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Estimating effective reproduction number using generation time versus serial interval, with application to COVID-19 in the Greater Toronto Area, Canada

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ABSTRACT

BACKGROUND. The effective reproduction number $R_e(t)$ is a critical measure of epidemic potential. $R_e(t)$ can be calculated in near real time using an incidence time series and the generation time distribution: the time between infection events in an infector-infectee pair. In calculating $R_e(t)$, the generation time distribution is often approximated by the serial interval distribution: the time between symptom onset in an infector-infectee pair. However, while generation time must be positive by definition, serial interval can be negative if transmission can occur before symptoms, such as in COVID-19, rendering such an approximation improper in some contexts. METHODS. We developed a method to infer the generation time distribution from parametric definitions of the serial interval and incubation period distributions. We then compared estimates of $R_e(t)$ for COVID-19 in the Greater Toronto Area of Canada using: negative-permitting versus non-negative serial interval distributions, versus the inferred generation time distribution. RESULTS. We estimated the generation time of COVID-19 to be Gamma-distributed with mean 3.99 and standard deviation 2.96 days. Relative to the generation time distribution, non-negative serial interval distribution caused overestimation of $R_e(t)$ due to larger mean, while negative-permitting serial interval distribution caused underestimation of $R_e(t)$ due to larger variance. IMPLICATIONS. Approximation of the generation time distribution of COVID-19 with non-negative or negative-permitting serial interval distributions when calculating $R_e(t)$ may result in over or underestimation of transmission potential, respectively.

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1. Introduction

The effective reproduction number $R_e(t)$ provides an instantaneous measure of transmission potential or the rate of spread of an epidemic. Cori et al. (2013) provide a method to estimate $R_e(t)$ in quasi-real time based on only two inputs: an incidence time series,[1] and the generation time distribution. The generation time is defined as the time between infection events in an infector-infectee pair.

When estimating $R_e(t)$ in previous epidemics (Ali et al., 2013; Aylward et al., 2014; Cori et al., 2013) and in COVID-19 (Cowling et al., 2020; Leung et al., 2020; Liu et al., 2020; Pan et al., 2020), the generation time has been approximated by the serial interval. The serial interval is defined as the time between symptom onset in an infector-infectee pair. Unlike infection events, symptom onset is directly observable. This approximation is reasonable for infectious diseases where onset of infectiousness and symptoms is effectively simultaneous (Cori et al., 2013) such for SARS and Ebola (Osterholm et al., 2015; Zeng et al., 2009). However, potential pre-symptomatic transmission of COVID-19 (Du et al., 2020; Kimball et al., 2020) renders approximation of generation time by serial interval problematic. Namely, while generation time is strictly positive, the serial interval can be negative, such as in 59 of 468 (12.6%) reported cases in (Du et al., 2020), due to variability in the incubation period. As a result, COVID-19 serial interval data have been used to fit both non-negative and negative-permitting distributions, yielding different estimates of $R_e(t)$ (Du et al., 2020; Ganyani et al., 2020; Zhang, Litvinova, et al., 2020).

We compared estimates of $R_e(t)$ and their implications using each of the following approximations of the generation time distribution: (a) negative-permitting distribution fit to serial interval data; (b) non-negative distribution fit to serial interval data; and (c) inferred generation time distribution based on the incubation period and the serial interval distributions. We used parametric distributions described in the literature for COVID-19, and reported cases from the Greater Toronto Area (GTA), Canada.

2. Methods

First, we designed a simple method to recover the generation time distribution from parametric definitions of the incubation period and serial interval distributions, similar to work by Kuk and Ma (2005) and Britton and Tomba (2019). We then applied the method to COVID-19 using published incubation period and serial interval distributions. Finally, we compared $R_e(t)$ estimated for the Greater Toronto Area (GTA) region of Canada between March 08 and April 15, 2020 using the estimated generation time distribution versus negative permitting and non-negative serial interval distributions reported in the literature.

