Disease outbreaks and metrics

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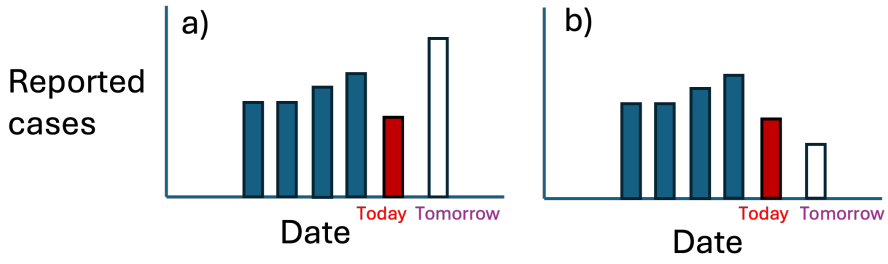
Overview

When an infectious disease outbreak begins, a time-sensitive question arises: "are things getting better or worse?" A great deal of research has gone into how to answer this question, and making sense of the findings is the purpose of this website.

Suppose you work at a public health agency, and you have the following reported case data in blue:



You may want to know, are cases tomorrow going to be a) higher than today or b) lower than today. Just looking visually, either seems plausible: in case a) perhaps today's cases are a outlier, and the true trend will continue upwards, and in case b) perhaps today's cases are not an outlier, and tomorrow's cases will be lower.

To make a more informed decision, there are **two critical questions** we need to answer:

1. How long does it take for an infected person to infect others? If you knew that it took at least 2 days for an infected person to infect others, you might be more inclined to think that tomorrow's cases may be higher than today's, as they are in a). However, if you knew that it only took 1 day at most for each infected person to infect others, you might think it more likely that tomorrow's cases will be lower than today's, as they are in b).

Therefore, this quantity, known as the generation interval, can help you make an informed decision about whether you think cases tomorrow will be higher or lower than today. The generation interval can estimated by a number of methods, including analyzing data of infector-infectee pairs.

2. How many previous days of information do you want to look at when deciding what tomorrow's cases will be? Again looking at the figure above, if you want to use the previous 4 days to make your decision, you will probably guess that tomorrow's cases will be

higher than today's. However, if you choose a smaller window of time, you may be inclined to think that tomorrow's cases will be lower.

The question of how many days to consider in your estimation (and how much weight each previous day recieves in estimating what the next day of cases will be) is characterized in a parameter known as the effective reproductive number, or $R(t)$.

Knowing $R(t)$ can help you begin to make an informed guess as to the current state of a disease outbreak, as it has the following values and interpretations *at a specific point in time*:

R(t)	Interpretation at time t	Outbreak is ...
< 1	Each infected person infects *on average* fewer than one additional person	shrinking
$= 1$	Each infected person infects *on average* about one additional person	stable
> 1	Each infected person infects *on average* more than one additional person	growing

However, estimating $R(t)$ is not straightforward, and is the subject of a wealth of academic research and proliferation of software packages. Guidance in choosing a choosing a method (and a package) is the purpose of this website.

How to choose a tool to estimate $R(t)$

There has been a proliferation of software tools that make inference about the current state of an infectious disease outbreak.

Important to keep in mind when choosing a tool to estimate $R(t)$ is this fact: $R(t)$ is a *latent* variable, which means *cannot be measured directly*. Instead, it can only be estimated from observable variables (like reported case counts).

The ideal estimator of $R(t)$ requires a list of the number of newly *infected* cases by infection date and the generation interval. This is because we want to know about the state of disease based on when people are infected, not when they report having symptoms. In reality we usually only observe the new number of newly *reported* cases and can only estimate the serial interval, which is the time between symptom onset of an infector-infectee pair. In this case the estimate of $R(t)$ will lag reality without some adjustments.

Each software package that estimates $R(t)$ makes different adjustments and assumptions about how these parameters relate, which leads to variations in estimated $R(t)$ *even if the same input data are used*. In addition, different packages require different levels on input data to provide additional robustness in estimated outputs.

The purpose of this document

Therefore, the purpose of this document is to provide guidance about which $R(t)$ estimation software to choose for different analytical goals. First, see our Example outbreak for the different components of disease outbreak that can be modeled differently. Next, see our Decision tool for how to choose software for different analytical goals.

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Example of R(t) usage

Decision matrix

$R(t)$ provides a link between reported cases of a disease and many additional dynamic processes, including disease characteristics (e.g., infectiousness under various conditions, mode of transport) and extrinsic factors (e.g., lockdowns that reduce person-to-person contact). It represents "… the expected number of new infections caused by an infectious individual in a population where some individuals may no longer be susceptible" (Gostic et al. (2020)), and has two main uses:

1. **Retrospective** understanding of the dynamics of historical outbreaks, and
2. **Real time tracking** ongoing infectious diseases.

For 1, one might wish to understand the impact on transmission of vaccines or non pharmaceutical interventions, such as masking or physical distancing.

For real time tracking of ongoing infectious diseases, there is often interest in determining if the current outbreak is getting worse, better or staying the same. In this case, live dashboards are often used to track $R(t)$ as new data on diagnosed cases emerges. This is currently done for COVID-19 and Influenza by the CDC and CA (add refs).

You can use the decision tool below to help choose which R packages may be right for your application:

1. Look first for the desired output that you want to produce
2. Then make a decision about whether you want to incorporate delay distributions.
3. Finally, estimate $R(t)$ using the packages that are appropriate for your use case

See below the table for the assessment framework used to decide which packages to recommend.

> ! Strong recommendation
>
> **Use multiple packages** in your analysis; an ensemble of approaches will be the best way to ensure a robust estimate of $R(t)$ for your use case.

Table 2: Decision matrix for choosing R(t) estimation tool

Desired output	Incorporates D
Forecasting: what will R(t) be next week	

Nowcasting: what was R(t) in the past week

Historical: what was R(t) over the past month

Assessment framework

An objective comparison of the performance of the methods in these packages would be highly complex, given the following challenges:

- These packages are really a combination of mathematical modeling, available data, and implementation. Any evaluation would have to disaggregate these features.
- Some of the most widely-used packages are not accompanied with a peer-reviewed manuscript that describes or evaluates the theory behind modeling choices.
- Each package contains a subset of the methods below for constraining $R(t)$ in time, but with subtle variations in implementation and presentation that are often not well-documented and have large implications on evaluation metrics.
- Some packages have not been recently updated, and even those that have are not maintained on Installation, instead leaving updates on a development version on GitHub.
- Performance may vary widely considering additional factors like ease of implementation and computational time.
- it also may be the case that some methods of temporal smoothing work better in some cases versus other (very low case counts, rapid changes)

Indeed, many published validation efforts are often not "apples to apples", i.e., comparing two models that are using different amounts of information in estimating R(t). For example, comparing a model that has used only data before time before t to estimate R(t) versus a model that uses the entire historical record to estimate R(t) at time t.

