# Epidemic models 1

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*2021-02-10 ©BMB (except textbook material/other images)*

*motivation*

- P & I data from Philadelphia 1918 flu:
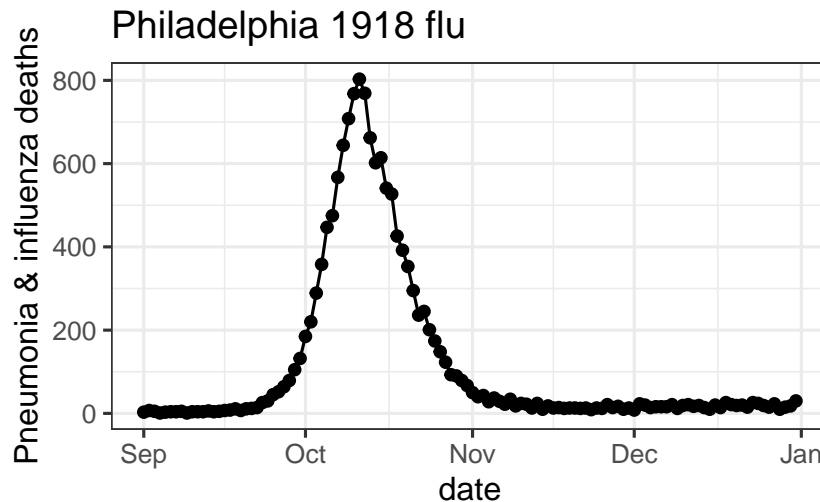
*what do we want to figure out?*

*what shall we assume?*

- classify individuals as $S$, $I$ (**compartmental** model; **microparasite** or **intensity-independent**)
- disease is transmitted from $S$ to $I$
- $S \to I$ instantaneously (zero latent period, no $E$)
- population is **homogeneous** (no heterogeneity in susceptibility, infectiousness, contact)
- fixed population size (birth = migration = 'natural' death = 0)
- transmission rate is time-invariant

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- assumption 2 is OK (Pasteur, Koch's postulates … )
- all the rest are approximations

  start simple!

- parsimony

- robustness?
- applicability/estimation?

Levins (1966) (also Orzack and Sober (1993), Levins (1993), Weisberg (2007))

*exponential growth*

- one variable (=1D model)
- how does disease spread? → equation

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*what variables should we use?*

- time ($t$)
- state variable: incidence, prevalence, death rate, death toll (= cumulative death?)
- deaths loosely connected to transmission

but deaths are observed!

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when are deaths a good **proxy** for incidence?

- infection -> death time is fixed
- homogeneity? (might not matters?)
- mortality curve is shifted epidemic

(COVID context ... we observe case reports, number of tests, hospitalizations, and deaths)

- **incidence**: number of infections per unit time (rate or flow)
- **prevalence**: number of currently infected people (quantity or stock)

prevalence is closer to the **mechanism**

_____

model components:

- $I(t)$ (state variable: prevalence)
- $I(0)$ (initial conditions)
- $\beta$ (parameter) = avg contacts **per susceptible per infective per unit time**

$$I(t + \Delta t) \approx I(t) + \beta I(t)\Delta t$$

Take $\lim \Delta t \to 0$ (and solve):

$$\frac{dI}{dt} = \beta I \to I(t) = I(0)exp(\beta t)$$

*model criticism*

- Ignored discrete nature of individuals
- Ignored time-varying $\beta$ (e.g. **diurnal** fluctuations)
- Ignored finite infectious periods (recovery/death)

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**Next**: What if we make infectious periods finite? (i.e., including recovery (**clearance**) or death

$$dI/dt = \beta I - \gamma I$$

*mean infectious period*

$$I(t) = I(0) \exp(-\gamma t)$$
$$\text{proportion uninfected} = \exp(-\gamma t)$$
$$\text{proportion infected} = 1 - \exp(-\gamma t)(= \text{CDF} := C(t))$$
$$\text{PDF} := C'(t) = \gamma \exp(-\gamma t)$$
$$\text{substitute } x = \gamma t \quad \to \quad dx = \gamma \, dt$$
$$\text{mean} = E[t] = \int t \exp(-\gamma t) \, dt = \int x \exp(-x) \, dx/\gamma = 1/\gamma$$

*dimensional analysis*

rates and characteristic times/scales

- is $I$ a proportion or a density or a number ... ?
- what are the units of $\beta$, $\gamma$ ?

*nondimensionalization*

- standardize any values that can be eliminated **without loss of (mathematical) generality**
- what can we do here?
- $\gamma = 1$
- $I$ ? (depends on how we have defined it initially) $\to I/N$
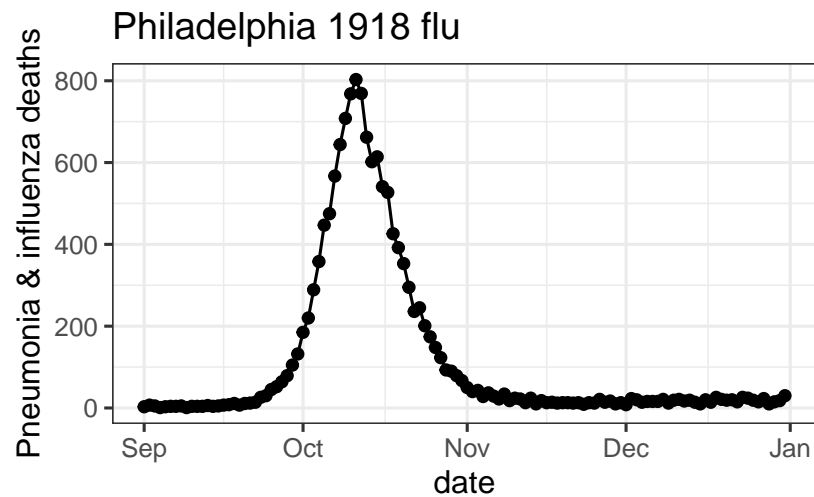
*compare with data???*