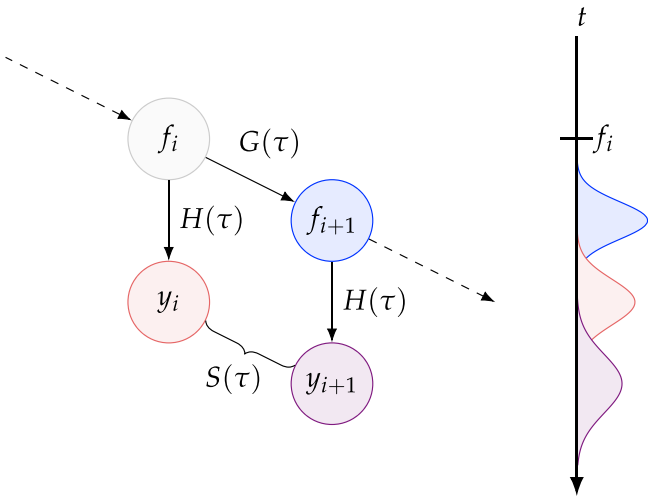

Fig. 1. Random variables involved in the serial interval
Notation — i: infector index; $i+1$: infectee index; f_i: time of infection; y_i: time of symptom onset; $G(\tau)$: generation time distribution; $H(\tau)$: incubation time distribution; $S(\tau)$: serial interval distribution.

[1] Incidence may be further stratified by imported versus locally generated cases to quantify local transmission dynamics.

2.1. Estimating the generation time distribution

Let i and $i+1$ be the indices of an infector-infectee pair. Let f_i and f_{i+1} be the respective times of infection, such that $g_i = [f_{i+1} - f_i] \sim G(\tau)$ is the generation time. Let y_i be the time of symptom onset in case i, such that $h_i = [y_i - f_i] \sim H(\tau)$ is the incubation period. Finally, let $s_i = [y_{i+1} - y_i] \sim S(\tau)$ be the serial interval. Fig. 1 illustrates the variables and distributions graphically. We assume all distributions are independent, although previous work has shown that the generation time and incubation period may be correlated, for example, in the context of measles (Klinkenberg & Nishiura, 2011).

Rearranging, we have: $s_i = g_i + h_{i+1} - h_i$. The probability distribution of the sum of independent random variables is the convolution of their respective distributions (Hogg et al., 2005), where convolution * is defined as:

$$[K * F](\tau) = \int_{-\infty}^{+\infty} K(z)\, F(\tau - z)\, dz \tag{1}$$

Thus $S(\tau)$ can be defined as:

$$S(\tau) = G(\tau) * H(\tau) * H(-\tau) \tag{2}$$

and $G(\tau)$ can be recovered using deconvolution $*^{-1}$ as:

$$G(\tau) = \left[S(\tau) *^{-1} H(\tau)\right] *^{-1} H(-\tau) \tag{3}$$

Some definitions of $S(\tau)$ and $H(\tau)$ may yield forms of $G(\tau)$ via deconvolution in (3) which are implausible or intractable. So, we defined a parametric form $\hat{G}(\tau \mid \theta)$, and found parameters θ^* that minimized the Kullback-Leibler divergence between the observed $S(\tau)$ and $\hat{S}(\tau \mid \theta)$ obtained via (2) using $\hat{G}(\tau \mid \theta^*)$. It can be shown that such parameters θ^* provide the maximum likelihood estimate (MLE) of $S(\tau)$ under $\hat{G}(\tau \mid \theta)$.

2.2. Application

2.2.1. Generation time

We identified several parameterizations of the COVID-19 incubation period and serial interval following the review by Park et al. (2020) (Table A.1).[2] For our analysis, we used the negative-permitting serial interval from (Du et al., 2020) ($N = 468$):

$$S(\tau) = Norm(\mu = 3.96,\ \sigma = 4.75) \tag{4}$$

and the incubation period from (Lauer et al., 2020) ($N = 181$):

$$H(\tau) = Gam(\alpha = 5.807,\ \beta = 0.948) \tag{5}$$

We assumed a Gamma parametric form for the generation time distribution $\hat{G}(\tau \mid \theta)$, with $\theta = [\alpha$ (shape), β (scale)], for consistency with downstream assumptions used in calculating $R_e(t)$. We then minimized the Kullback-Leibler divergence between $S(\tau)$ and $\hat{S}(\tau \mid \theta)$ using the Nelder-Mead optimization method in the optimization R package[3] to obtain the MLE generation time distribution parameters θ^*.

