Estimating the Exponential Growth Rate and $\mathcal{R}_0$

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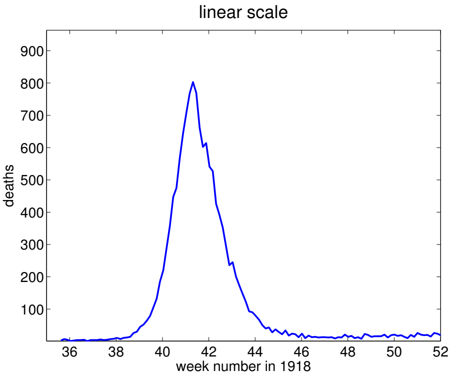
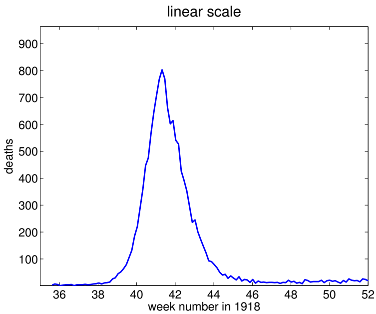
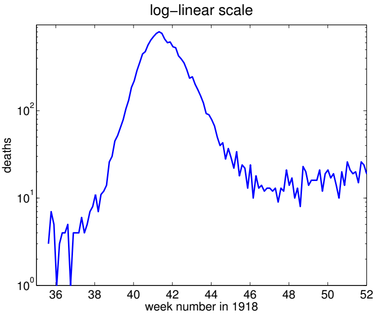
Introduction

Daily pneumonia and influenza (P&I) deaths of 1918 pandemic influenza in Philadelphia.



Re-examine 1918 Daily Philadelphia P&I Deaths





- An exponential growth phase
- Given infectious period and latent period, this rate implies $\mathcal{R}_0$

What We Will Learn

- Estimate the exponential growth rate
- Fit (phenomenological or mechanistic) models to data
- Estimate $\mathcal{R}_0$ from the exponential growth rate

The Exponential Growth Phase

- The 1918 pandemic epidemic curve, and most others, show an initial exponential growth phase,
- That is, during the initial growth phase, the epidemic curve can be modeled as

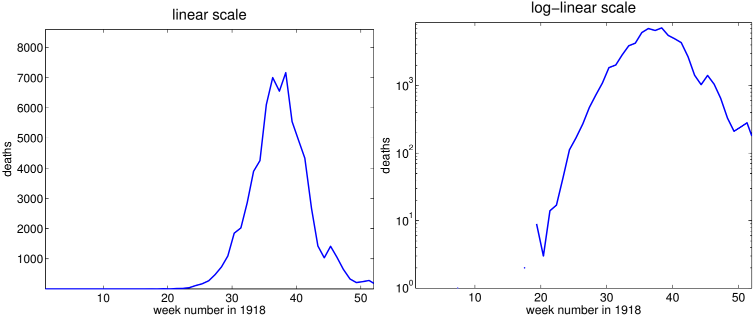
$$X(t) = X(0)e^{\lambda t},$$

  where λ is the exponential growth rate, $X(0)$ is the initial condition.
- So, $\ln X(t)$ and the time t have a linear relationship during the initial growth phase

$$\ln X(t) = \ln X(0) + \lambda t.$$

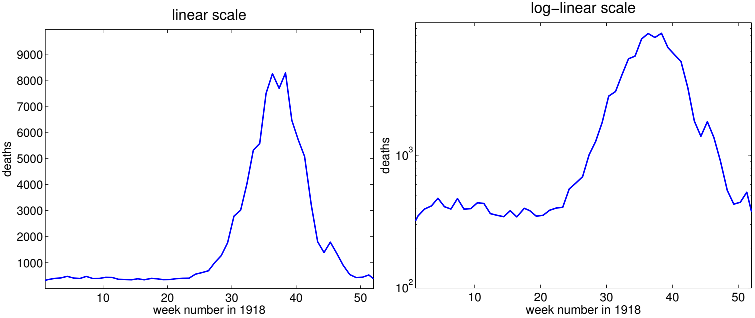
- The exp growth rate measures how fast the disease spreads

Example: 1665 Great Plague Deaths in London



- Exponential growth rate decreases around week 25?