Original scale:



Figure 2: Philadelphia P&I

Log scale:
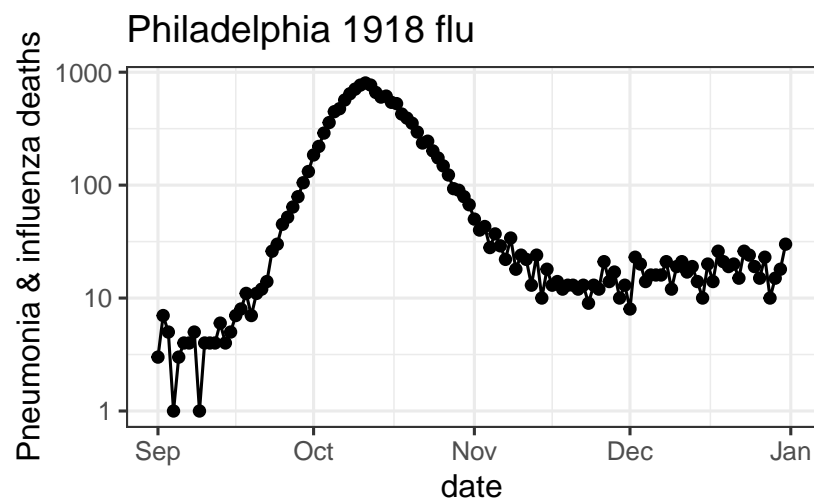


Figure 3: Philadelphia P&I, log scale

- Fit a straight line through the straight part of the curve
- slope is $\beta N$
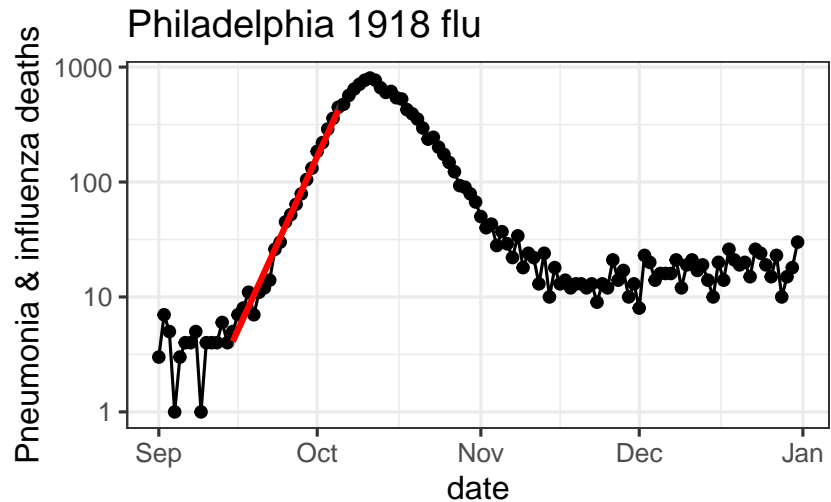- "intercept" is $\log(I(0))$ (zero is defined in a tricky way)

```python
import pandas as pd
import numpy as np
import matplotlib.pyplot as plt
from sklearn.linear_model import LinearRegression
dd = pd.read_csv("data/pim_us_phila_city_1918_dy.csv")
## plt.plot(dd.pim)
## plt.plot(np.log10(dd.pim))
t = np.arange(20)
lw = np.log10(dd.pim)[20:40]
plt.plot(t,lw,'o')
## https://docs.scipy.org/doc/scipy/reference/generated/scipy.linalg.lstsq.html
## https://scikit-learn.org/stable/modules/generated/sklearn.linear_model.LinearRegression.html
ta = t.reshape(-1,1)  ## make this into a column vector
reg = LinearRegression().fit(ta,lw)
plt.plot(t,reg.intercept_+reg.coef_[0]*t)
```
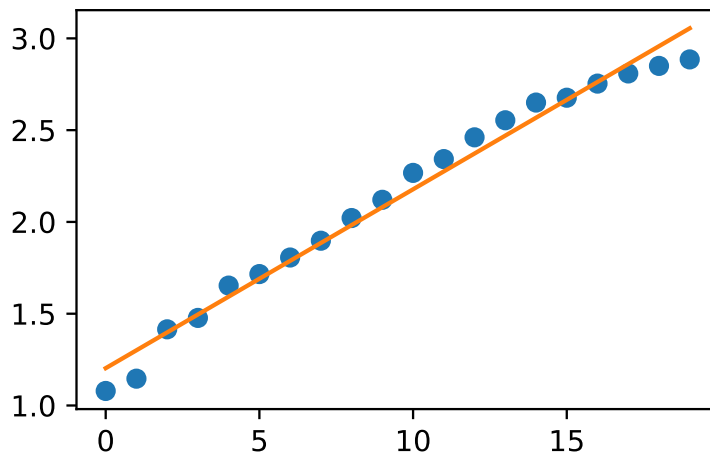
*model assessment*

- math is super-easy!
- clear, testable predictions
- parameter estimation is easy
- only consistent over a short time window