2.2.2. Effective reproduction number

In the model described by Cori et al. (2013), the incidence I at time t is given by the integral over all previous infections, multiplied by their respective infectivity ω at time τ since infection, collectively multiplied by the effective reproduction number R_e at time t. This model yields the following definition of $R_e(t)$:

$$R_e(t) = I(t) \left[\int_0^t I(t-\tau)\, \omega(\tau)\, d\tau\right]^{-1} \tag{6}$$

The infectivity profile $\omega(\tau)$ is equivalent to the generation time distribution $G(\tau)$. Given $I(t)$ and $G(\tau)$, probabilistic estimates of $R_e(t)$ can then be resolved in a Bayesian framework, as implemented in the EpiEstim R package.[4]

[2] Some studies did not provide enough information to define a parametric form (e.g. only reported the mean).
[3] https://cran.r-project.org/web/packages/optimization.
[4] https://cran.r-project.org/web/packages/EpiEstim.

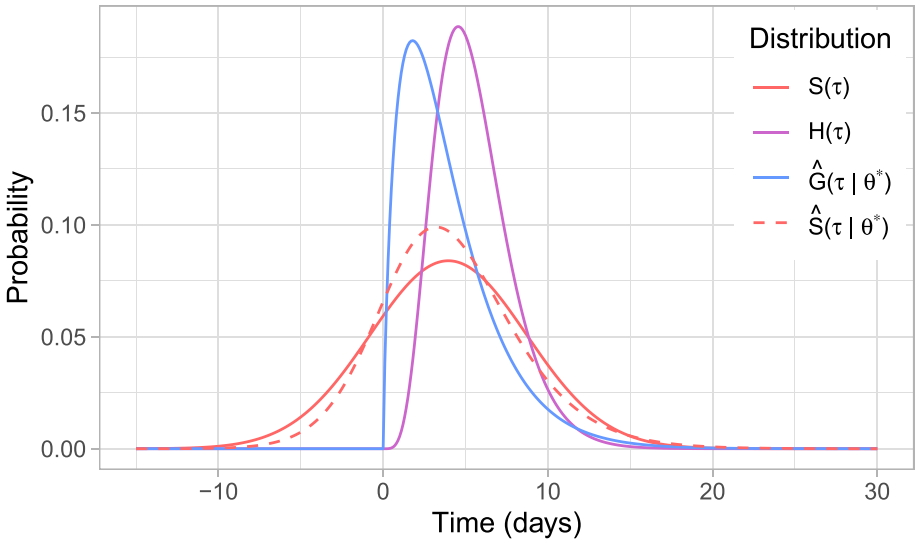

Fig. 2. Recovered generation time distribution $\hat{G}(\tau \mid \theta^*)$ based on MLE approximation of the serial interval distribution $S(\tau)$ by $\hat{S}(\tau \mid \theta^*)$ and the incubation period distribution $H(\tau)$.

In order to quantify $R_e(t)$ of COVID-19 in GTA, Canada, we used reported cases in the region with episode dates between March 09 and May 04, 2020 as the incidence time series $I(t)$.[5] We smoothed $I(t)$ using a Gaussian kernel with $\sigma = 1$ day to reflect uncertainty in reporting delay. We then compared estimates of $R_e(t)$ using the MLE generation time distribution versus

