Introduction to Mathematical Epidemiology: Basic Models

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Basic models considered:

Deterministic compartmental models suitable to understand or predict the spread of infectious diseases among humans
Knowledge driven rather than data driven models

Simple models that leave out a lot of the biology but give some observed qualitative behavior
"A scientific theory should be as simple as possible but no simpler" Albert Einstein

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Taking continuous time, models are formulated as
ordinary differential equations (ODEs)
Taking discrete time, models are formulated as difference equations

Start with a simplified version of the continuous time model
introduced by Kermack, McKendrick 1929, and use a modeling framework

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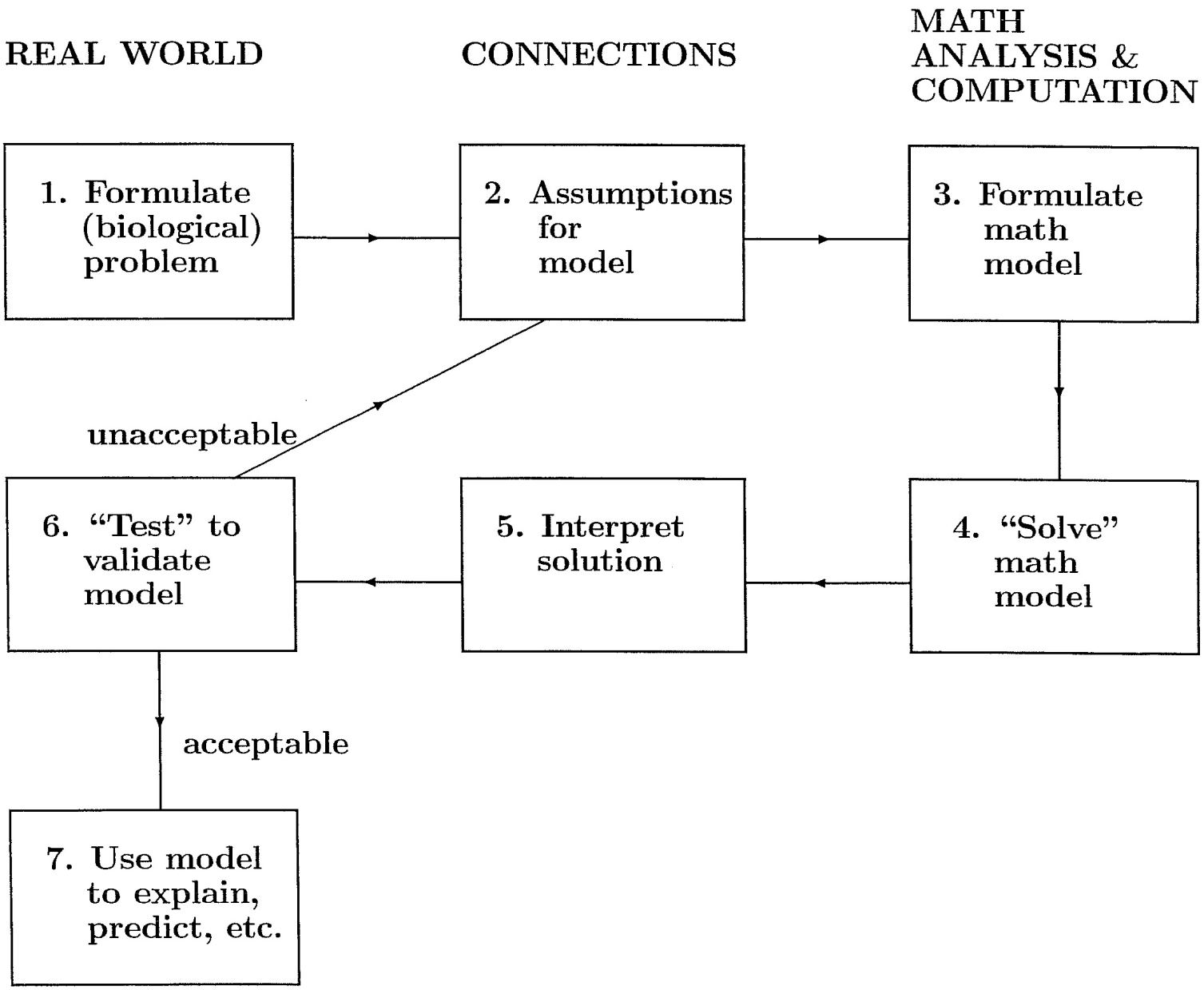
REAL WORLD
CONNECTIONS
MATH ANALYSIS & COMPUTATION
1. Formulate (biological) problem
2. Assumptions for model
3. Formulate math model
unacceptable
6. "Test" to validate model
5. Interpret solution
4. "Solve" math model
acceptable
7. Use model to explain, predict, etc.