    – small $t$: arbitrarily close to zero
    – large $t$: ridiculous

## Simple (SI) epidemic

- what are we missing?
- **depletion of susceptibles**
- let's take a step back and ignore death & recovery for now

$$dS/dt = -\beta SI$$
$$dI/dt = \beta SI$$

This looks 2D **but** what if we assume $S + I = N$ is constant? Then $S = N - I$

$$dI/dt = \beta(N - I)I$$

How do we solve this? **Partial fractions**

$$\frac{dI}{\beta(N-I)I} = dt$$

$$dI\left(\frac{A}{N-I} + \frac{B}{I}\right) = dI \cdot \frac{A + B(N-I)}{I(N-I)}$$

$$A = B; \quad B = 1/N$$

$$\frac{1}{\beta N}\left(-\log(N-I) + \log(I)\right)\Big|_{I(0)}^{I} = t - t_0$$

$$\left(-\log(N-I) + \log(I)\right)\Big|_{I(0)}^{I} = (\beta N)(t - t_0) \quad (\text{set } t_0 = 0)$$

$$\log\left(\frac{I}{N-I}\right) - \log\left(\frac{I(0)}{N-I(0)}\right) = \beta N t$$

$$\log\left(\frac{I}{N-I}\right) = \beta N t + -\log\left(\frac{I(0)}{N-I(0)}\right)$$

$$\frac{I}{N-I} = \exp(\beta N t)\frac{I(0)}{N-I(0)} \equiv Q$$

$$I = Q(N-I)$$

$$I(t)(1+Q) = QN$$

$$I(t) = \frac{QN}{1+Q} = \frac{N}{1+\frac{1}{Q}}$$

$$= \frac{N}{1 + \left(\frac{N-I(0)}{I(0)}\right)\exp(-\beta N t)}$$

$$?? \equiv I(0)\exp(\beta N t)/(1 + (I0/N)(\exp(\beta N t) - 1)) ??$$

*Qualitative analysis*

- $I \ll N$ ? exponential growth
- **per capita growth rate** $((dI/dt)/I = d(\log(I))/dt)$ decreases monotonically with increasing $I$
- asymptotic behaviour? equilibria? periodic orbits?
- periodic orbits impossible in 1D (uniqueness of flows)

*equilibrium analysis*

- $I = 0$, **disease free equilibrium** (DFE)
- $I = N$, **endemic equilibrium** (EE)

Stability? (Assume $\beta > 0$)

- **local asymptotic stability**
- **global asymptotic stability** (Lyapunov functions)

*model criticism/conclusions*

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(Comparison to metapop, logistic growth model)

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*SIR model*

*Basic SIR model*

- put the pieces together

$$\frac{dS}{dt} = -\beta SI$$

$$\frac{dI}{dt} = \beta SI - \gamma I$$

$$\frac{dR}{dt} = \gamma I$$

- really 2D (because $S + I + R = N$)
- rescale to $N = 1$ (*S, I, R* as proportions)

Numerical solution (R version):

```
## define gradient function
SIRgrad <- function(t, y, parms) {
    g <- with(as.list(c(y,parms)), {
        c(-beta*S*I, beta*S*I-gamma*I, gamma*I)
    })
    return(list(g))
}
library(deSolve)
## initial conditions and parameters
y0 <- c(S=0.99, I=0.01, R=0)
p0 <- c(beta=4, gamma=1)
tvec <- seq(0,8,length=101)
## solve (LSODA by default)
sir_R <- ode(y=y0, times=tvec, parms=p0, func=SIRgrad)

## plot
par(las=1,bty="l") ## cosmetic
matplot(tvec, sir_R[,-1],
        type="l", lwd=2, ## solid lines, thicker
        xlab="time",ylab="proportion")
legend("right",names(y0), col=1:3, lty=1:3, lwd=2)
```
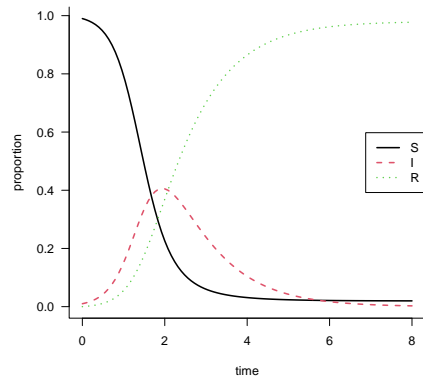
Figure 5: SIR model (R)

## Phase plane plot

```r
par(las=1,bty="l") ## cosmetic
plot(I~S,type="l",data=as.data.frame(sir_R))
with(as.data.frame(sir_R), points(S,I, cex=0.75,pch=16))
```
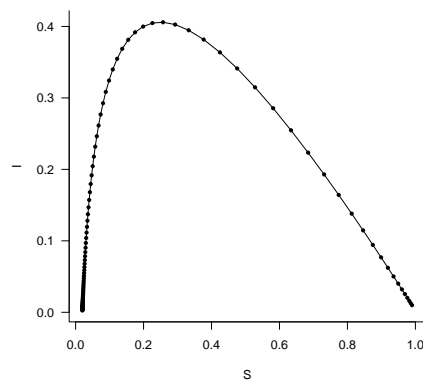


Figure 6: SIR phase plane (R)