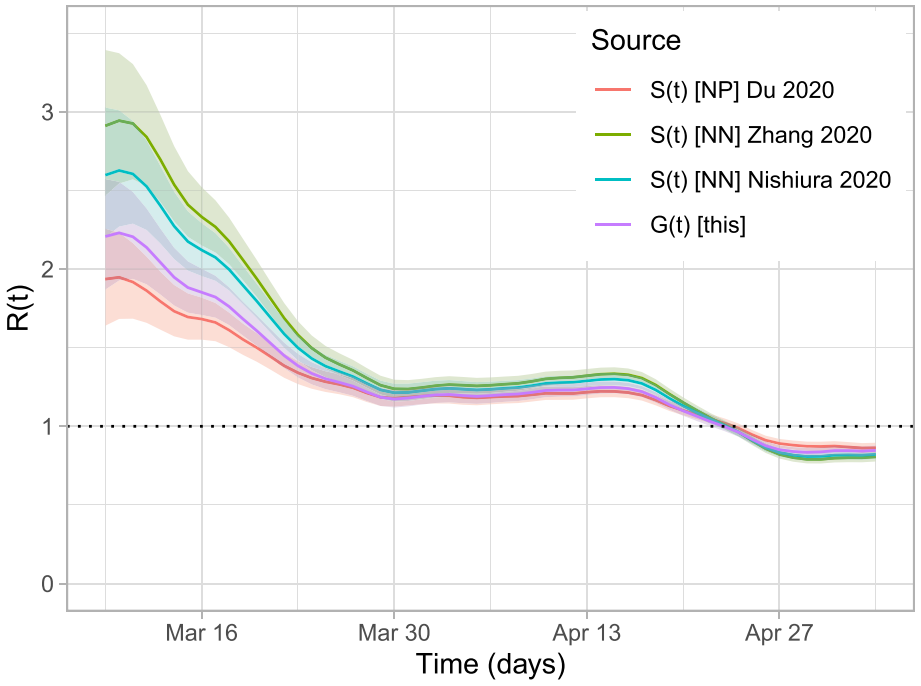

Fig. 3. $R_e(t)$ of COVID-19 in GTA using serial interval versus generation time
Notation — $S(\tau)$: serial interval; $G(\tau)$: generation time; [NP]: negative-permitting; [NN]: non-negative. See Figure A2 for zoom-in of later dates.

[5] We did not stratify incidence by "imported" vs "local" transmission events, in order to quantify overall epidemic growth. The relative influence of different $G(\tau)$ approximations on $R_e(t)$ should not be affected by this lack of stratification.

serial interval distributions reported in the literature, including negative-permitting [Normal (Du et al., 2020)], and non-negative [Gamma (Zhang, Litvinova, et al., 2020), Log-Normal (Nishiura et al., 2020)] distributions.

3. Results

Fig. 2 shows the serial interval and incubation period distributions from (Du et al., 2020) and (Lauer et al., 2020) respectively, and the generation time distribution estimated via the proposed method. The MLE parameters of $\hat{G}(\tau \mid \theta)$ were: shape $\alpha = 1.813$ and scale $\beta = 2.199$, yielding $\hat{S}(\tau \mid \theta^*)$ that reasonably approximated the target $S(\tau)$.

Comparing the estimated generation time to published serial interval distributions (Figure A1) showed the following. The mean generation time of 3.99 was similar to the mean serial interval of 3.96 based on the negative-permitting distribution (Du et al., 2020), but shorter than mean serial interval based on non-negative distributions, such as 5.1 in (Zhang, Litvinova, et al., 2020) and 4.7 in (Nishiura et al., 2020). The SD of the generation time distribution was smaller at 2.96 than the SD of the negative permitting serial interval at 4.75 (Du et al., 2020), but similar to the SD of the non-negative serial interval distributions, including 2.7 in (Zhang, Litvinova, et al., 2020) and 2.9 in (Nishiura et al., 2020).

Fig. 3 shows $R_e(t)$ for COVID-19 in GTA, Canada based on reported cases and estimated using the generation time distribution versus selected serial interval distributions reported in the literature.[6] The $R_e(t)$ based on non-negative serial interval distribution was higher versus $R_e(t)$ using the estimated generation time distribution (e.g. using (Zhang, Litvinova, et al., 2020): 2.33 vs 1.85 on March 16; and 1.32 vs 1.24 on April 13). Higher $R_e(t)$ can be attributed to longer mean serial interval under non-negative distributions versus the estimated mean generation time, since inferred $R_e(t)$ must be higher to compensate for longer delay between infections.[7] By contrast, the $R_e(t)$ estimated using a negative-permitting serial interval distribution was the smallest of all three approaches (e.g. using (Du et al., 2020): 1.68 on March 16; and 1.22 on April 13). In this case, lower $R_e(t)$ can be attributed to increased variance in the negative-permitting serial interval distribution versus in the generation time distribution, as shown in (Britton & Tomba, 2019).