Example: 1665 Great Plague All-cause Deaths in London



- The decrease of the exponential growth rate in plague deaths may be caused by under reporting

Theoretical Exponential Growth Rate: SIR Model

$$S' = -\frac{\beta}{N} SI\,,\ I' = \frac{\beta}{N} SI - \gamma I\,.$$

- Near the disease free equilibrium (DFE) $(N, 0)$

$$I' = (\beta - \gamma) I$$

- This is a linear ODE, with an exponential solutions

$$I(t) = I(0) e^{(\beta - \gamma)t}$$

- So, the exponential growth rate is $\lambda = \beta - \gamma$.
- What is the growth rate of the incidence curve $X(t) = \beta SI$?

Theoretical Growth Rate: SEIR Model

$$S' = -\frac{\beta}{N} S I\,,\ E' = \frac{\beta}{N} S I - \sigma E\,.\ I' = \sigma E - \gamma I\,.$$

- Near the disease free equilibrium (DFE) $(N, 0, 0)$

$$\frac{d}{dt}\begin{bmatrix} E \\ I \end{bmatrix} = \begin{bmatrix} -\sigma & \beta \\ \sigma & -\gamma \end{bmatrix}\begin{bmatrix} E \\ I \end{bmatrix} = J \begin{bmatrix} E \\ I \end{bmatrix}$$

- The exponential growth rate is

$$\lambda = \rho(J) = \frac{1}{2}\left(\lambda + \gamma + \sqrt{(\sigma-\gamma)^2 + 4\beta\gamma}\right)$$

Theoretical Growth Rate: General Case

Assume that a disease can be modeled with

- Susceptible classes $S \in \mathbb{R}^m$ and infected classes $I \in \mathbb{R}^n$
- parameters $\theta \in \mathbb{R}^p$.
- Assume a disease free equilibrium (DFE) $(S = S^*, I = 0)$.

$$S' = f(S, I; \theta)\,,\ \ I' = g(S, I; \theta)\,,\ \text{where } \frac{\partial}{\partial S} g(S^*, 0) = 0$$

- Linearize about the DFE $(S^*, 0)$:

$$I' = \frac{\partial g}{\partial I}(S^*, 0; \theta) I\,.$$

- The exponential growth rate

$$\lambda = \rho\left(\frac{\partial g}{\partial I}(S^*, 0; \theta)\right)$$

Fitting an Exponential Curve

- Model

$$x(t) - x(0)e^{\lambda t}$$

- Naive methods that have been widely used:
  - Least square and linear regression
  - Poisson regression
  - Negative binomial regression
- These methods
  - assume a mean that can be described by a deterministic model
  - only consider observation errors around the deterministic model
  - ignore the process errors are completely ignored

Point Estimates and Confidence Intervals

- The best estimate for (λ, x_0) is called a *point* estimate.
- A 95% confidence interval (CI) (a, b) for λ is an *interval* estimate that satisfies

$$\text{Prob}\{\lambda \in (a, b)\} = 95\%$$

- 95% is called the confidence level. Other examples, 99% CI
- Infinitely many CI with the same confidence level (95%)
- Wider CIs means the true paramter value may differ more widely from the point estimate
- E.g.: The 1918 pandemic influenza (fall wave) has $\mathcal{R}_0 = 1.86$ with 95% CI $(1.82, 1.90)$ (Chowell et al Proc B 2008).