Instead, we present some quantifiable reflections on various aspects of utilizing each package.
:

Table 3: Assessme

Category	Notes
Features	
Ability to nowcast/forecast	Does the package have functionality to incorporate both right-tru
Incorporates delay distributions	Does the package have methodology for incorporating delay distr
Estimates expected cases	Does the package provide an estimate of expected cases and/or ir
Communicates uncertainty	Does the package detail how uncertainty is incorporated into pres
Documentation	

Documentation of package methods	Is there a written report (or published manuscript) that describes
Documentation of package implementation	Are there sufficiently detailed vignettes that would permit a new

Part I

Estimating R(t)

To aid with interpretation of package outputs, we summarize the currently used inputs, data, methods and assumptions in $R(t)$ estimation across the following categories:

: How the relationship between $R(t)$ and infections is defined : How $R(t)$ is constrained using distributions for key variables : How $R(t)$ is constrained over time : Additional data and distributions that are used to constrain $R(t)$: Inference frameworks that are used to estimate $R(t)$

We also present:

: An Rshiny application for simulation of case data and $R(t)$: A list of open research questions

We limit the methods discussed here to those for estimating historical to present-day $R(t)$ values using **daily case count data**, where a case can be flexibly defined as an individual with a reported positive test (either through healthcare-seeking behavior, routine surveillance, or a hospital admission).

Other methods not discussed here include:

- inference of $R(t)$ exclusively from alternative data sources (e.g., genetic data,2 behavioral data,3 or viral loads in waste-water4),
- calculations from compartmental, agent-based models, or network.5–7

We also limit the discussion to packages in the statistical software R,8 which may exclude some packages in other software programs that combine many of the methodological considerations discussed below.9

The methods discussed below and references to specific R packages are current as of December 1, 2024. We attempt to harmonize the mathematical choices between each package using terminology from each.

Relating infections to $R(t)$

Overview

There are two primary classes methods of estimating R(t) from case count data that are used in most R software packages.

(1) The first class of methods assumes there is a formulaic relationship between infections and reproduction number, a relationship known as the renewal equation.10 These infections are then assumed to result in (some fraction of) the observed cases.

(2) A second class of methods involves empirically calculating a quantity that approximates the latent quantity represented by a reproduction number by fitting a curve to the case count time-series and finding the time-varying slope in log space (and then performing other transformations). Empirical calculations are discussed in detail below in our examination of ways in which R(t) is constrained over time.

Renewal equation estimates of R(t)

The renewal equation relates $R(t)$ and infections on day t, $I(t)$, using a third parameter known as the generation interval. The generation interval, ω, is the time between infection in the infector and infection in the infectee, and assuming independence is the linear combination of incubation time, the time between infection and symptom onset in an individual, and transmission time, the time between symptom onset in the infector and infection of the infectee.11 A similar parameter to the generation interval is the serial interval, which is the time between symptom onset in the infector and symptom onset in the infectee. The serial interval and generation interval are interchangeable if the incubation time is independent from the transmission time, and some formulations of the renewal equation use generation interval. In this paper we use the generation interval described by a probability mass function with non-zero values from day 1 (assuming that disease incubation takes at least 1 day) to a maximum day s, i.e., the longest interval between symptom onset in infector and infectee. Taking care to note that R(t) is undefined on day 0 since there has been no transmission yet (and assuming the initial infections are I(0)), the formulation of the renewal equation is thus:

$I(t) = R(t) \sum_{(} i = max\ (1, t - s + 1))^{t}\blacksquare\omega(i)I(t - i)$ (Eq.1)

$$I(t) = R(t) \sum_{i=\max(1,t-s+1)}^{t} \omega(i)\, I(t-i)$$

For brevity, we write the inner sum of (Eq.1) as:

```
$Λ(t)= _(i=max(1,   t-s+1))^t  (i) I(t-i)$          (Eq.2)
```

The assumptions of this formulation, as per Green et. al. 2022,12 are that incident infections can be described deterministically within each window of t [t-s+1,t] and that the generation interval distribution does not change over the modeling time.

A common reframing of the renewal equation is to equate R(t) with an exponential growth rate, r. Under specific conditions and within a small time window (t [t-s+1,t]), infections can be assumed to grow exponentially at a constant rate (r).12–14 Using Eq. 1 in the time window t [t- s+1,t] and assuming some initial infections k, R(t) for t [t- s+1,t] can be inferred from only r and :

$I(t) = ke^r t, t \in [t-s+1, t]$ (Eq.3)

R(t)=[_(i=max(1, t-s+1))^t (i) e^(-ri)]^(-1) ,t [t- s+1,t] (Eq.4)

Again, we will omit the writing the bounds for time in remaining formulae. A single R(t) value, say R_0, can also be put in the form of an infection attack rate, z,15 or in the final size equation,16 to estimate the proportion of all individuals that were affected by a disease with this R_0:

z=1-exp(-R_0 z) (Eq.5)

The attack rate function and others are implemented in the package epigrowthfit.17 The major difference between calculating R(t) from a renewal equation or an exponential growth rate equation is whether I(t) is used. If for a given time window both r and can be estimated independently, then R(t) can be inferred without infection data. Otherwise, infection data are needed to estimate R(t).

Using the renewal equation (Eq. 1) and given that I(t) and are known, R(t) can be solved for algebraically starting with R(t=1) and iterating forwards in time. However, this will produce highly volatile estimates of R(t) that recover the incidence curve directly. This is undesirable for several reasons: real-world infectivity likely does not vary dramatically from day to day, and real-world infection data are rarely complete, especially in an emerging epidemic, meaning that a certain amount of uncertainty must be incorporated into any estimation framework. In addition, infection incidence, I(t), are the data of interest but it is impossible to observe, so many calculations instead may use the observed reported cases, C(t), which requires some additional processing to incorporate into calculations of R(t). Therefore, a variety of constraints on R(t) are added in the inferential process: using distributions on key variables,

placing restrictions on how R(t) varies through time, and with additional data sources and delay distributions. These choices dictate which estimation framework is used, which can add additional constraints.