## Solve using Python

```python
import numpy as np
import scipy.integrate
def SIR_grad(x,t,params):
    """basic gradient definitions for SIR model"""
    beta,gamma = params    ## unpack parameters
    S,I,R = x              ## unpack state variables
    return(np.array([-beta*S*I, beta*S*I-gamma*I, gamma*I]))


t_vec = np.linspace(0,8,101)
params = (4,1) ## extra parameters (beta, gamma)
y0 = (0.99, 0.01, 0)
SIR_sol1 = scipy.integrate.odeint(SIR_grad,
                                    y0=y0,
```

```
                                     t=t_vec,
                                     args=(params,))
```

```
## https://community.rstudio.com/t/how-to-display-the-plot-in-the-python-chunk/22039/3
import matplotlib.pyplot as plt
fig, ax = plt.subplots()
ax.plot(SIR_sol1);
plt.show()
```
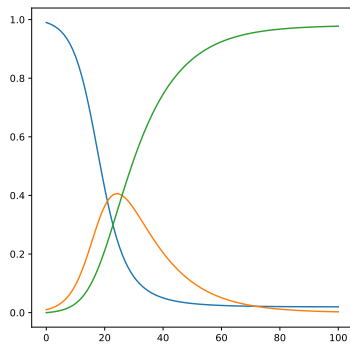


*dimensional analysis*

- initial growth rate (time$^{-1}$) $\beta - \gamma$
- mean infectious period $1/\gamma$ (time)
- basic reproduction number $\mathcal{R}_0 = \beta/\gamma$

*initial growth rate*

$$\frac{dI}{dt} = \beta S - \gamma I$$
$$= (\beta S - \gamma)I$$
$$\approx (\beta - \gamma)I \quad \text{near } DFE$$

or calculate **Jacobian** ($\partial X_i / \partial X_j$):

$$\begin{pmatrix} -\beta I & -\beta S & 0 \\ \beta I & \beta S - \gamma & 0 \\ 0 & \gamma & 0 \end{pmatrix}$$

Evaluate at DFE ($\{1, 0, 0\}$):

$$\begin{pmatrix} 0 & -\beta & 0 \\ 0 & \beta - \gamma & 0 \\ 0 & \gamma & 0 \end{pmatrix}$$

Eigenvalues of this are pretty boring! But useful approach.

*Per capita rates*

In general we can express *per capita* gradients in $X$ as gradients of $\log(X)$:

$$\frac{dX}{dt} = Xf(X,Y,Z,\dots)$$
$$\frac{\frac{dX}{dt}}{X} = f(X,Y,Z,\dots)$$
$$\frac{d\log(X)}{dt} = f(X,Y,Z,\dots)$$

Another way to see that $\beta - \gamma$ is the slope on the log scale.

*Stability of DFE*

- $\beta > \gamma$ $(r > 0)$
- $\beta/\gamma > 1$ $(\mathcal{R}_0 > 1)$

  Local asymptotic stability **or**

- $\frac{dI}{dt} = \beta SI - \gamma I$
- non-dimensionalize: $\gamma = 1$, $\beta = \mathcal{R}_0$
- $\frac{dI}{dt} = (\mathcal{R}_0 S - 1)I$
- $\frac{d\log I}{dt} = \mathcal{R}_0 S - 1$

  Since $S \leq 1$, $\mathcal{R}_0 < 1 \to$ deriv of $\log I$ is always negative (don't really need the last step)

*Automated analysis*

```r
library(phaseR)
```

```
## ------------------------------------------------------------------------------
## phaseR: Phase plane analysis of one- and two-dimensional autonomous ODE systems
## ------------------------------------------------------------------------------
##
## v.2.1: For an overview of the package's functionality enter: ?phaseR
##
## For news on the latest updates enter: news(package = "phaseR")
```

```r
par(las=1,bty="l",xaxs="i",yaxs="i") ## cosmetic
SIRgrad_2d <- function(t, y, parms) {
    g <- with(as.list(c(y,parms)), {
        c(-beta*S*I, beta*S*I-gamma*I)
    })
    return(list(g))
```

```
}
## plot(0:1,0:1,type="n",xlab="S",ylab="I")
f1 <- flowField(SIRgrad_2d,
         xlim=c(0,1),
         ylim=c(0,1),
         parameters=p0,
         state.names=c("S","I"),
         add=FALSE)
n1 <- nullclines(SIRgrad,
            xlim=c(0,1),
            ylim=c(0,1),
            parameters=p0,
            state.names=c("S","I"))
t1 <- trajectory(SIRgrad_2d,parameters=p0,
         state.names=c("S","I"),
         ## n=10,
         y0=y0[1:2],
         tlim=c(0,5))
```
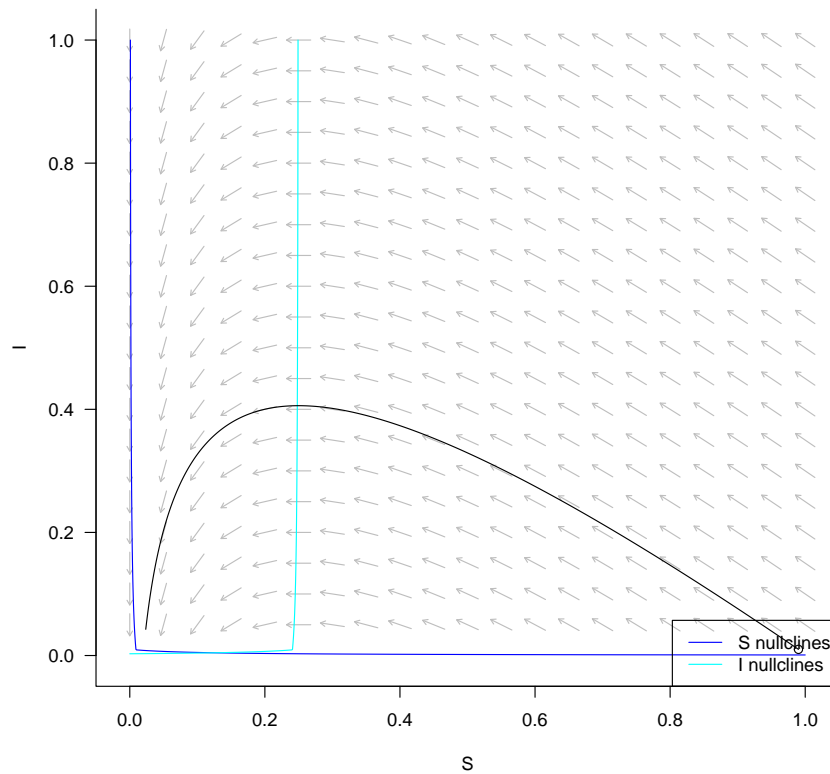