Linear Regression

$$x(t) = x(t)e^{\lambda t} \Rightarrow \ln x(t) = \ln x(0) + \lambda t$$

Commonly use the least square method:

- For a data set (t_i, x_i), minimize

$$F(\lambda, x_0) = \sum_{t=1}^{n} (\ln x(t_i) - \ln x_i)^2$$

- Confidence intervals:
  - Assume that $\ln x_i$ are normally distributed,
    - i.e., x_i are log-normally distributed
    - Then (λ, x_0) are joint normal
    - The covariance matrix is $(D^2 F)^{-1}$.
  - If x_i is not log-normal, not an easy problem.

Poisson Regression

- For an epidemic curve (t_i, x_i), x_i usually not $\sim$ log-normal.
- If infection events have exponentially distributed waiting time, x_i are *Poisson* distributed.
- Poisson regression for these type of data, which is a maximum likelihood method.
  - A likelihood function is the probability of observing the data with a given set of parameters

$$L(\{x_i\}_{i=1}^n|\lambda, x_0) = \prod_{i=1}^n \mathrm{Prob}(x_i|\lambda, x_0) == \prod_{i=1}^n \frac{E[x_i]^{x_i} e^{-E[x_i]}}{x_i!}$$

$$= \prod_{i=1}^n \frac{x(t_i)^{x_i} e^{-x(t_i)}}{x_i!} = \prod_{i=1}^n \frac{x_0^{x_i} e^{\lambda t_i x_i - x_0 \exp(\lambda t_i)}}{x_i!}.$$

- Find the parameters λ, x_0 that maximize L

Poisson Regression: Maximize Log-likelihood

- Because L is a product, it is convenient to maximize $\ln L$, called the log likelihood

$$\ln L(\lambda, x_0) = \sum_{i=1}^{n} x_i \ln x_0 + \lambda t_i x_i - x_0 e^{\lambda t_i} - \ln(x_i!)\,.$$

- Because x_i are constants, drop $\ln(x_i!)$ to maximize

$$\ln \tilde{L}(\lambda, x_0) = \sum_{i=1}^{n} x_i \ln x_0 + \lambda t_i x_i - x_0 e^{\lambda t_i}\,.$$

- This can only be maximized numerically.
- Covariance matrix of the parameters:

$$\mathrm{Var}[\lambda, x_0] = \left(D^2 \ln \tilde{L}\right)^{-1}$$

Condifence Intervals: Likelihood Ratio Test

- To estimate the CI for λ, We use the likelihood ratio test
- Construct a likelihood profile for λ
  - λ is stepped to both directions of the point estimate $\hat{\lambda}$
  - At each step $k = \pm 1, \pm 2, \cdots$
    - Find $L_k = \max L(x_0|\lambda_k)$
    - Compute the likelihood ratio

$$D(\lambda_k) = 2 \ln \frac{L_0}{L_k} = 2 \ln L_0 - 2 \ln L_k$$

where L_0 is the likelihood at the point estimate.
  - Best practice for step size is to use the standard deviation from the covariance matrix.
- Approx. $D_k \sim \chi_1^2$, find the 95% CI for $D(\lambda) : (D(\lambda_a), D(\lambda_b))$.
- The 95% for λ is (λ_a, λ_b).

Negative Binomial Regression

- Poisson regression assumes $E[x_i] = \mathrm{Var}[x_i]$.
- Over-dispersion: $\mathrm{Var}[x_i] > E[x_i]$ because of
  - observation errors
  - non-exponentially distributed waiting times
- Solution: assume that x_i is Negative-Binomial with parameters r and $0 < p < 1$

$$\mathrm{Prob}(x_i|r,p) = \frac{\Gamma(x_i + r)}{x_i!\Gamma(r)} p^r (1-p)^{x_i}\,.$$

