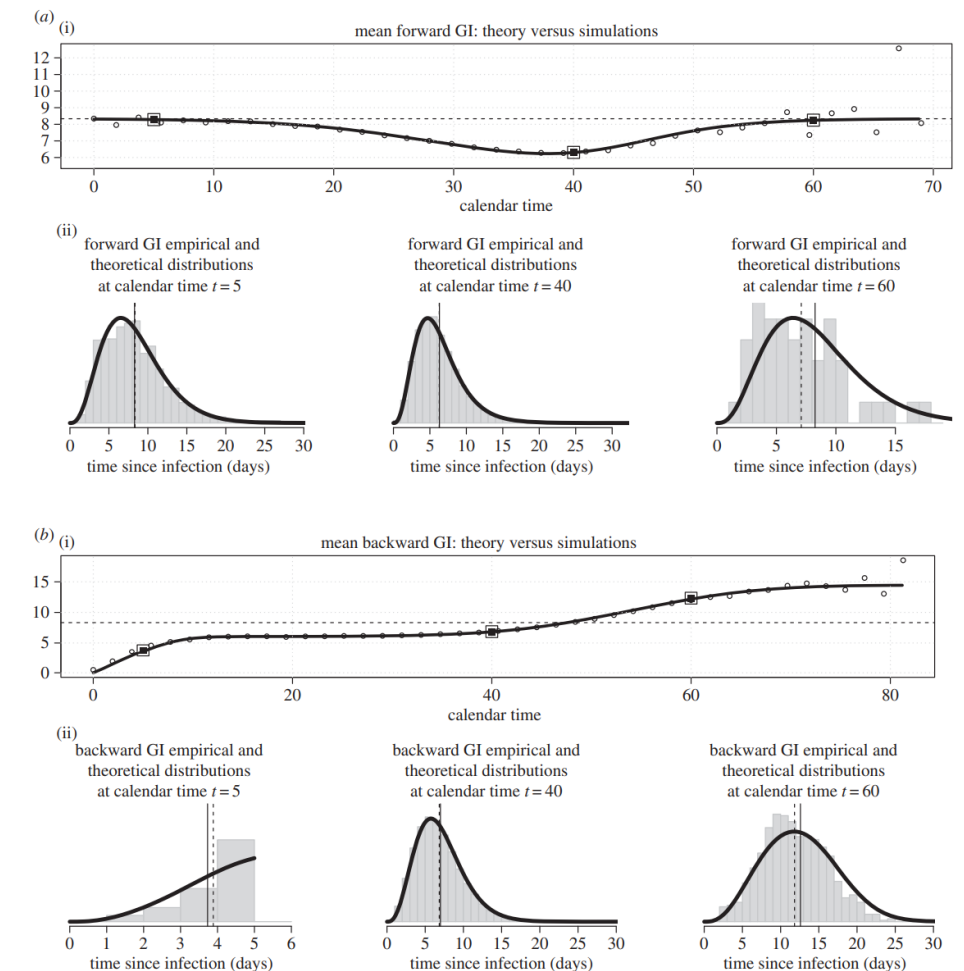
- $g(\tau)$: intrinsic generation time
- $g_c(\tau)$: cohort (forward) generation time
- $g_p(\tau)$: period (backward) generation time
- $i(t)$: incidence at time t
- $S(t)$: the proportion of susceptible individuals in the population
- τ : infection age

Biased estimates of generation time

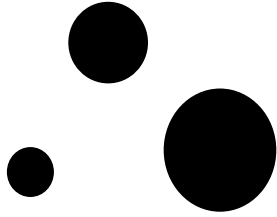
Nishiura [5]



Champredon et al. [6]



Today's main papers

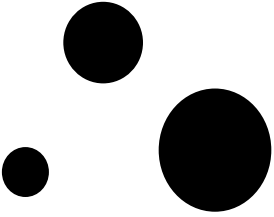


- Linton NM, Kobayashi T, Yang Y, et al. Incubation Period and Other Epidemiological Characteristics of 2019 Novel Coronavirus Infections with Right Truncation: A Statistical Analysis of Publicly Available Case Data. *J Clin Med*. 2020;9(2):538. Published 2020 Feb 17. doi:10.3390/jcm9020538
- Nishiura H, Linton NM, Akhmetzhanov AR. Serial interval of novel coronavirus (COVID-19) infections. *Int J Infect Dis*. 2020;93:284-286. doi:10.1016/j.ijid.2020.02.060
- Ganyani T, Kremer C, Chen D, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Euro Surveill*. 2020;25(17):2000257. doi:10.2807/1560-7917.ES.2020.25.17.2000257