Figure 7: phase plane analysis in R

```
phasePlaneAnalysis(SIRgrad_2d,xlim=c(0,1),
                   parameters=p0,
```

```
               state.names=c("S","I"),
               ylim=c(0,1))
```

*Solution*

- can't get analytical solution for $S(t)$, $I(t)$
- **but**: we can solve for $I(S)$:

$$\frac{dI}{dS} = \frac{dI/dt}{dS/dt} = -1 + \frac{1}{\mathcal{R}_0 S}$$

$$\int_{I(0)}^{I}(t)\,dI = \int_{S(0)}^{S(t)} \left( -1 + \frac{1}{\mathcal{R}_0 S} \right) dS$$

$$I - I(0) = -(S - S(0)) + \frac{1}{\mathcal{R}_0} \log(S/S(0))$$

$$I + S - (I(0) + S(0)) = \frac{1}{\mathcal{R}_0} \log(S/S(0))$$

*Final size calculations*

- $t \rightarrow \infty$:

$$(I_\infty + S_\infty) - (I(0) + S(0)) = \frac{1}{\mathcal{R}_0} \log S_\infty / S(0)$$

- newly invading pathogen: $S \approx 1$, $I(0) \ll 1 \ (\approx 0)$, $I_\infty \rightarrow 0$
- in the limit $I(0) \rightarrow 0$:

$$S_\infty) - 1 = \frac{1}{\mathcal{R}_0} \log S_\infty$$

- "final size" $Z = 1 - S_\infty$
- $-Z = \frac{1}{\mathcal{R}_0} \log(1 - Z)$

*Lambert W functions*

- How do we solve this?
- Newton's method (or whatever)
- *Lambert W* (Corless et al. 1996): solves $W \exp(W) = Z$

```
import sympy as sym
z, R = sym.symbols('z R')
sym.solve(sym.Eq(z,-1/R*sym.log(1-z)),z)

## [(R + LambertW(-R*exp(-R)))/R]

finalsize <- function(R0) {
    1+1/R0*lambertW(-R0*exp(-R0))
}
```
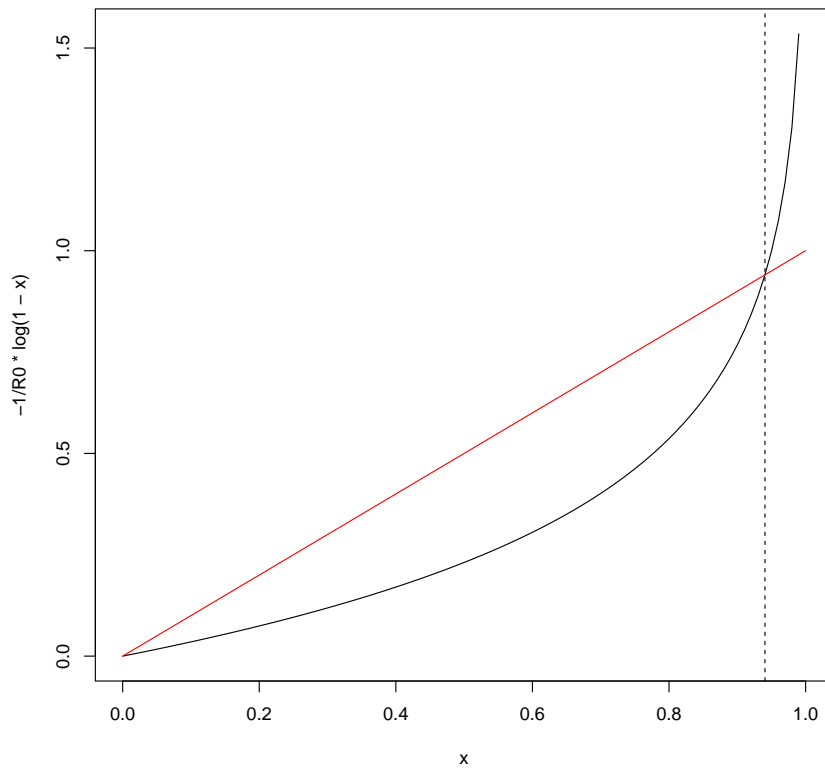
```
R0 <- 3
curve(-1/R0*log(1-x), from=0,to=1)
curve(1*x, add=TRUE,col="red")
library(emdbook)
abline(v=finalsize(R0),lty=2)
```



*Epidemic threshold*

Assuming vaccination (or other perfect *prophylaxis* [protection]) at rate $p$

$$R_0 = 1 - 1/p$$

speed-based intervention:

$$\beta SI - (\gamma + \phi)I < 0$$
$$I(\beta - \gamma - \phi) < 0$$
$$\phi > (\beta - \gamma) = r$$