Susceptible-Infectious-Recovered plus demographics

1. Biological Problem: Will measles become endemic in the population?

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2. Assumptions: Measles is a viral disease, so SIR model appropriate
Include demographics, but ignore death due to measles

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3. Formulation of Model:

S, I, R denote the number of susceptible, infectious, recovered people with $N = S + I + R$ as the total population

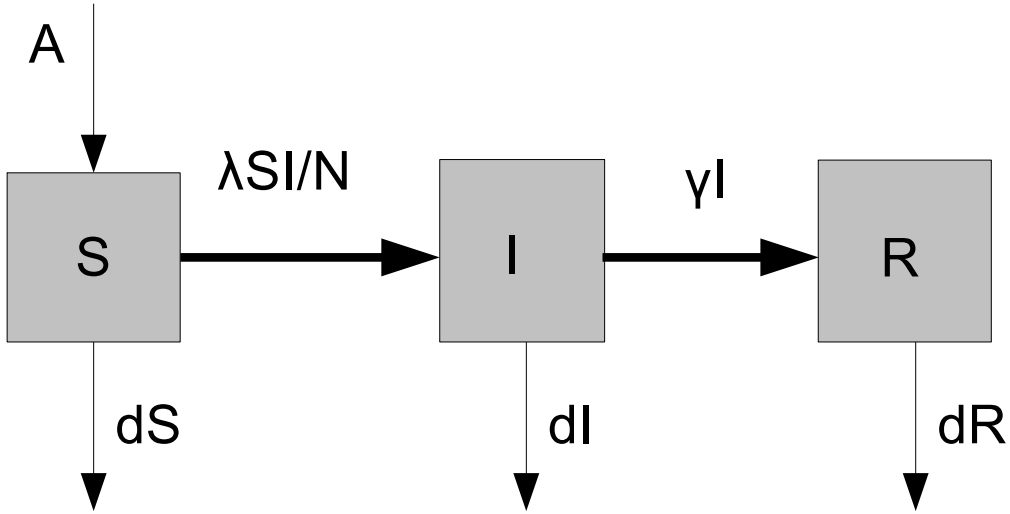
A denotes the rate of input into S

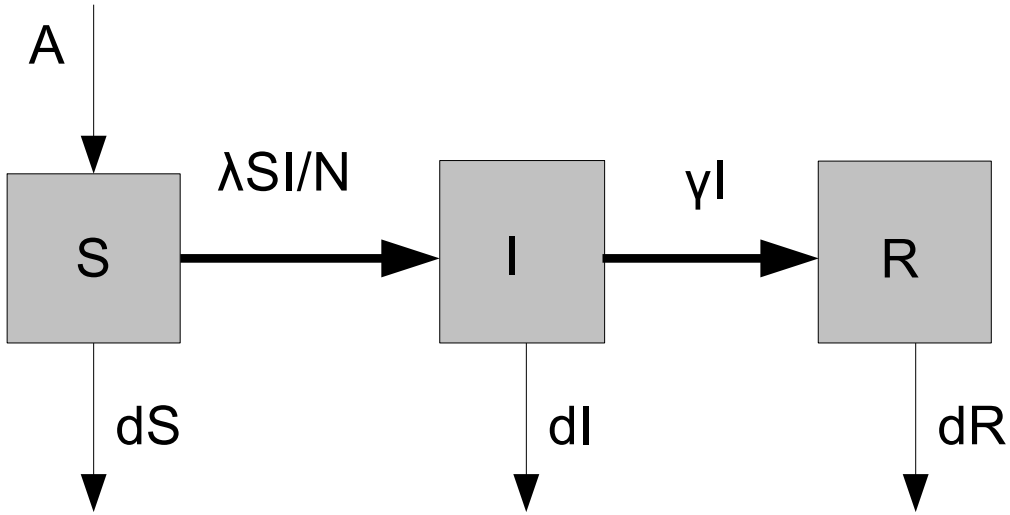
d denotes the natural death rate

γ denotes the rate of recovery (this assumes that the infectious period is exponentially distributed; $\int_0^\infty e^{-\gamma s} ds = 1/\gamma$)

λ denotes the number of contacts in unit time by an infectious person called the transmission parameter

Assume standard incidence, and all parameters are positive


A
λSI/N
γI
S
I
R
dS
dI
dR



$$\begin{aligned}
\frac{dS}{dt} &= A - dS - \frac{\lambda SI}{N} \\
\frac{dI}{dt} &= \frac{\lambda SI}{N} - (d+\gamma)I \\
\frac{dR}{dt} &= \gamma I - dR
\end{aligned}$$

Initial conditions are $S(0) > 0 \approx N$, $I(0) > 0$ small, $R(0) = 0$

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$$\frac{dS}{dt} = A - dS - \frac{\lambda SI}{N}, \quad \frac{dI}{dt} = \frac{\lambda SI}{N} - (d+\gamma)I$$

4. Analysis of Model:

The model is well posed, solutions remain nonnegative and are bounded

There is a disease free equilibrium (DFE):