Empirical estimates of $R(t)$

In contrast to models that assume that renewal equation defines the relationship between infections and R(t), smoothing or regression models calculate time-varying R(t) directly from slope of the log of the infections time-series. Using this method, the relationship between R(t) and infections is empirically defined, being only constrained by the smoothing parameters of curve fit to infections data.

EPINOW2 also has a non-renewal equation-based approach https://epiforecasts.io/EpiNow2/articles/estimate_i mechanistic-infection-model

Zac's Gam Rt: https://github.com/CDCgov/cfa-gam-rt A GAM model will estimate this using a hierarchical spline w different components and weights

Distributions for key variables

Distributions for key variables

A primary component of constraining R(t) is how distributions are used to constrain key variables in R(t) estimation: for I(t), , and for R(t) itself.

Assuming some prior distributions for R(t) and the generation interval permit an analytical solution for the posterior distribution of R(t), as in Cori et. al. (2013) and the R package EpiEstim.18

These simplifying assumptions greatly constrain the space of potential R(t) and thus calculation times are relatively fast. Other software packages, such as EpiNow2,19 do not assume any distributional structure for R(t) or ; this increases model flexibility at the cost of computational runtime and resources.

Distributions used to define new offspring from cases

Another primary component of constraining R(t) is how distributions are used to define the next generation of infections, or I(t) from I(t-1).

The renewal equation provides a mechanism for estimating the next batch of infectees that occur due to transmission from the current round of infectors, a branching process. For time = t-1 the I(t) calculated in the renewal equation provides the expected value for a draw from a discrete distribution, the value of which represents the next generation of infectees. The discrete distribution chosen is commonly a Poisson distribution (in which the mean and variance parameter (t)=I(t)). Thus, using this constraint, the time-series of I(t) represents draws from a series of Poisson distributions with means of (t). Alternatively, a Negative Binomial distribution can be used (with a mean parameter again equal to I(t)), although this requires additionally fitting the size parameter (roughly, the spread of the distribution) to account the infectee distribution being "over-dispersed".20

Importantly, if additional delay distributions are included in the process of estimating R(t), the parameter that distributions are being used to estimate for the next generation may change (e.g., from I(t) to D(t), the mean value for daily reported cases calculated after applying delay distributions to I(t)).

Constraining $R(t)$ over time

Overview

The largest variety in constraints of R(t) exists in methods that impose structure on how R(t) varies with time. Each method confers various assumptions and implications for resulting estimates of R(t), and new methods represent a large area of innovation with regards to real-time infectious disease modeling. With these constraints, we can make inference from sampled case-count data as a signal of unobserved infections in the larger unobserved population.

Fixed sliding windows

A straightforward method of imposing structure on R(t) over time involves constraining R(t) to be drawn from the same distribution within moving time subsets, called sliding windows. We add the prefix of "fixed-size" to distinguish from methods that may adapt the size of the sliding window over time. » make a destinction between deriving it and doing it by Bayesian.

Consider the scenario where I(t) are drawn from a series of Poisson distributions and where R(t) are drawn from a series of Gamma distributions. Using a sliding window size, , of 5 days, R(t) on days 2 to 6 are assumed to be drawn from the Gamma distribution with parameters a_1 and b_1, R(t) days 3 to 7 are drawn from a Gamma distribution with parameters a_2 and b_2, and so on. In the above scenario, days 3 through 6 are in both windows and thus will be values that could be reasonably drawn from Gamma distributions with either a_1 and b_1 or a_2 and b_2. Using an assumption of Gamma distributions for the prior distribution of and R(t), Cori et. al. (2013)18 analytically derived a posterior distribution R(t) using fixed-size sliding windows, which has the following directly calculated (rather than inferred) mean and coefficient of variation of R(t):

E[R(t)]=[a+ _(i=max(1, t-))^t I(i)]/[1/b+ _(i=max(1, t-))^t Λ(i)] (Eq.6) C.V.[R(t)]=[a+ _(i=max(1, t-))^t I(i)]^(-1) (Eq.7)

Thus, sliding windows with larger improve the stability of the estimate of R(t) over smaller because the coefficient of variation of R(t) decreases as number of infections increases (see Web Appendix 1 of Cori et. al., 2013).18 Sliding windows are a key feature of EpiEstim.21 There are limitations of this derived sliding window approach, articulated well in Gostic et. al., (2020)1 and summarized here. There is no posterior distribution for the expected value of incidence In the fixed size sliding window approach, must be explicitly defined prior to

inference. Shorter will lead to quicker response but more variable estimates of R(t), which increases the risk of over-fitting. At the extreme, if the is set to 1 day, the resulting R(t) will recover exactly the infection data. In addition, there is debate in the literature about where in time the estimate of R(t) for each window should go: Gostic et. al., (2020)1 recommends using the midpoint of each sliding window rather than time t. The choice of both and the location of the estimate of R(t) within each window results in gaps in predictions for R(t), barring other modifications: at the end of the modeling period to account for reporting delays or time between the midpoint of and the end of , and at the beginning of the time period to allow for enough cases to materialize. Web Appendix 4 of Cori. et. al (2013) gives the following recommendation for when to calculate R(t): "Overall, we suggest starting estimating once those three criteria are fulfilled: at least after , at least after one mean serial interval, and when at least 12 cases have been observed since the beginning of the epidemic." The default recommendation for is one week (7 days);18

Accumulated Prediction Error (APE) framework

Alternatively the package APEestim integrates with EpiEstim to propose a non-default choice of that minimizes one-step-ahead prediction errors (Parag and Donnelly (2020)).

In APEestim, Parag et al. adapt an approximation known as the accumulated prediction error (APE) to identify the window length best justified by the available epi-curve, k*, to opitmizing the window length k.