*Comparing Epidemic threshold vs. final size*

```
library(emdbook)
finalsize <- function(R0) {
```

```
    1+1/R0*lambertW(-R0*exp(-R0))
}
par(las=1,bty="l")
curve(finalsize(x),from=1,to=10,xlab=expression(R[0]),
      ylab="proportion")
curve(1-1/x, add=TRUE, col=2)
legend("bottomright",
       c("final size","herd immunity threshold"),
       col=1:2, lty=1)
```
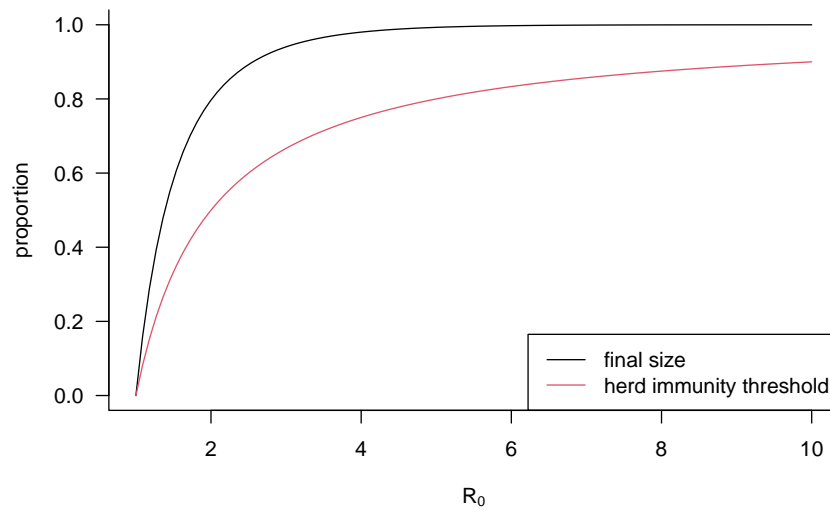


Figure 8: final size vs herd immunity

*Estimating R from data*

- Euler-Lotka equation

$$I(t) = \int_0^t I(t - \tau) K(\tau) \, d\tau$$

$$I(0) \exp(rt) = \int_0^t I(0) \exp(r(t - \tau)) K(\tau) \, d\tau$$

$$1 = \int_0^t \exp(-r\tau) K(\tau) \, d\tau$$

$$1 = \int_0^t \exp(-r\tau) \mathcal{R}_0 g(\tau) \, d\tau$$

$$\frac{1}{\mathcal{R}_0} = \int_0^t \exp(-r\tau) g(\tau) \, d\tau$$

*SIRS/SIR with vital dynamics*

- models of **endemic** disease

- e.g. "childhood diseases" (measles, mumps, rubella, pertussis, polio, chickenpox, . . . )

  – directly transmitted, acute, immunizing

- SIRS model: influenza (evolution), coronaviruses/SARS-CoV-2 (maybe???), cholera (King et al. 2008)
- SIR model *with vital dynamics*

$$\frac{dS}{dt} = \mu N - \beta/N SI - \mu S$$
$$\frac{dI}{dt} = \beta/N SI - \gamma I - \mu I$$
$$\frac{dR}{dt} = \gamma I - \mu R$$

- Balanced population (birth rate = $\mu N$). Can consider more complex demography but often don't need to

  – disease-induced death rates low relative to natural mortality
  – demographic time scales much longer than epidemic time scales (exceptions: **chronic** diseases like tuberculosis, HIV/AIDS, diseases of non-human animals an dplants . . . )

- Scaling $\beta/N$ is much easier for dealing with applications/real data, scaling $N = 1$ is easier for doing math
- $\mathcal{R}_0$ is $\beta/(\mu + \gamma)$ ($\approx \beta/\gamma$ for most human diseases)

Most of the following is taken from Brauer, Castillo-Chavez, and Feng (2019)

$$S^* = \frac{\mu + \gamma}{\beta} = 1/\mathcal{R}_0 \quad \text{(this is \textbf{very general})}$$
$$I^* = \frac{\mu}{\mu + \gamma} - \frac{\mu}{\beta} = \frac{\mu}{\beta}(\mathcal{R}_0 - 1)$$

- at equilibrium the **force of infection** is $\beta I^*$, so the **average age at infection** is $A = 1/(\beta I^*)$
- average lifespan is $L = 1/\mu$
- $L/A = \beta I^*/\mu = \mathcal{R}_0 - 1$

  – another way to estimate $\mathcal{R}_0$! (also, $S^* = 1/\mathcal{R}_0$)
  – tells us something about risk by age, effects of vaccination

Jacobian at EE:

$$\begin{pmatrix} -\mu\mathcal{R}_0 & -(\mu + \gamma) \\ \mu(\mathcal{R}_0 - 1) & 0 \end{pmatrix}$$

Trace = $-\mu\mathcal{R}_0$, Det = $\mu(\mu + \gamma)(\mathcal{R}_0 - 1)$

$$\lambda = (1/2) \left( -\mu \mathcal{R}_0 \pm \sqrt{\mu^2 \mathcal{R}_0^2 - 4\mu(\mathcal{R}_0 - 1)(\mu + \gamma)} \right)$$

$$\approx (1/2) \left( -\mu \mathcal{R}_0 \pm \sqrt{-4\mu(\mathcal{R}_0 - 1)\gamma} \right)$$

$$= -\frac{\mu \mathcal{R}_0}{2} \pm i \sqrt{(1/L)(L/A)\gamma}$$

$$= -\frac{\mu \mathcal{R}_0}{2} \pm i \cdot 1/\sqrt{A\tau}$$

where $\tau = 1/\gamma$ is the infectious period. Both parts of the eigenvalue have units of time$^{-1}$.