4. Discussion

We have demonstrated how to estimate a non-negative generation time distribution based on negative serial interval and non-negative incubation period parametric distributions. We showed that estimates of $R_e(t)$ will vary depending on the approach used to approximate/estimate the generation time distribution. Specifically, relative to the estimated generation time distribution, non-negative and negative-permitting serial interval distributions may over and underestimate $R_e(t)$, respectively.

Our estimated generation time for COVID-19 was Gamma-distributed with mean 3.99 and SD 2.96, similar to results by Ganyani et al. (2020) (Table A1). However in (Ganyani et al., 2020), person-level serial interval data on infector-infectee pairs are required for a joint Bayesian model of generation time, incubation period, and serial interval, characterized via MCMC sampling. In our approach, we used parametric distributions as inputs because we did not have access to person-level and paired data. As such, our approach could also use pooled estimates via meta-analyses of serial interval and incubation period as parameter inputs.

In several recent works (You et al., 2020; Tang et al., 2020; Zhang, Litvinova, et al., 2020, Zhang, Diao et al., 2020), non-negative serial interval distributions have been used as an approximation of the generation time distribution when estimating $R_e(t)$ for COVID-19.[8] We found that such an approximation may result in overestimation of $R_e(t)$, and thus overestimation of COVID-19 transmission potential. The finding that $R_e(t)$ may be overestimated when using (non-negative) serial interval versus generation time seemingly contradicts the conclusion of Britton and Tomba (2019), but can be explained as follows. In our study of COVID-19, the mean serial interval under non-negative distributions (Nishiura et al., 2020; Zhang, Litvinova, et al., 2020) was longer than the mean generation time estimated using negative-permitting serial interval (Du et al., 2020). If time between infections is assumed to be longer, then we would *overestimate* $R_e(t)$ to fit the same incidence. By contrast, Britton and Tomba (2019) modelled both serial interval and generation time as Gamma-distributed (non-negative), resulting in equal means, but different variances. They then showed how increased variance in the serial interval distribution can cause *underestimation* of $R_e(t)$, relative to the generation time distribution. In fact, we also find underestimation of $R_e(t)$ when comparing negative-permitting serial interval to the generation time distribution, which had equal means.

Our approach to estimating generation time had three notable limitations. First, like similar works (Ganyani et al., 2020; Kuk & Ma, 2005), we assumed that generation time and incubation period were independent, although Klinkenberg and Nishiura (2011) showed that correlation between the two exist in infections such as measles. Second, as noted above, our approach did not use person-level serial interval or incubation period data such as in (Ganyani et al., 2020) and (Klinkenberg

[6] Generation time and serial interval distributions are also illustrated in Figure A1.

[7] Relative differences in $R_e(t)$ between input distributions are "flipped" after $R_e < 1$, since a longer delay between infections has opposite implications for $R_e(t)$ in the context of a shrinking versus growing epidemic.

[8] In early characterizations of COVID-19 (Li et al., 2020; Nishiura et al., 2020; You et al., 2020; Zhang, Litvinova, et al., 2020; Zhao et al., 2020), negative serial interval (and pre-symptomatic transmission) was either unobserved or considered implausible.

& Nishiura, 2011), possibly resulting in compounding errors from parametric approximation of both input (serial interval, incubation period) and output (generation time) distributions. However, depending on the availability and reliability of person-level data, our approach could in some cases be favourable. Finally, we did not perform uncertainty analysis using the reported confidence intervals for the serial interval and incubation period distribution parameters. Future work could overcome this limitation by exploring joint estimation of generation time, serial interval, and $R_e(t)$ within the Bayesian framework defined in (Cori et al., 2013).