Random walk

Another method of constraining how R(t) evolves in time is to define the relationship between R(t), infections, and time in a random walk or auto-regressive framework. In this framework, there are latent or unobserved variables, e.g., R(t), that depend on observed variables, e.g., I(t) via the renewal equation, and the evolution of the unobserved variables through time can be parameterized. The auto-regressive component means that the current value of R(t) is correlated via some mechanism with R(t-1) (and potentially other past values). The packages epidemia23 and EpiNow2 contain an implementations of a random walk procedure that look generally as follows:

f(R(t))=f(R(t-1))+N(0, _R) (Eq.8) _R ~ HalfNormal(,) (Eq.9)

The random walk implies that adjacent R(t) values may be drawn from similar or even the same distribution, and would be correlated in time based on previous values. The variables and are hyperparameters. The function f can be a transformation of R(t), e.g. in log space as in EpiNow2 to correct for the skewness of R(t), provide a variable that is more Gaussian, provide a variable that obeys the properties that we expect from R(t) (i.e., is non-negative),

and aid in interpretability. The function f in epidemia contains more layers for pooled effects and group-level variables.

Filtering

Filtering is another way that R(t) is constrained in common packages. Filtering means [...]. One way that a filter could be implemented is in a Hidden Markov Model.24 A simple forward-looking linear filter for R(t) in an Hidden Markov Model might look as follows, with a tuning parameter ( ) to influence the amount that R(t) can vary between time-steps and a standard white noise component ( ):

R(t)=R(t-1)+(√(R(t-1))) (t-1) (Eq.10)

The package EpiFilter25 implements a two-stage filtering and smoothing method for estimating R(t). A key innovation of EpiFilter is that the states of historical R(t) are constrained to a predefined set of values; this dramatically reduces calculation time. The smoothing stage refines estimates of R(t) by incorporating future incidence, in this way using all available data in estimates of historical R(t). These modeling steps help avoid R(t) instability when infections are low and instability at the beginning and (more importantly) the end of the modeling period. Another way that filtering can be implemented is across the entire R(t) time-series.

RtEstim:28 https://dajmcdon.github.io/rtestim/articles/delay-distributions.html

We propose a discrete spline-based approach, RtEstim, that solves a convex optimization probl
Poisson trend filtering-using the proximal Newton method. It produces a locally adaptive esti
EpiLPS:29

In EpiFilter, RtEstim, and EpiLPS, each R(t) estimated in this way thus contains information about past and pending infections, e.g., for R(t=i), the smoothing step will affect R(t=i) using information from 0<i t_max. This complicates comparisons to outputs from other methods that only use historical information to estimate R(t), e.g., estimates for R(t=i) containing only information from t<i.

Gausian Process models

Gaussian Process models26 are a more flexible method of constraining the evolution of R(t) in time than the methods discussed thus far (in fact, a random-walk process can be thought of as a simplified case of Gaussian Process model). In Gaussian Process modeling, a family of basis functions are fit to available data, permitting inference about continuous processes without needing to a priori define where inflection points occur. The core of Gaussian Process

operations is a kernel, which is used to assess the similarity between input vectors, say x and x^'. There are many options for potential kernels, and each contains different hyperparameters that are used to control the amount of smoothing that is enforced, as well as other factors. One such choice is the squared exponential kernel:

k(x,x^')= ^2 exp[-(x-x^')$^{2/(2l}$2)] (Eq.10)

In this kernel, the hyperparameters are the length scale, l, which controls the smoothness of the model, and the magnitude, , which controls the range of values used in the fitting process. These parameters can be given prior distributions and fit using optimization. EpiNow2 uses contains options to use Gaussian Process models to control how R(t) in time. As one example, the relationship between first difference values of R(t) can be constrained using a zero-mean Gaussian Process model with the above kernel as the covariance function:

log R(t)=logR(t-1)+ GP(0,k(R(t), R(t ^'))) (Eq.11)

The advantage of Gaussian Process models is that R(t) is enforced to change smoothly in time using Eq.10. Limitations include complexity and computational time: Gaussian Process models have a computational complexity of O(n^3) for n observations.27 Although EpiNow2 in practice implements faster approximations of Gaussian Process models,27 in general Gaussian Process runtimes and required computational resources are considerable as compared to other methods.

Additional data

Estimates of R(t) can also be improved using additional data. , you can beef up the calculation by including other pieces of information about counts.

Reconstruction of missing data

Extending EpiEstim • The package bayEStim30 also extends EpiEstim o Our method extends that of Cori et al (2013), adding Bayesian imputation of missing symptom onset dates, imputation of infection times using an external estimate of the incubation period, and an adjustment for reporting delay. • Tenglong's work31 and the accompanying package WhiteLabRt32 use the sliding window approach to estimating missing reporting delay information from line-list data (originally implemented as a Gibbs sampler, later updater to STAN). • The package estimateR involves estimating missing count data using smoothing [confirm].33

• Does EpiNow2 do this?

Epidemia: 23 . We introduce a Bayesian mechanistic model linking the infection cycle to observed deaths, inferring the total population infected (attack rates) as well as Rt.

Delay distributions

Importantly, the definition of R(t) is linked to the data that are being used, so models that calculate a similar quantity as R(t) but instead from infections, symptom onset, or reports are important quantities but differ in definition from the instantaneous reproduction number R(t) as defined throughout the literature. sometimes R(t) is calculated directly from reported case data and then shifted backwards by a delay distribution, whereas other times R(t) is calculated from inferred dates of infection using reported case data.

Reporting delay, Onset delays etc Delay PMFs that you can pass in series which have cascading impacts.

```
EpiNow2 has this:
Our estimates overcome some of the limitations of naive implementations that derive estimates
Our approach also incorporates multiple sources of uncertainty that if excluded can bias esti
```

`EpiFilter was also recently generalized to incorporate hetereogeonous transmission rates and`

Several packages have been created to extend EpiEstim to use delay distributions:

- bayEStim: Our method extends that of Cori et al (2013), adding Bayesian imputation of missing symptom onset dates, imputation of infection times using an external estimate of the incubation period, and an adjustment for reporting delay.
- estimateR involves combining various delay distributions with EpiEstim
- EpiInvert also has methods for including delay disributions with EpiEstim

Clinical data distributions

Again, some packages just modify EpiEstim:

- The ern package ultimately uses the EpiEstim package for the core of the computation as EpiEstim already provides a robust and one of the fastest implementations of well-tested estimation algorithms. However, ern wraps complex and critical features for estimating from real-world clinical and wastewater data that have not all been implemented in any one existing package for estimation

Here, we present the library ern to address the gaps identified above, specifically: o to disaggregate the clinical reports into a shorter time unit to enable estimation of using an intrinsic generation interval on a useful timescale; o to provide a framework to estimate from wastewater data, consistent with an estimation based on clinical data; o to provide a user-friendly interface geared at public-health practitioners that may have limited proficiency in the programming language; o to perform an efficient and rapid estimation.