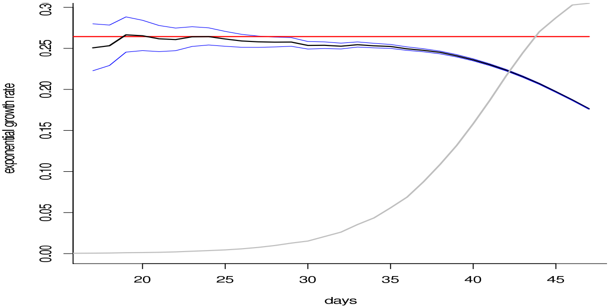
- Assume the same r for all x_i.

$$E[X_i] = r(1-p)/p \;\Rightarrow\; p = r/(r + E[x_i] = \frac{r}{r + x_0 e^{\lambda t_i}}$$

- The parameters are λ, x_0, and r.
- As $r \to \infty$, the Negative Binomial approaches Poisson.

Application to Simulated Epidemics

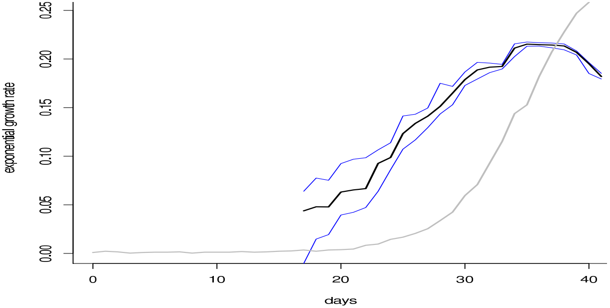
The trend of estimated exponential growth rate when using more data points towards the peak of epidemic:



Red: theoretical rate; Black: estimation; blue: 95% CI; grey: epidemic curve

1918 Pandemic Influenza in Philadelphia

The trend of estimated exponential growth rate when using more data points towards the peak of epidemic:



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Baseline

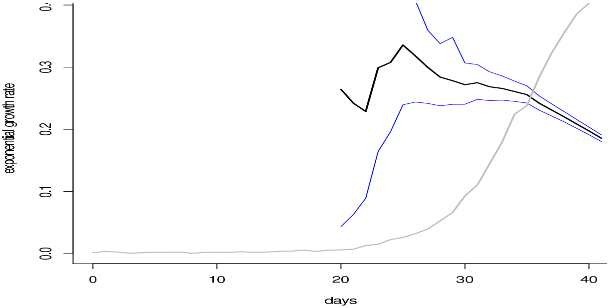
- The early flat phase are non-flu deaths, such deaths are called the baseline P&I deaths
- In a pandemic, most P&I deaths are flu deaths. We can thus ignore the variation in the baseline
- So, we can use a new model for the mean P&I deaths

$$x(t) = b + x_0 e^{\lambda t}$$

  where b is the baseline.
- We use Poisson regression.

1918 Pandemic Influenza in Philadelphia with Baseline

The trend of estimated exponential growth rate when using more data points towards the peak of epidemic:



Black: estimation; blue: 95% CI; grey: epidemic curve

Taking Account of Decreasing Growth Rate

- Exponential growth rate decreases because of the depletion of the susceptibles.
- Use the exponential model,
  - Find the best fitting window by testing goodness of fit.
- Use more sophisticated phenomenological models
  - Logistic model for cumulative cases
  - Richards model for cumulative cases
- Use a mechanistic model, e.g., SIR, SEIR, ...

Single Epidemic Phenomenological Models

- Logistic model:
  - The cumulative cases $C(t)$ initially grow exponentially, then approach the final size
  - The same shape as the logistic model.