$$S = \frac{A}{d}, \quad I = 0, \quad R = 0$$

Linearizing about the DFE gives

$$\frac{dI}{dt} = (\lambda - (d+\gamma))I = (d+\gamma)(\mathcal{R}_0 - 1)I$$

where $\mathcal{R}_0 = \frac{\lambda}{d+\gamma}$

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There is also an endemic equilibrium $I^* > 0$ with

$$I^* = \frac{dN}{d+\gamma}(1 - \frac{1}{\mathcal{R}_0})$$

provided the the bracket is positive, i.e. $\mathcal{R}_0 > 1$

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5. Interpret Solution:

$\mathcal{R}_0 = \frac{\lambda}{d+\gamma}$ is the *basic reproduction number*
and is the product of the contact rate λ
and the average death adjusted infectious time $1/(d+\gamma)$

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$\mathcal{R}_0 = \frac{\lambda}{d+\gamma}$ is the *basic reproduction number*
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If $\mathcal{R}_0 < 1$ then the DFE is (locally) stable, measles dies out

If $\mathcal{R}_0 > 1$ then there is an endemic equilibrium $I^*, R^* = \gamma I^*/d$
and $I \to I^*$ as $t \to \infty$ so measles is endemic in the population

$\mathcal{R}_0$ determines a sharp threshold with a forward bifurcation at $\mathcal{R}_0 = 1$

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6. Validate Model:

Sometimes measles and other viral diseases die out quickly but other times they give rise to an endemic situation

Data for $\mathcal{R}_0$ in countries where measles is endemic confirms that $\mathcal{R}_0 > 1$ but data is confounded by vaccination