Linear predictor model components

ViaEpidemia School closures etc

EpiFusion:37 We propose a model of Rt that estimates outbreak trajectories conditional upon both phylodynamic (time-scaled trees estimated from genetic sequences) and epidemiological (case incidence) data.

Inference frameworks

Finally there are different ways of acutally calculating the numbers once you have the theory lined up.

Bayesian optimization

Assumes a distribution –> solved analytically • EpiEstim o restricted set of GI options (gamma?) enables analytical solve for the posterior estimate of R(t) which is also a Gamma, using conjugate priors

Doesn't assume a distribution of R(t) or I(t) –> Uses MCMC • EpiNow2, implemented in STAN • Hierarchical NUTS

MaxLiklihood optimization

• Frequentist o RtEstim

Wallinga, J., and P. Teunis. "Different Epidemic Curves for Severe Acute Respiratory Syndrome Reveal Similar Impacts of Control Measures." American Journal of Epidemiology 160,no. 6 (2004): 509. • ^ this has the likelihood calculation in it

One of the most widely used methods for estimating time-varying reproduction number is a maximum likelihood-based approach {White, 2008}. • White LF, Pagano M. A likelihood-based method for real-time estimation of the serial interval and reproductive number of an epidemic. Stat Med 2008; 27(16): 2999–3016.

Open research questions

- Need to add a page of existing research questions
  - sub-regional or pooling ...
  - other stuff, i think you had a list of this somehwere

Part II

Packages

APEestim

REF	Parag and Donnelly (2020)
Docs	None
Github	Github
Last commit	Feb 12, 2021
Installation	None, this is code to augment EpiEstim

Description

Copied from the developer site

APEestim estimates the time-varying reproduction number on cases by date of infection (using a similar approach to that implemented in EpiEstim).

The quality of this estimate is highly dependent on the size of a smoothing window (k) that is employed. This code presents a method for optimally selecting k in a manner that balances reliable R(t) estimation with short-term forecasts of incidence. This method is based on the accumulated prediction error (APE) idea from information theory.

Methods

This package aims to improve upon the limitation of fixed sliding windows, specifically by optimizing the choice of the window size in an APE Framework.

Assessment

Features	
Ability to nowcast/forecast	No
Incorporates delay distributions	No
Estimates expected cases	No
Communicates uncertainty	Yes
Validation	
Documentation of package methods	Yes

Documentation of package implementation	No

Sample Code

See this file in the Github repo.

bayEstim

REF	medrxiv.org/content/10.1101/2020.09.19.20198028v1
Docs	None
Github	github.com/thlytras/bayEStim
Last commit	Aug 3, 2020
Installation	None

Brief description

Package never submitted to CRAN, no further action taken

earlyR

REF	None
Docs	repidemicsconsortium.org/earlyR/articles/earlyR.html
Github	github.com/reconhub/earlyR
Last commit	October 27, 2020
Installation	CRAN

Brief description

Copied from the developer site

Implements a simple, likelihood-based estimation of the reproduction number (R0) using a branching process with a Poisson likelihood. This model requires knowledge of the serial interval distribution, and dates of symptom onsets. Infectiousness is determined by weighting R0 by the probability mass function of the serial interval on the corresponding day. It is a simplified version of the model introduced by Cori et al. (2013).

Methods

This package does not constrain R in time, instead this is meant to predict a single R value (R0) and then uses this to nowcast and forecast cases.

Assessment

Features	
Ability to nowcast/forecast	Yes
Incorporates delay distributions	No
Estimates expected cases	Yes
Communicates uncertainty	Yes
Validation	
Documentation of package methods	No
Documentation of package implementation	Yes

Sample Code

This vignette gives a basic example of usage

Epidemia

REF	Flaxman et al. (2020)
Peer reviewed	
Docs	imperialcollegelondon.github.io/epidemia
Github	github.com/ImperialCollegeLondon/epidemia
Last commit	Feb 12, 2021
Installation	Broken, see below

Brief description

This package cannot currently be installed so no further analysis is provided at this time

EpiEstim

REF	Cori et al. (2013), Nash et al. (2023)
Peer reviewed	
Docs	mrc-ide.github.io/EpiEstim
Github	github.com/mrc-ide/EpiEstim
Last commit	Aug 30, 2024
Installation	CRAN

Brief description

Copied from the developer site

EpiEstim is a tool to estimate the time-varying instantaneous reproduction number during epidemics. In order to estimate Rt, EpiEstim needs to be supplied with an estimate of the serial interval distribution (step A) and the incidence of confirmed cases (step B). Once you have an incidence object (based on the dates of symptom onset) and information on the serial interval distribution, we can use the renewal equation (a form of branching process model) to estimate Rt. The incidence of symptom onset at time t is approximated by a Poisson process using the renewal equation.

Note: EpiEstim runs quickly owing

Methods

This package contains the following methods:

- fixed sliding windows

Assessment

Features	
Ability to nowcast/forecast	No
Incorporates delay distributions	No, although some right-censoring is included

Estimates expected cases	No
Communicates uncertainty	Yes
Validation	
Documentation of package methods	Yes
Documentation of package implementation	Yes

Sample Code

This vignette gives a basic example of usage of EpiEstim.

The end of this vignette suggests using the `projections` package to estimate future cases, and we cannot recommend this package. The estimation of future values of R(t) in this package comes from resampling different past values of R(t) rather than trends dervied from recent infections.

EpiFilter

REF	Parag (2021)
Docs	
Github	https://github.com/kpzoo/EpiFilter
Last commit	Dec 9, 2023
Installation	

Brief description

Copied from the developer site

Maximally informed, mean square error optimised estimates of reproduction numbers (R) over time.

Uses Bayesian recursive filtering and smoothing to maximise the information extracted from the incidence data used. Takes a forward-backward approach and provides estimates that combine advantages of EpiEstim and the Wallinga-Teunis method. Method is exact (and optimal given a grid over R) and deterministic (produces the same answer on the same data).