Author contributions

Jesse Knight: Conceptualization, Methodology, Formal Analysis, Investigation, Software, Visualization, Writing – drafting & editing; Sharmistha Mishra: Conceptualization, Investigation, Writing – review & editing, Resources, Funding acquisition.

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Declaration of competing interest

None.

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Reported COVID-19 cases were obtained from the Public Health Ontario (PHO) integrated Public Health Information System (iPHIS), via the Ontario COVID-19 Modelling Consensus Table, and with approval from the University of Toronto Health Sciences REB (protocol No. 39253).

Appendix A. Data & Code

All code and results for this project is available online at: https://github.com/mishra-lab/covid19-Re.

Table A1 summarizes the reported parametric COVID-19 distributions, and Fig. A.1 illustrates the serial interval and generation time distributions explored for estimating $R_e(t)$. Fig. A.2 provides a zoom-in of Fig. 3 after March 30.

Table A.1
Summary of reported parametric COVID-19 distributions

	Ref	N	Distribution	Mean	SD
$S(\tau)$	Du et al. (2020)	468	$Norm(\mu = 3.96,\ \sigma = 4.75)$	3.96	4.75
	Zhang, Litvinova et al., (2020)	35	$Gam(\alpha = 3.619,\ \beta = 1.416)$	5.1	2.7
	Nishiura et al. (2020)	28	$LogN(\mu = 4.7,\ \sigma = 2.9)$	4.7	2.9
	Zhao et al. (2020)	21	$Gam(\alpha = 2.151,\ \beta = 2.045)$	4.4	3.0
	Li et al. (2020)	6	$Gam(\alpha = 4.866,\ \beta = 1.541)$	7.5	3.4
	Tindale et al. (2020)	4	$Norm(\mu = 4.22,\ \sigma = 0.4)$	4.22	0.4
	Tindale et al. (2020)	4	$Norm(\mu = 4.56,\ \sigma = 0.95)$	4.56	0.95
$H(\tau)$	Lauer et al. (2020)	181	$Gam(\alpha = 5.807,\ \sigma = 0.948)$	5.51	2.28
	Tindale et al. (2020)	135	$Weib(\alpha = 2.25,\ \beta = 10.15)$	8.99	4.23
	Tindale et al. (2020)	93	$Weib(\alpha = 1.88,\ \beta = 7.97)$	7.07	3.91
	Linton et al. (2020)	52	$LogN(\mu = 5.6,\ \sigma = 2.8)$	5.6	2.8
	Backer et al. (2020)	88	$Weib(\alpha = 3.038,\ \beta = 7.163)$	6.4	2.3
	Li et al. (2020)	10	$LogN(\mu = 5.2,\ \sigma = 3.91)$	5.2	3.91
$G(\tau)$	this	–	$Gam(\alpha = 1.813,\ \beta = 2.199)$	3.99	2.96
	Ganyani et al. (2020)	*	$Gam(\alpha = 9.140,\ \beta = 0.569)$	5.20	1.72
	Ganyani et al. (2020)	*	$Gam(\alpha = 6.843,\ \beta = 0.577)$	3.95	1.51

Notation — N: sample size; *: indeterminate; $S(\tau)$: serial interval; $H(\tau)$: incubation time; $G(\tau)$: generation time; μ: mean; σ: std dev (SD); α: shape; β: scale.
Notes — some parameters were back-calculated based on reported distribution statistics like mean, SD, and quantiles; LogN mean and SD are in linear, not log scale.