Some other articles

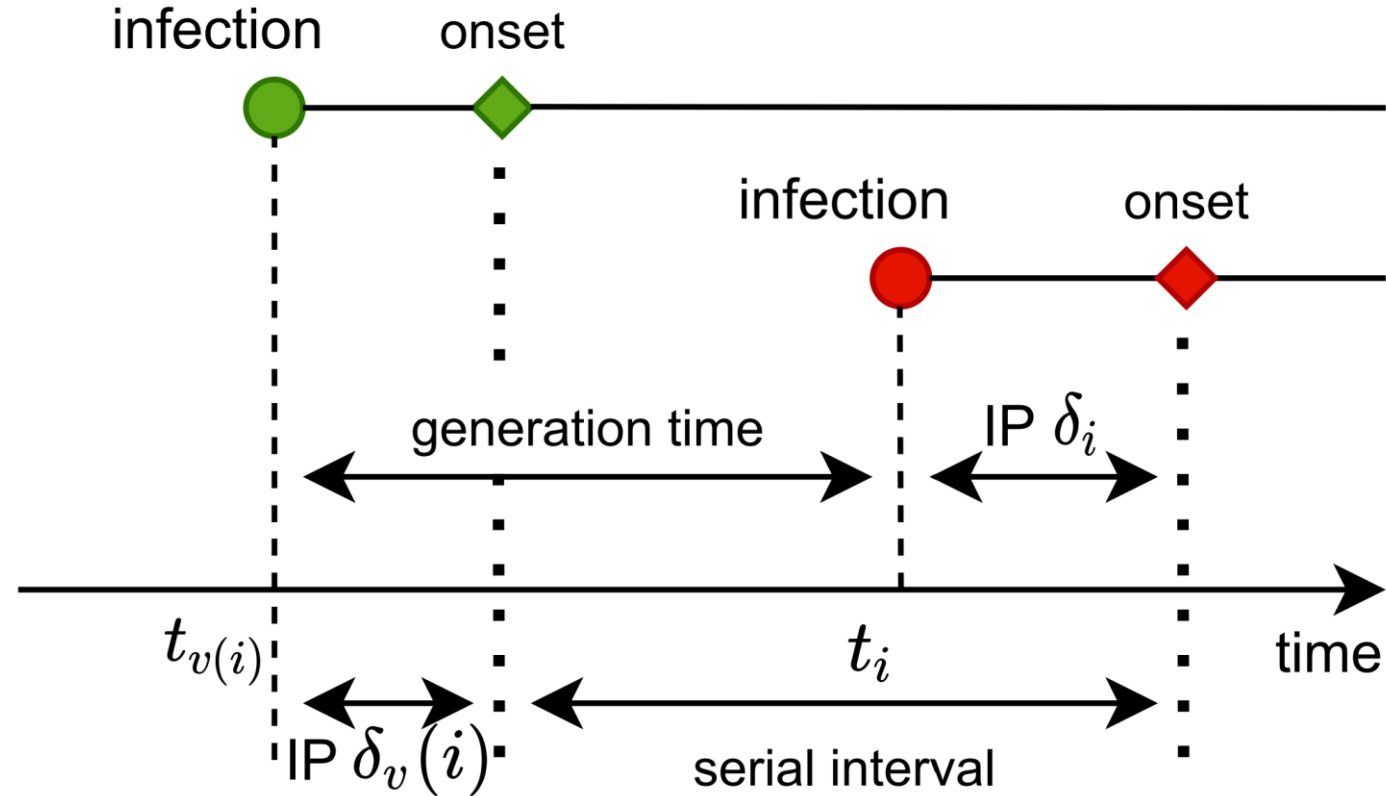
Notations



- This paper mainly estimated the generation time distribution and serial interval distribution.
- Also they revealed the biased estimates of reproduction number based on SI and quantified the contribution of pre-symptomatic transmission in the epidemic.
- Let us follow the stuff about time interval here.