Methods

This package contains the following methods to solve for $R(t)$ in time:

- filtering

Assessment

Features	
Ability to nowcast/forecast	No
Incorporates delay distributions	No, although some right-censoring is included
Estimates expected cases	No
Communicates uncertainty	Yes
Validation	

Documentation of package methods	Yes
Documentation of package implementation	No

Sample code

The primary sample code comes from this R script.

EpiFusion

REF	Judge et al. (2024)
Docs	
Github	github.com/ciarajudge/EpiFusion
Last commit	Nov, 2024
Installation	

Brief description

Brief summary of EpiFusion method from the paper

EpiFusion is a Bayesian framework designed to estimate the effective reproduction number by jointly analyzing epidemiological (case incidence) and phylodynamic (genomic) data using particle filtering within a particle Markov Chain Monte Carlo (pMCMC) framework. It addresses the limitations of using only epidemiological or genomic data, particularly in under-sampled outbreaks. EpiFusion combines a stochastic infection dynamics model with dual observation models: one for case incidence data and another for phylodynamic tree data. The approach involves sequential particle filtering to simulate infection trajectories, with particles weighted and resampled based on their fit to both data sources. Parameter inference is achieved through Metropolis-Hastings MCMC. EpiFusion has been validated through simulations, benchmarking against existing tools, and application to real-world outbreaks, including the 2014 Ebola outbreak in Sierra Leone.

Methods

This package contains the following methods:

-

Assessment

Features	
Ability to nowcast/forecast	No, Designed for retrospective analysis
Incorporates delay distributions	Yes, Handles delays between infection and reporting implicitly
Estimates expected cases	Yes
Communicates uncertainty	Yes, Highest Posterior Density (HPD) intervals
Validation	
Documentation of package methods	Yes
Documentation of package implementation	No

Sample code

epigrowthfit

REF	Earn et al. (2020)
Docs	
Github	github.com/davidearn/epigrowthfit
Installation	

Brief description

Copied from the developer site.

Maximum likelihood estimation of nonlinear mixed effects models of epidemic growth using Template Model Builder ('TMB'). Enables joint estimation for collections of disease incidence time series, including time series that describe multiple epidemic waves. Supports a set of widely used phenomenological models: exponential, logistic, Richards (generalized logistic), subexponential, and Gompertz. Provides methods for interrogating model objects and several auxiliary functions, including one for computing basic reproduction numbers from fitted values of the initial exponential growth rate. Preliminary versions of this software were applied in Ma et al. (2014) doi:10.1007/s11538-013-9918-2 and in Earn et al. (2020) doi:10.1073/pnas.2004904117

Methods

This package contains the following methods:

-

Assessment

Features	
Ability to nowcast/forecast	No
Incorporates delay distributions	No
Estimates expected cases	No
Communicates uncertainty	No

Validation	
Documentation of package methods	No
Documentation of package implementation	Yes

Sample code

EpiInvert

REF	Alvarez et al. (2021)
Docs	
Github	github.com/lalvarezmat/EpiInvert
Last commit	Dec, 2023
Installation	

Brief description

Brief summary of the method from the paper

EpiInvert is an epidemiological method that estimates the time-varying reproductive number and restores incidence curves by inverting the renewal equation using variational techniques. The approach corrects biases introduced by reporting inconsistencies, including weekly and festive biases, ensuring robust epidemic trend estimation. EpiInvert estimates Rt by inverting the renewal equation using signal processing techniques, providing a reliable measure of epidemic dynamics. It corrects systematic underreporting due to weekends and holidays by detecting anomalies based on historical trends, redistributing cases across affected days to reduce artificial fluctuations, and adjusting Rt estimates to reflect true transmission patterns. It also includes a forecasting model that predicts epidemic trends using historical trends.

Methods

This package contains the following methods:

-

Assessment

Features	
Ability to nowcast/forecast	Yes, Use 'EpiInvertForecast' for forecasting
Incorporates delay distributions	No
Estimates expected cases	Yes

Communicates uncertainty	Yes
Validation	
Documentation of package methods	Yes
Documentation of package implementation	Yes

Sample code

See this vignette for an example of forecasting, and this vignette for a comparison between EpiInvert and other related packages.

EpiLPS

REF	Gressani et al. (2022)
Docs	
Github	github.com/oswaldogressani/EpiLPS
Last Commit	Oct, 2024
Installation	

Brief description

Brief summary of the method from the paper

EpiLPS is a Bayesian tool for estimating the time-varying reproduction number using a robust, efficient approach. It models case counts with a Negative Binomial distribution to handle overdispersion and employs Bayesian P-splines for smoothing epidemic curves. The methodology leverages Laplace approximations to estimate the posterior distribution of the spline coefficients rapidly. Two inference methods are provided: a fast maximum a posteriori approach for quick estimates and an MCMC scheme using Langevin dynamics for thorough posterior sampling. EpiLPS delivers accurate estimates without arbitrary smoothing assumptions and has been applied to SARS-CoV-1, H1N1, and COVID-19 datasets.

Methods

This package contains the following methods:

-

Assessment

Features	
Ability to nowcast/forecast	Nowcasting,adjusts for underreporting by estimating unreported infections and combining them with reported cases to reflect actual daily epidemics

Incorporates delay distributions	Some, It accounts for the uncertainty associated with reporting delays
Estimates expected cases	Yes
Communicates uncertainty	Yes, The credible intervals are calculated via the delta method
Validation	
Documentation of package methods	Yes
Documentation of package implementation	Yes

Starter code

EpiNow2

REF	Wellcome report
Docs	Docs
Github	Github
Last commit	Feb 25, 2021
Installation	Installation

Brief Description

Copied from the developer site

EpiNow2 estimates the time-varying reproduction number on cases by date of infection (using a similar approach to that implemented in EpiEstim). True infections, treated as latent and unobserved, are estimated and then mapped to observed data (for example cases by date of report) via one or more delay distributions (in the examples in the package documentation these are an incubation period and a reporting delay) and a reporting model that can include weekly periodicity.

Uncertainty is propagated from all inputs into the final parameter estimates, helping to mitigate spurious findings. This is handled internally. The time-varying reproduction estimates and the uncertain generation time also give time-varying estimates of the rate of growth.

Forecasting is also supported for the time-varying reproduction number, infections, and reported cases using the same generative process approach as used for estimation.