7. Use Model Results:

If a fraction p of the population is vaccinated so that $(1-p)\mathcal{R}_0 < 1$ then measles will be eradicated

$$p > (1 - \frac{1}{\mathcal{R}_0})$$

is the fraction needed to give *herd immunity*

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For example:
if $\mathcal{R}_0 = 2$ then need to vaccinate 50%
if $\mathcal{R}_0 = 5$ then need to vaccinate 80%
if $\mathcal{R}_0 = 10$ then need to vaccinate 90%
Note: this assumes that the vaccine is perfect

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Thus $I = 0$ is the only equilibrium and $I(t) \to 0$ as $t \to \infty$
To see how the dynamics evolve consider

$$\frac{dI}{dS} = -1 + \frac{\gamma N}{\lambda S}$$

integrating gives

$$I + S - \frac{\gamma N}{\lambda} \log S = C$$

where C is a constant

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The parameter $\mathcal{R}_0 = \frac{\lambda}{\gamma}$ still acts as a threshold

If $\mathcal{R}_0 < 1$, then $I \to 0$ monotonically, influenza dies out
If $\mathcal{R}_0 > 1$, then I first increases to a peak, then $I \to 0$

Approximating: $I(0) = 0$, $I(\infty) = 0$ the *final size equation* can be written

$$\log \frac{S(0)}{S(\infty)} = \mathcal{R}_0 (1 - \frac{S(\infty)}{N})$$

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$$\log \frac{S(0)}{S(\infty)} = \mathcal{R}_0 (1 - \frac{S(\infty)}{N})$$

The total number of people infected is $I(0) + S(0) - S(\infty)$

The *attack ratio*, i.e. fraction of people infected is approx. $1 - \frac{S(\infty)}{N}$
If $\mathcal{R}_0 = 2$ then is $\approx 79\%$

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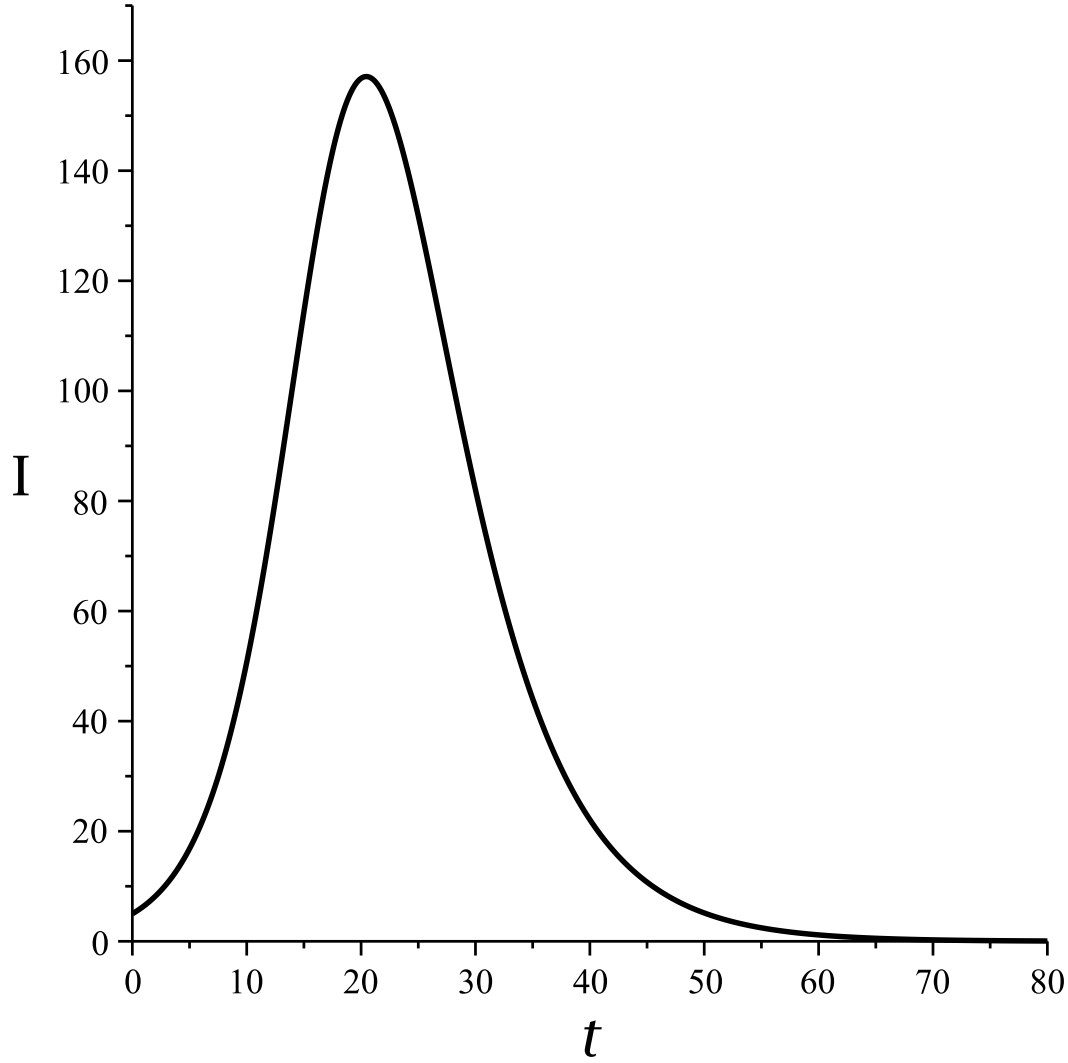