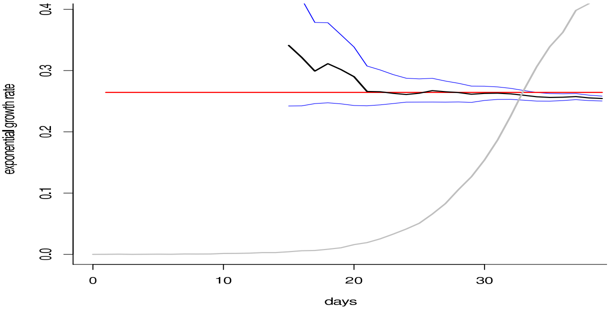
    $$C'(t) = \lambda C[1 - C/K]$$

    This model introduces one more parameter K.
  - But we should not directly fit the cumulative cases data $c_k \sum_{i=0}^{k} x_k$ to this model, because c_k are not independent.
  - Instead, we compute the interval cases $x(t) = c(t+1) - c(t)$, and fit $x(t)$ to the data x_i.
- Richards model: cumulative cases has a mean

$$C'(t) = \lambda C[1 - C/K]^{\alpha}$$

Fit Logistic Model to Simulated Epidemics

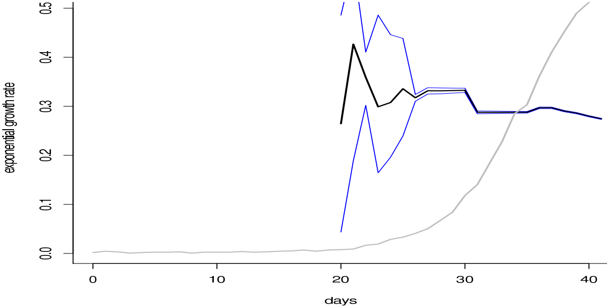
Allows the use of more data points:



Red: theoretical rate; black: estimation; blue: 95% confidence interval; grey: epidemic curve

Philadelphia 1918 Pandemic w/ Baseline + Logistic Model

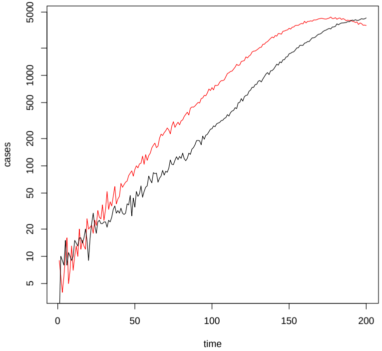
The trend of estimated exponential growth rate when using more data points towards the peak of epidemic:



Black: estimation; blue: 95% confidence interval; grey: epidemic curve

Process Errors

Same disease parameters may produce different epidemic curves.



Coverage Probability

- Coverage probability of a CI is the probability that CI contains the true parameter value.
- A 95% CI should have 95% coverage probability.
- Because we ignored process errors, this method generally produces narrower confidence intervals
- Simulations can verify that the coverage probability for incidence cases is poor.
- Larger observation errors, for example, small reporting rates, improve coverage.

Methods that can handle process errors include: one-step ahead, particle filters, MCMC, ...

Estimate $\mathcal{R}_0$: SIR Model

First, as an example, we look at an SIR model

$$S' = -\frac{\beta}{N} SI\,, \;\; I' = \frac{\beta}{N} SI - \gamma I\,.$$

- Recall that $\lambda = \beta - \gamma$, so $\beta = \lambda + \gamma$

$$\mathcal{R}_0 = \frac{\beta}{\gamma} = \frac{\lambda + \gamma}{\gamma} = 1 + \frac{\lambda}{\gamma}\,.$$

- What if λ is the exponential growth rate of the incidence curve $X(t) = \beta SI$?

Estimate $\mathcal{R}_0$: SEIR Model

$$S' = -\frac{\beta}{N} SI \,,\; E' = \frac{\beta}{N} SI - \sigma E \,.\; I' = \sigma E - \gamma I \,.$$

- Recall that

$$\lambda = \rho(J) = \frac{1}{2}\left(\lambda + \gamma + \sqrt{(\sigma-\gamma)^2 + 4\beta\gamma}\right)$$

- Isolate β,

$$\beta = \sigma + \frac{\lambda}{\gamma}(\lambda + \gamma + \sigma)$$

$$\mathcal{R}_0 = \frac{\beta}{\gamma} = 1 + \lambda\left(\frac{\lambda}{\sigma\gamma} + \frac{1}{\gamma} + \frac{1}{\sigma}\right) \,.$$

Estimate $\mathcal{R}_0$ with a Model: in General

$$S' = f(S, I; \theta),$$
$$I' = g(S, I; \theta).$$

where $S \in \mathbb{R}^m$, $I \in \mathbb{R}^n$, θ is the vector of parameters.