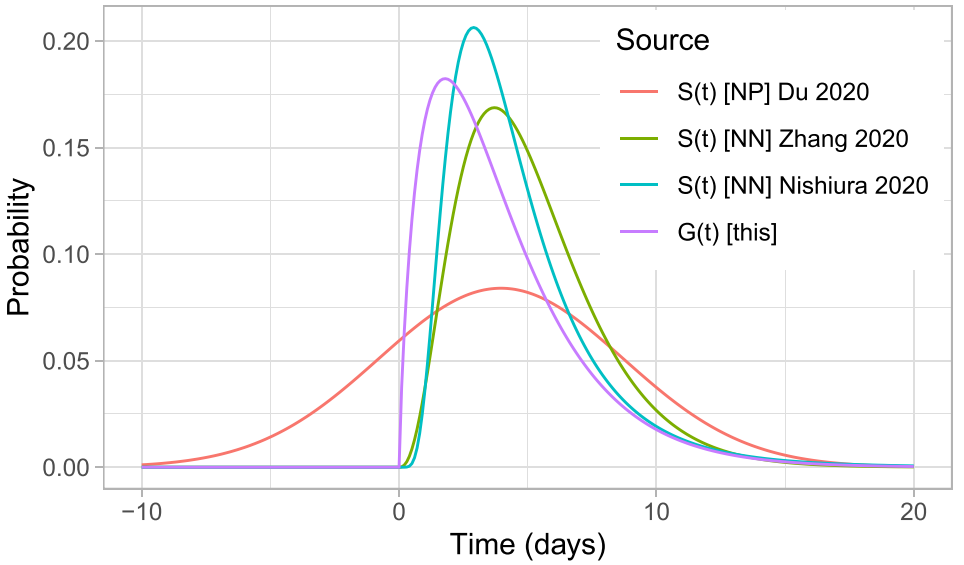

Fig. A.1. Illustration of reported serial interval and generation time distributions used for calculating $R_e(t)$ in COVID-19.

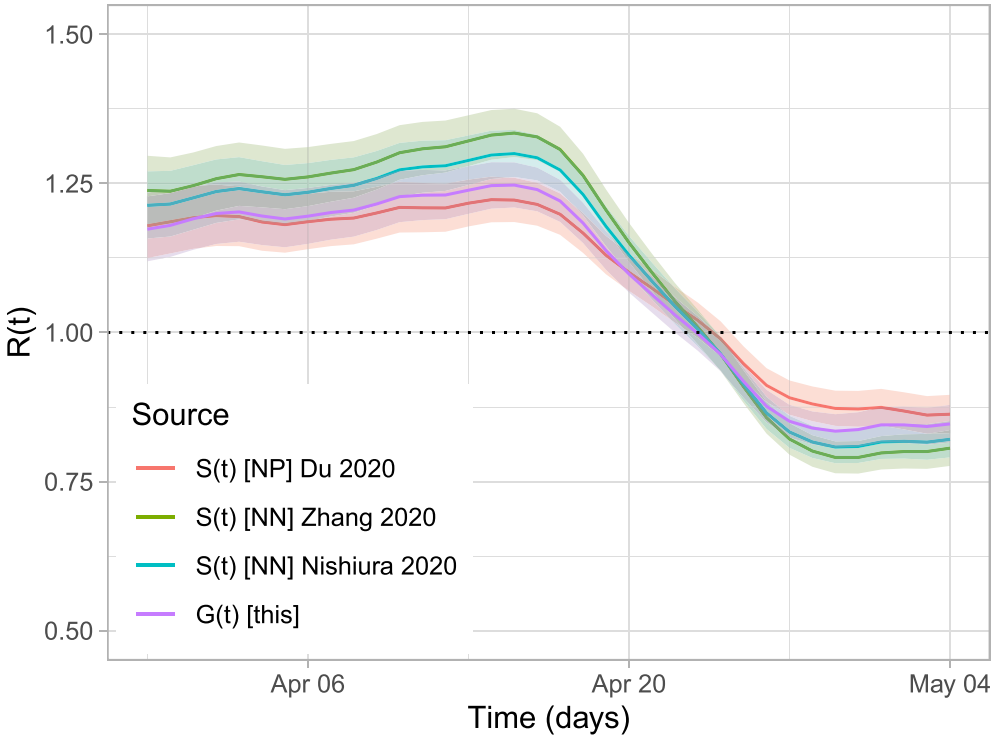

Fig. A.2. $R_e(t)$ of COVID-19 in GTA using serial interval versus generation time (zoom of March 30 to May 4)
Notation — $S(\tau)$: serial interval; $G(\tau)$: generation time; [NP]: negative-permitting; [NN]: non-negative.

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