Simulation of the influenza *SIR* model showing the number of infectious people against time, with $\lambda = 0.5, \gamma = 0.25, N = 1,000, I(0) = 5$.

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BUT there are many strains of influenza, the virus mutates, some people are asymptomatic, some are latently infected, age structure is important...

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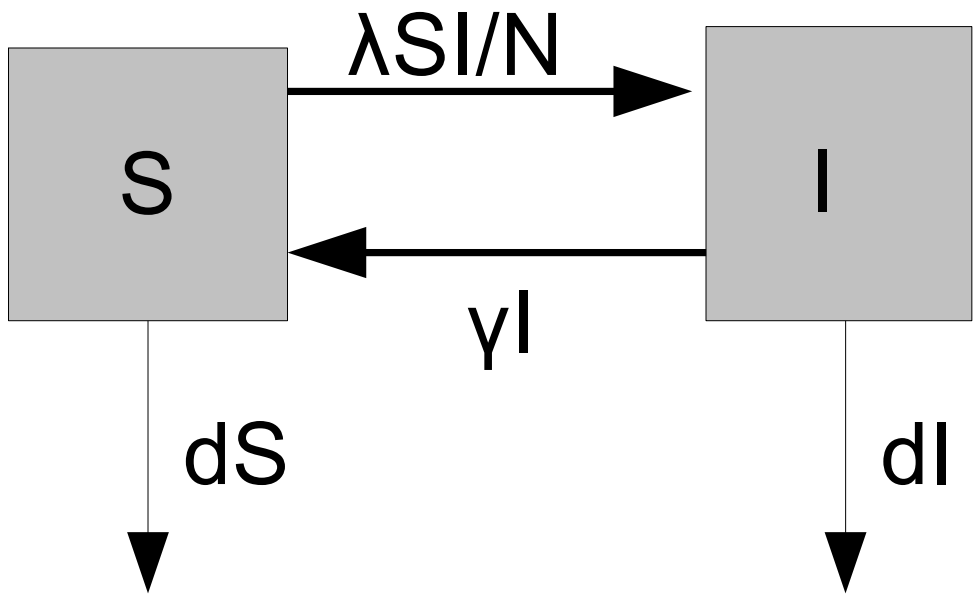
Susceptible-Infectious-Susceptible Model

Bacterial diseases (e.g. gonorrhea) do not usually give immunity on recovery so an SIS model is appropriate



$$\frac{dI}{dt} = \lambda I \frac{N-I}{N} - (d+\gamma)I$$

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with $S = N - I$ and initial condition $I(0) > 0$ small
Logistic equation!