Important links:

Methods

This package contains the following methods:

- Gaussian Process

Assessment

Features	
Ability to nowcast/forecast	Yes
Incorporates delay distributions	Yes
Estimates expected cases	Yes
Communicates uncertainty	Yes
Validation	
Documentation of package methods	Yes
Documentation of package implementation	Yes

Starter code

epinowcast

REF
Peer reviewed
Docs
Github
Installation

Description

epinowcast | Abbott S, Lison A, Funk S, Pearson C, Gruson H, Guenther F, DeWitt M | | Sep 30, 2024 |

Copied from the developer site

Tools to enable flexible and efficient hierarchical nowcasting of right-truncated epidemiological time-series using a semi-mechanistic Bayesian model with support for a range of reporting and generative processes. Nowcasting, in this context, is gaining situational awareness using currently available observations and the reporting patterns of historical observations. This can be useful when tracking the spread of infectious disease in real-time: without nowcasting, changes in trends can be obfuscated by partial reporting or their detection may be delayed due to the use of simpler methods like truncation. While the package has been designed with epidemiological applications in mind, it could be applied to any set of right-truncated time-series count data.

Methods

This package contains the following methods:

-

Assessment

Table 25: Assessment rubric

Category	Notes	Scales
Usage		
Runtime length	Some description	Time (minutes)
Features		
Ability to nowcast/forecast	Some description	Yes/no
Incorporates delay distributions	Some description	Yes/no
Estimates expected cases	Some description	Yes/no
Communicates uncertainty	Some description	Yes/no
Validation		
Documentation of package methods	Some description	Yes/no
Documentation of package implementation	Some description	Yes/no

Sample code

ern

REF
Peer reviewed
Docs
Github
Installation

Brief description

The ern package was developed to adapt the EpiEstim package for real world data, including wastewater and clinical data. Specifically the package:

- disaggregates clinical reports into a shorter time unit to enable estimation of R_t using an intrinsic generation interval on a useful timescale;
- provides a framework to estimate R_t from wastewater data, consistent with an estimation based on clinical data;
- provides a user-friendly interface geared at public-health practitioners that may have limited proficiency in the R programming language;
- uses EpiEstim for efficient and rapid estimation.

ern | Champredon et al. (2024) | | May 22, 2024|

Methods

This package contains the following methods:

- EpiEstim for estimation of R_t.
- Disagregation of data into shorter time units, as necessary.

Assessment

Table 27: Assessment rubri

Category	Notes
Usage	
Runtime length	Runs with EpiEstim platform, which is fast and efficient.
Features	
Ability to nowcast/forecast	No documentation of this capability.
Incorporates delay distributions	Includes incubation period and reporting delay for clinical data.
Estimates expected cases	Doing this from wastewater or aggregated clincal case data.
Communicates uncertainty	Uncertainty from both EpiEstim approach, as well as assumption
Validation	
Documentation of package methods	Some description
Documentation of package implementation	Some description

-

Sample code

There is a lot of sample code and worked examples in the Plos One publication for this method
.

EstimateR

REF
Peer reviewed
Docs
Github
Installation

Brief description

EstimateR is a package that is built on the EpiEstim framework for estimating R_t and includes steps to smooth, backcalculate data to infection dates and create confidence intervals for estimates. Specifically, the method takes observed observations of infection events, such as case confirmations, hospital admissions, intensive care unit admissions, or deaths and performs the following four steps:

- Smooth the data to reduce noise in the data.
- Backcalculate data to date of infection.
- Estimate R_t using EpiEstim.
- Calculate 95% confidence intervals using bootstrapping.

Each of these tasks can be done separately and the users is not required to perform all tasks.

There is apparently an option to nowcast data described and implemented in the package, though provided mathematical details are limited.

EstimateR | Scire et al. (2023) | | Sep 10, 2024|

Methods

This package contains the following methods:

- Data is smoothed using LOESS with a first order polynomial. Users should adapt the smoothing parameter consistent with the noise in the input data.
- Deconvolution with an Expectation-Maximization (EM) algorithm is used to create an estimate of the time series of infection events.

- EpiEstim is used to estimate R_t with a Bayesian framework.
- Block bootstrapping is used to estimate 95% confidence intervals.

Details of the methods used are provided in the supplement of Scire et al. (2023).

Assessment

Table 29: Assessment rubric

Category	Notes
Usage	
Runtime length	Comparison of Estimate R with epidemia and EpiNow2 on simula
Features	
Ability to nowcast/forecast	Appears possible; limited details provided.
Incorporates delay distributions	Uses deconvolution.
Estimates expected cases	This is a separate module that is calculated.
Communicates uncertainty	Uses Block boostrapping to create 95% CIs.
Validation	
Documentation of package methods	Peer reviewed publication.
Documentation of package implementation	GitHub site and R package.

Sample code

R0

REF
Peer reviewed
Docs
Github
Installation

Brief description

A package that implements existing methods to estimate R_0 and R_t. The advantage of this package is that it standardizes data formats and the parameterization of the generation interval.

This package was developed in 2012 before many of the current methods were developed and most of the methods that are described in the package are not commonly used.

R0 | Obadia et al. (2012) | | Sep 20, 2023|

Methods

This package contains the following methods:

- Function to define the generation interval. Options include empiric (i.e. multinomial), lognormal, gamma, and weibull distributions.
- Estimation of R_0 as a function of the attack rate (user must provide this).
- Method to estimate R_0 from the exponential growth rate described by `Wallinga and Lipsitch`.
- Maximum likelihood based estimate of R_0 and serial interval introduced by `White and Pagano`.
- Sequential Bayesian method to estimate time-varying reproductive number introduced by `Bettencourt and Ribiero`.
- Retrospective estimation of the time-varying reproductive number introduced by `Wallinga and Teunis`.

Assessment

Table 31: Assessment rubric

Category	Notes
Usage	
Runtime length	Not described. But methods used are not computationally compl
Features	
Ability to nowcast/forecast	Not available in the provided methods.
Incorporates delay distributions	Not available in the provided methods
Estimates expected cases	Not available in the provided methods
Communicates uncertainty	Some methods allow for this.
Validation	
Documentation of package methods	Peer reviewed paper published describing the package.
Documentation of package implementation	Package is on Installation.

Sample code

RtEstim

REF
Peer reviewed
Docs
Github
Installation

Brief description

Rtestim is a method that uses the renewal equation and a provided serial interval distribution to estimate R_t. Distinct from other methods, it uses a frequentist approach with an L1 smoothing penalty which decreases computation time and allows for locally adaptive estimates. The method estimates confidence bands for R_t and incidence.