- Recall that the exponential growth rate is the largest eigenvalue of
$$\frac{\partial g}{\partial I}(S_0, 0; \theta).$$
- This replationship usually gives us an estimate of the transmission rate given all the other disease parameters.
- $\mathcal{R}_0$ can be computed using the infered transmission rate and all other given parameter values.

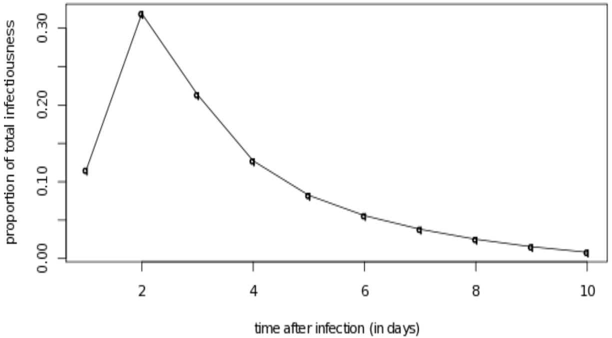
Estimate $\mathcal{R}_0$ using Generation Interval

See Wallinga and Lipsitch (Proc B 2007, 274:599604)

- Generation interval (serial interval): the waiting time from being infected to secondary infections
  - The generation interval distribution $w(t)$ can be estimated (e.g., from contact tracing) without a mechanistic model.
- Let $n(t)$ is the transmission rate at age of infection τ.
  - $\mathcal{R}_0 = \int_0^\infty n(\tau)d\tau$, and $w(\tau) = n(\tau)/\mathcal{R}_0$.
  - The incidence curve $x(t) = x(t) * n(t)$
- Assume $x(t) = x(0)e^{\lambda t}$,

$$\mathcal{R}_0 = \frac{1}{\int_0^\infty e^{-\lambda\tau} w(\tau)d\tau}$$

The Influenza Generation Interval Distribution



Taken from N.M. Ferguson, et al., (Nature 2005, 437:209-214)

The Basic Reproduction Number of 1918 Pandemic Influenza in Philadelphia

Given that we have estimated the exponential growth rate to be

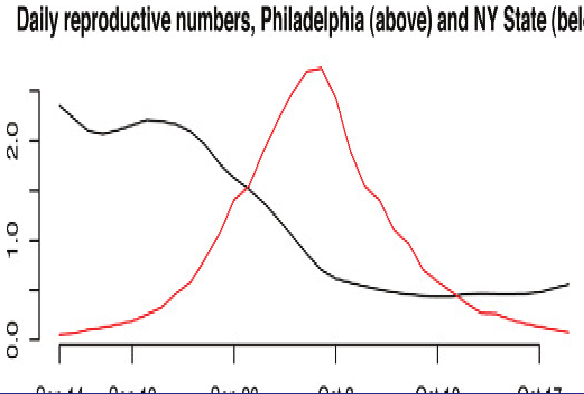
$$\lambda = 0.288, \quad \text{with 95\% confidence interval: } (0.286, 0.290)$$

and with the above generation interval distribution, we can compute that

$$\mathcal{R}_0 = 2.16, \quad \text{with 95\% confidence interval: } (2.15, 2.17)$$

This is consistent with other estimations such as Mills et al. (Nature 2004) and Goldstein et al. (PNAS 2009)

Basic Reproduction Number Estimated by Goldstein et al (2009)



Some Considerations

- Deaths v.s. incidences
- Temporal aggregation (e.g., weekly incidences)
- Spatial aggregation (e.g., overall Canada v.s. city level curves)

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