- the period is $2\pi$ *divided by* the imaginary part = $2\pi\sqrt{A\tau}$
- e.g. for measles $A \approx 5\text{yr}$, $\tau \approx 1/26$, epidemic interval is `2*pi*sqrt(5/26)` $\approx 2.76$ years.
- **Damping factor**: amplitude decreases by a factor $\exp(-\mu \mathcal{R}_0 T/2)$ per cycle (factor of 1/2 because we are measuring the size of the excursions, not the size of the envelope)
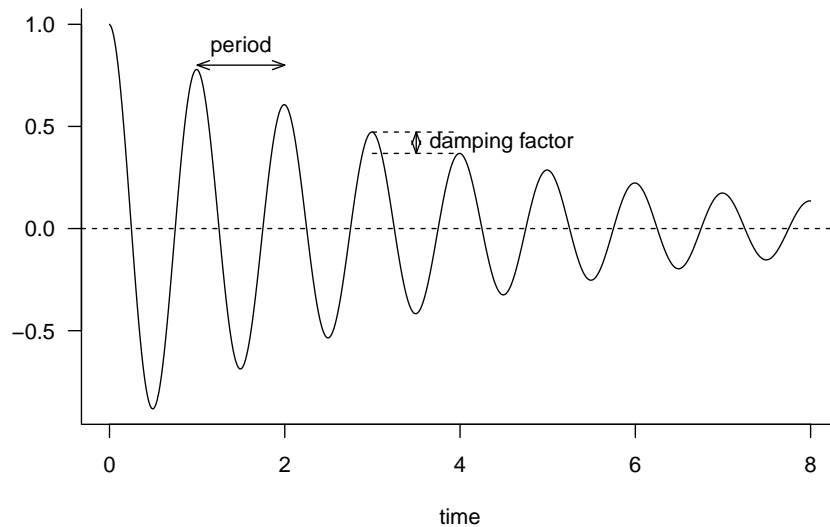


Figure 9: damping

*Stochasticity*

Allen (2017)

*Reed-Frost model*

- notes on history: 1927-1928, 1951-1952 (Abbey 1952; Reed 1951), 1976 (Frost 1976)

- household infection model: fixed (small) population, discrete infection generations
- start with **index cases**
- then allow infection: probability of infection $= 1 - (1 - p_i)^I$
- expected number of infections $= S\left(1 - (1 - p_i)^I\right)$
- $\mathcal{R}_0 = p_i N$
- **hazard** interpretation

  - probability of infection per $I$ per small $\Delta t = \beta$
  - prob of **non-infection** by 1 inf at time $\tau = \exp(-\beta\tau) = 1 - p_i$
  - prob of non-inf by $I$ inf $= \exp(-\beta\tau)^I = \exp(-(\beta I)\tau)$
  - hazard $\equiv$ FOI

- can do standard analysis of equilibria, stability, etc. ($\mathbf{X}_{t+1} = \mathbf{X}_t$; stability based on $|\lambda| \lessgtr 1$)
- what is $\mathcal{R}_0$ ?
- $r$ vs $R$ relationship: $\mathcal{R}_0 = (1 + \kappa r\bar{G})^{1/\kappa}$

  - $\kappa$ is the the reciprocal of the *shape parameter* ($\kappa = \mathrm{CV}^2$)
  - SIR: $\kappa = 1$, $\mathcal{R}_0 = 1 + r\bar{G}$. R-F: $\kappa \to 0$ so $\mathcal{R}_0 = \exp(r\bar{G})$