Model

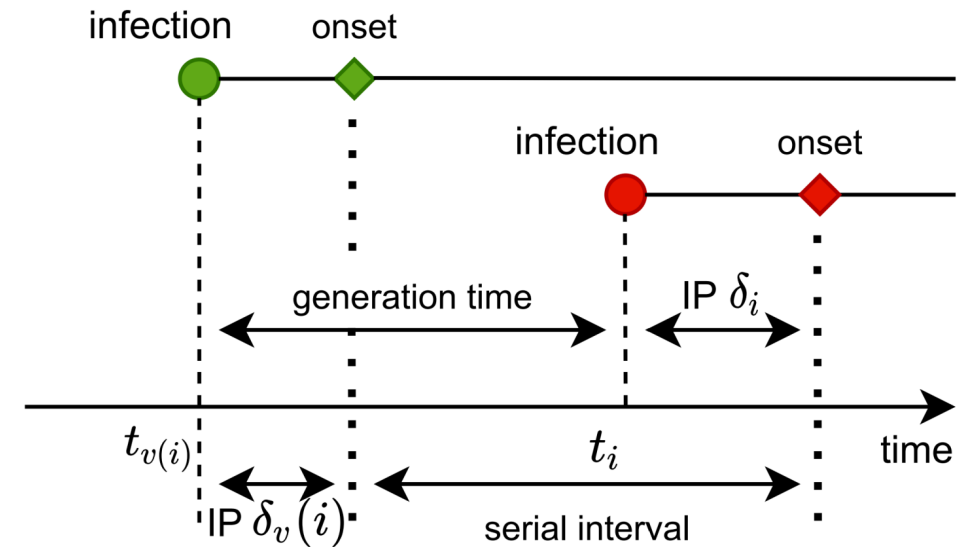
- The relationship of GT, SI, and IP



Model

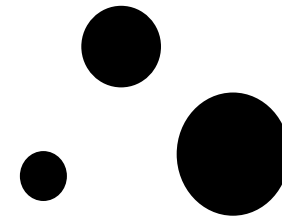
$$\begin{aligned} Z_i &= (t_i + \delta_i) - (t_{v(i)} + \delta_{v(i)}) \\ &= (t_i - t_{v(i)}) + (\delta_i - \delta_{v(i)}) \\ &= X_i + Y_i \end{aligned}$$

- X_i and δ_i are positive and independent [9]
- $X_i \sim f(x; \Theta_1)$
- $\delta_i \sim k(\delta; \Theta_2)$
- $Y_i \sim g(y_i; \Theta_2)$



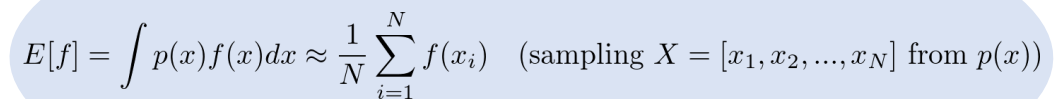
➡ SI and GT has the same mean but SI has larger variance because containing two IP

Model



- $z_i = x_i + y_i$: observed SI ← Latent variables
- $z_i \sim h(z_i; \Theta_1, \Theta_2)$

$$h(z; \Theta_1, \Theta_2) = (f * g)(z) = \int_{-\infty}^{\infty} f(z - y; \Theta_1) g(y; \Theta_2) dy$$


$$E[f] = \int p(x) f(x) dx \approx \frac{1}{N} \sum_{i=1}^N f(x_i) \quad (\text{sampling } X = [x_1, x_2, \dots, x_N] \text{ from } p(x))$$

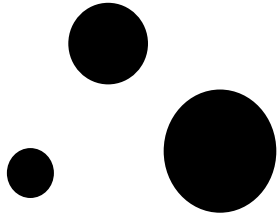
$$\begin{aligned} h(z; \Theta_1, \Theta_2) &= (f * g)(z) = \int_{-\infty}^{\infty} f(z - y; \Theta_1) g(y; \Theta_2) dy \\ &= E_Y[f(z - y; \Theta_1)] \\ &= \frac{1}{J} \sum_{j=1}^J f(z - y_j; \Theta_1) \end{aligned}$$

Monte Carlo integration

Likelihood function

$$L(\Theta | z_i, v(i)) = \prod_{i=2}^n \frac{1}{J} \sum_{j=1}^J f(z - y_j; \Theta_1) \quad (\Theta = [\Theta_1, \Theta_2])$$

Parameter estimation



- In this article, the estimated GT represents “period generation time”.
- Assume that some cases with no infector information missing could have been infected by any other case within the same cluster.

Bayesian method

- First step: update the missing links

$v(i)^{missing}$ are assigned equal prior probabilities

MCMC: independence sampler

- Second step: update the parameter vector Θ_1 IP and GT are gamma distributed.