RtEstim | Liu et al. (2024) | | Sep 25, 2024|

Methods

This package contains the following methods:

- Locally adaptive estimator using Poisson trend filtering
- L1 smoothing
- Cross validation to select tuning parameters for the smoother

Assessment

Table 33: Assessment rubric

Category	Notes
Usage	
Runtime length	Not provided, but states that runs take seconds.
Features	
Ability to nowcast/forecast	Not described.

Incorporates delay distributions	Not described.
Estimates expected cases	Predicts this based on estimated R_t.
Communicates uncertainty	Provides 95% confidence bands.
Validation	
Documentation of package methods	Published paper in Plos Comp Biol.
Documentation of package implementation	R package and details [‘here‘](https://dajmcdon.github.io/rtestim

Sample code

WhiteLabRt

REF
Peer reviewed
Docs
Github
Installation

Brief description

This package implements methods described in Li & White for backcalculation and nowcasting and Zhou et al for small area estimation using mobility data. The package uses stan to improve computational efficiency and stability. All methods are implemented in a Bayesian framework. Currently the package does not allow the user to incorporate both mobility data and do nowcasting and account for reporting delays.

WhiteLabRt | Li and White (2021) | | Aug 16, 2024|

Methods

This package contains the following methods:

- Bayesian methods to integrate multiple data sources.
- Mobility data in a hierarchical model to obtain spatially granular estimates.
- Adjustment for reporting delay and nowcasting estimates.

Assessment

Table 35: Assessment rubric

Category	Notes	Scales
Usage		
Runtime length	Some description	Time (minutes)
Features		

Ability to nowcast/forecast	Included in the package.	Yes
Incorporates delay distributions	Bayesian implementation of this.	Yes
Estimates expected cases	Included in all methods.	Yes
Communicates uncertainty	Credible intervals included for all estimates.	Yes
Validation		
Documentation of package methods	Peer reviewed publications for both methods.	Yes
Documentation of package implementation	Vignette and documentation provided.	Yes

Sample code

Glossary

Effective reproduction number

From Gostic et al. (2020):

> The effective reproductive number, denoted as or R_e or R_t, is the expected number of new infections caused by an infectious individual in a population where some individuals may no longer be susceptible

Also called the instantaneous reproductive number.

Generation interval

The time between the infection date of an individual and the infection date of the person who infected them. This is typically described by a statistical distribution, such as a gamma, lognormal or weibull.

Serial interval

The time between the infection date of an individual and the infection date of the person who infected them. This is typically described by a statistical distribution, such as a gamma, lognormal or weibull.

References

Alvarez L, Colom M, Morel J-D, Morel J-M. 2021. Computing the daily reproduction number of COVID-19 by inverting the renewal equation using a variational technique. Proceedings of the National Academy of Sciences 118:e2105112118; doi:10.1073/pnas.2105112118.

Champredon D, Papst I, Yusuf W. 2024. Ern: An R package to estimate the effective reproduction number using clinical and wastewater surveillance data. PLOS ONE 19:e0305550; doi:10.1371/journal.pone.0305550.

Cori A, Ferguson NM, Fraser C, Cauchemez S. 2013. A New Framework and Software to Estimate Time-Varying Reproduction Numbers During Epidemics. American Journal of Epidemiology 178:1505–1512; doi:10.1093/aje/kwt133.

Earn DJD, Ma J, Poinar H, Dushoff J, Bolker BM. 2020. Acceleration of plague outbreaks in the second pandemic. Proceedings of the National Academy of Sciences 117:27703–27711; doi:10.1073/pnas.2004904117.

Flaxman S, Mishra S, Gandy A, Unwin HJT, Mellan TA, Coupland H, et al. 2020. Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. Nature 584:257–261; doi:10.1038/s41586-020-2405-7.

Gostic KM, McGough L, Baskerville EB, Abbott S, Joshi K, Tedijanto C, et al. 2020. Practical considerations for measuring the effective reproductive number, Rt. PLOS Computational Biology 16:e1008409; doi:10.1371/journal.pcbi.1008409.

Gressani O, Wallinga J, Althaus CL, Hens N, Faes C. 2022. EpiLPS: A fast and flexible Bayesian tool for estimation of the time-varying reproduction number. PLOS Computational Biology 18:e1010618; doi:10.1371/journal.pcbi.1010618.

Judge C, Vaughan T, Russell T, Abbott S, Plessis L, Stadler T, et al. 2024. EpiFusion: Joint inference of the effective reproduction number by integrating phylodynamic and epidemiological modelling with particle filtering. PLOS Computational Biology 20:e1012528; doi:10.1371/journal.pcbi.1012528.

Li T, White LF. 2021. Bayesian back-calculation and nowcasting for line list data during the COVID-19 pandemic. PLOS Computational Biology 17:e1009210;

doi:10.1371/journal.pcbi.1009210.

Liu J, Cai Z, Gustafson P, McDonald DJ. 2024. Rtestim: Time-varying reproduction number estimation with trend filtering. PLOS Computational Biology 20:e1012324; doi:10.1371/journal.pcbi.1012324.

Nash RK, Bhatt S, Cori A, Nouvellet P. 2023. Estimating the epidemic reproduction number from temporally aggregated incidence data: A statistical modelling approach and software tool. PLOS Computational Biology 19:e1011439; doi:10.1371/journal.pcbi.1011439.

Obadia T, Haneef R, Boëlle P-Y. 2012. The R0 package: A toolbox to estimate reproduction numbers for epidemic outbreaks. BMC medical informatics and decision making 12: 1–9.

Parag KV. 2021. Improved estimation of time-varying reproduction numbers at low case incidence and between epidemic waves. PLOS Computational Biology 17:e1009347; doi:10.1371/journal.pcbi.1009347.

Parag KV, Donnelly CA. 2020. Using information theory to optimise epidemic models for real-time prediction and estimation. PLoS Computational Biology 16:e1007990; doi:10.1371/journal.pcbi.1007990.

Scire J, Huisman JS, Grosu A, Angst DC, Lison A, Li J, et al. 2023. estimateR: An R package to estimate and monitor the effective reproductive number. BMC Bioinformatics 24:310; doi:10.1186/s12859-023-05428-4.