*discrete-time stochastic R-F*

- stochastic version: $I_{t+1} \sim \mathrm{Binom}\left(S_t, 1 - (1 - p_i)^{I_t}\right)$

```
set.seed(101)
rf <- function(nt,y0,p_i) {
    res <- numeric(nt)
    S <- y0[["S"]]
    I <- res[1] <- y0[["I"]]
    for (t in 2:nt) {
        I <- rbinom(1, prob=1-(1-p_i)^I, size=S)
        S <- S-I
        if (I==0) break
        res[t] <- I
    }
    return(res)
}
r0 <- rf(20, y0=c(S=99,I=1), p_i=0.02)
r1 <- replicate(300, rf(20, y0=c(S=99,I=1), p_i=0.02))
par(las=1,bty="l")
matplot(r1,type="l",col=adjustcolor("black",alpha.f=0.2),lty=1)
lines(rowMeans(r1),col=2,lwd=3)
```
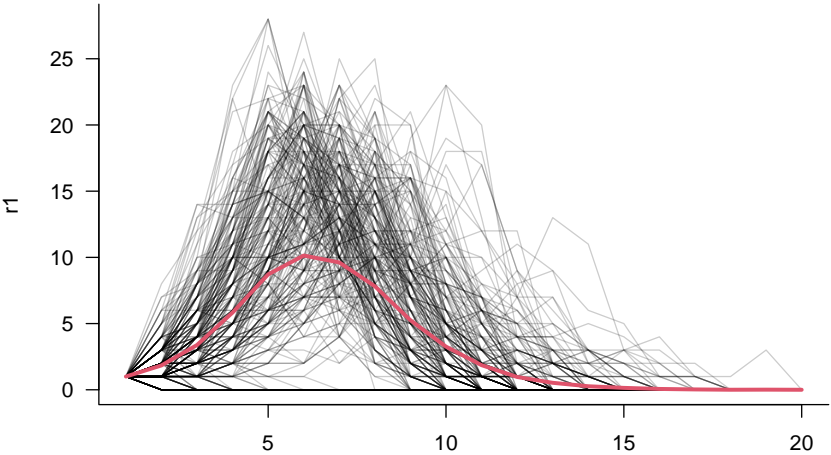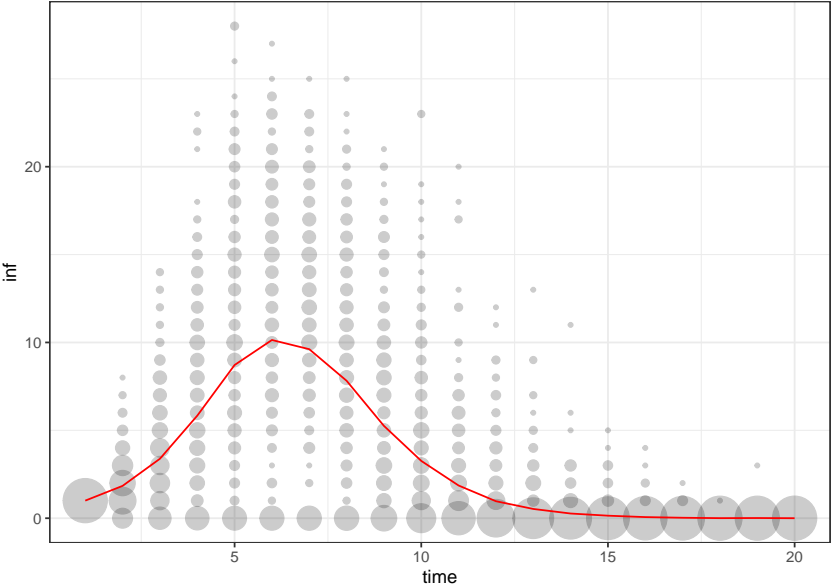
Figure 10: Reed-Frost ensemble



Figure 11: Reed-Frost ensemble 2

## Gillespie algorithm

- define all processes in terms of *rates* (SIR: $\beta SI$, $\gamma I$), rather than gradients
- *Poisson process*: exponentially distributed

```r
library(GillespieSSA2)
parms <- c(beta = 5 , gamma = 1, N=100)
final_time <- 10
initial_state <- c(S = 99, I=1, R=0)
reactions <- list(
  reaction("beta*S*I/N",  c(S = -1, I=+1), name="transmission"),
  reaction("gamma*I",     c(I = -1, R = +1), name="recovery")
)
set.seed(1)
g1 <- ssa(initial_state,reactions,final_time,parms,
          method=ssa_exact(),
          sim_name="SIR")

plot_ssa(g1) + geom_step()
```
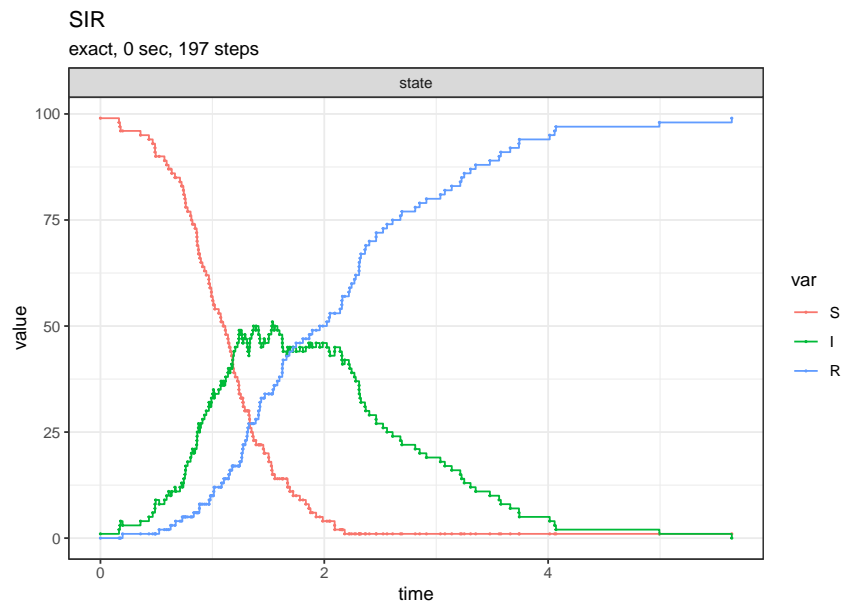


Figure 12: Gillespie realization

## stochastic ODEs

- take limits of very large population size, short time, so that stochastic changes become a *Wiener process* (continuous, non-differentiable, changes are Gaussian)

$$dX(t) = \underbrace{f(X(t))\,dt}_{\text{deterministic}} + \underbrace{G(X(t))\,dW(t)}_{\text{stochastic}}$$

- $f(X(t))$ is the original gradient vector
- $G(X(t))$:

  - need $(G\,dW)(G\,dW)^T$ to equal the **covariance** of $\Delta X$.

$$C = E\begin{pmatrix} (\Delta S)^2 & \Delta S \Delta I \\ \Delta S \Delta I & (\Delta I)^2 \end{pmatrix} = \begin{pmatrix} \beta SI/N & -\beta SI/N \\ -\beta SI/N & \beta SI/N + \gamma I \end{pmatrix}\Delta t$$

Need the **matrix square root** of $C$, i.e. $G$ such that $GG^T = C$. (**Cholesky decomposition** or other)

- **Euler-Maruyama** method: Euler integration + noise scaled by $\sqrt{\Delta t}$

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