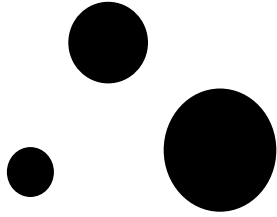
GT: $f(x; \Theta_1) \equiv \Gamma(\alpha_1, \beta_1)$, $\alpha_1 \sim U(0, 30)$, $\beta_1 \sim U(0, 20)$

IP: $k(\delta; \Theta_2) \equiv \Gamma(\alpha_2 = 3.45, \beta_2 = 0.66)$, mean=5.2 (The parameter vector Θ_2 is fixed.)

MCMC: random-walk Metropolis-Hastings algorithm

Iteration: 3,000,000 Burn-in: 500,000 Thinning: every 200th iteration (implemented in R version 3.6.2)

Results



Dataset	Scenario	Interval	Estimate (95% credible interval) (days)	
			Mean	SD
Singapore ^a	Baseline	GI	5.20 (3.78 - 6.78)	1.72 (0.91 - 3.93)
		SI	5.21 (-3.35 - 13.94)	4.32 (4.06 - 5.58)
Tianjin (China) ^b	Baseline	GI	3.95 (3.01 - 4.91)	1.51 (0.74 - 2.97)
		SI	3.95 (-4.47 - 12.51)	4.24 (4.03 - 4.95)

COVID-19: coronavirus disease; GI: generation interval; SD: standard deviation; SI: serial interval.

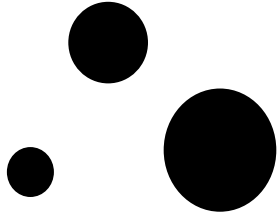
^a Source: Ministry of Health (<https://www.moh.gov.sg/news-highlights/>, as at 26 February).

^b Source: Tianjin Municipal Health Commission (<http://www.tjbd.gov.cn/zjbd/gsgg/>, as at 27 February).

Ganyani et al. 2020

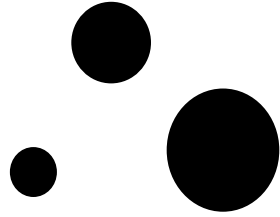
They replied a letter to this article here (https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.29.2001269#abstract_content).

The assumption of the independence

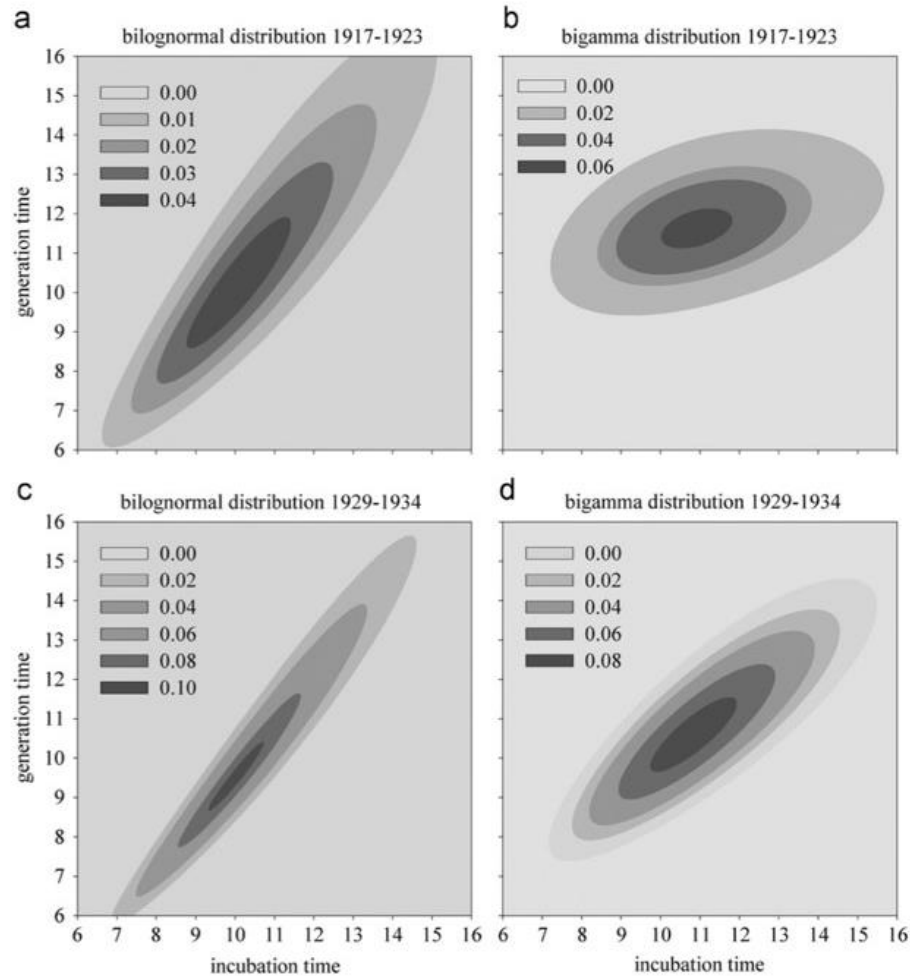


- Assume that generation time and incubation period are independent in this article.
- Similar method and assumptions are also adopted elsewhere [8]. (they obtained GT using deconvolution)
- Klinkenberg et al.[9] revealed the positive correlation between incubation period and generation time using household data of measles.
- Also it is biologically plausible to take into account the correlation.

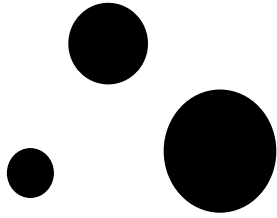
The correlation between GT and IP



Klinkenberg et al. [9]



The properties of time intervals



- The correlation of incubation period and generation time [9]
- Spatial heterogeneity of generation time [7]
- Generation time and serial interval contract when a case exposes more infectious contacts (competing risk) [10].
- Other relationships between SI, infectiousness profile, and GT has been also explored [12].

When constructing a model, we need to well understand the characteristics of natural histories, limitations of a model, and what can be indicated still there.

Reference

1. Linton NM, Kobayashi T, Yang Y, et al. Incubation Period and Other Epidemiological Characteristics of 2019 Novel Coronavirus Infections with Right Truncation: A Statistical Analysis of Publicly Available Case Data. *J Clin Med*. 2020;9(2):538. Published 2020 Feb 17. doi:10.3390/jcm9020538
2. Nishiura H, Linton NM, Akhmetzhanov AR. Serial interval of novel coronavirus (COVID-19) infections. *Int J Infect Dis*. 2020;93:284-286. doi:10.1016/j.ijid.2020.02.060
3. Ganyani T, Kremer C, Chen D, et al. Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020. *Euro Surveill*. 2020;25(17):2000257. doi:10.2807/1560-7917.ES.2020.25.17.2000257
4. Ali ST, Wang L, Lau EHY, et al. Serial interval of SARS-CoV-2 was shortened over time by nonpharmaceutical interventions. *Science*. 2020;369(6507):1106-1109. doi:10.1126/science.abc9004
5. Nishiura H. Time variations in the generation time of an infectious disease: implications for sampling to appropriately quantify transmission potential. *Math Biosci Eng*. 2010;7(4):851-869. doi:10.3934/mbe.2010.7.851
6. Champredon D, Dushoff J. Intrinsic and realized generation intervals in infectious-disease transmission. *Proc Biol Sci*. 2015;282(1821):20152026. doi:10.1098/rspb.2015.2026
7. Park SW, Champredon D, Dushoff J. Inferring generation-interval distributions from contact-tracing data. *J R Soc Interface*. 2020;17(167):20190719. doi:10.1098/rsif.2019.0719
8. Knight J, Mishra S. Estimating effective reproduction number using generation time versus serial interval, with application to covid-19 in the Greater Toronto Area, Canada. *Infect Dis Model*. 2020;5:889-896. doi:10.1016/j.idm.2020.10.009
9. Klinkenberg D, Nishiura H. The correlation between infectivity and incubation period of measles, estimated from households with two cases. *J Theor Biol*. 2011;284(1):52-60. doi:10.1016/j.jtbi.2011.06.015
10. Kenah E, Lipsitch M, Robins JM. Generation interval contraction and epidemic data analysis. *Math Biosci*. 2008;213(1):71-79. doi:10.1016/j.mbs.2008.02.007
11. Chan YH, Nishiura H. Estimating the protective effect of case isolation with transmission tree reconstruction during the Ebola outbreak in Nigeria, 2014. *J R Soc Interface*. 2020;17(169):20200498. doi:10.1098/rsif.2020.0498
12. Lehtinen S, Ashcroft P, Bonhoeffer S. On the relationship between serial interval, infectiousness profile and generation time. *J R Soc Interface*. 2021;18(174):20200756. doi:10.1098/rsif.2020.0756
13. Britton T, Scalia Tomba G. Estimation in emerging epidemics: biases and remedies. *J R Soc Interface*. 2019;16(150):20180670. doi:10.1098/rsif.2018.0670
14. Scalia Tomba G, Svensson A, Asikainen T, Giesecke J. Some model based considerations on observing generation times for communicable diseases. *Math Biosci*. 2010;223(1):24-31. doi:10.1016/j.mbs.2009.10.004