Again $\mathcal{R}_0 = \frac{\lambda}{d+\gamma}$ acts as sharp threshold

If $\mathcal{R}_0 < 1$ then the disease dies out

If $\mathcal{R}_0 > 1$ then it goes to an endemic level $I^* = N(1 - \frac{1}{\mathcal{R}_0})$

This result remains true if $d = 0$: unlike the epidemic in the SIR model so input into the S class is important

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SIS with heterosexual transmission

Assuming that gonorrhea is transmitted heterosexually, how does the dynamics evolve?

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$\lambda_{MF}, \lambda_{FM}$ are transmission coefficients from M to F, F to M
$\frac{1}{\gamma_F}, \frac{1}{\gamma_M}$ are mean infectious periods for F, M
The number of infectious F and M evolve according to the equations:

$$\begin{aligned} \frac{dI_F}{dt} &= \lambda_{MF}\frac{N_F - I_F}{N_F} I_M - (d+\gamma_F) I_F \\ \frac{dI_M}{dt} &= \lambda_{FM}\frac{N_M - I_M}{N_M} I_F - (d+\gamma_M) I_M \end{aligned}$$

Suppose there is initially a small number of M or F infected with gonorrhea, will it die out or persist?

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$$\begin{aligned}\frac{dI_F}{dt} &= \lambda_{MF}\frac{N_F - I_F}{N_F}I_M - (d+\gamma_F)I_F \\ \frac{dI_M}{dt} &= \lambda_{FM}\frac{N_M - I_M}{N_M}I_F - (d+\gamma_M)I_M\end{aligned}$$

There is a DFE $I_F = I_M = 0$ and linear stability is determined by the eigenvalues of

$$J = \begin{bmatrix} -(d+\gamma_F) & \lambda_{MF} \\ \lambda_{FM} & -(d+\gamma_M) \end{bmatrix}$$

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Eigenvalues of J are given by the roots of the characteristic equation

$$z^2 + z(2d+\gamma_F+\gamma_M) + (d+\gamma_F)(d+\gamma_M) - \lambda_{MF}\lambda_{FM} = 0$$

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$$z^2 + z(2d + \gamma_F + \gamma_M) + (d + \gamma_F)(d + \gamma_M) - \lambda_{MF}\lambda_{FM} = 0$$

Both roots of this quadratic have negative real parts if and only if the constant term is positive. Can $\mathcal{R}_0$ be calculated?
With this condition small perturbations from the DFE decay and the DFE is linearly stable and can be proved to be globally stable

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There is also the possibility of an endemic (positive) equilibrium:

$$I_M^* = \frac{(\lambda_{MF}\lambda_{FM} - (d + \gamma_F)(d + \gamma_M))N_F N_M}{(d + \gamma_M)\lambda_{MF}N_M + \lambda_{MF}\lambda_{FM}N_F}$$

if the numerator is positive, with a corresponding formula for I_F^*

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Global stability of the endemic state (when it exists) can be proved but it may still be an open problem to prove this if disease deaths are incorporated into the model

Discrete time model

Data on outbreaks of diseases are often given at regular intervals:
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Consider a discrete-time, deterministic, compartmental, spatially homogeneous model with recruitment and disease transmission

SEIR discrete-time model

For childhood diseases, e.g. chickenpox (*varicella*),
at time $t \in \{0, 1, 2, \ldots\}$ each member of a population is

S_t : susceptible
E_t : exposed and mildly infectious
I_t : infectious or
R_t : recovered with life long immunity

Total population $N_t = S_t + E_t + I_t + R_t$

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Recruitment and total population

At each time $t \in \{0, 1, 2, \cdots\}$ the total population

$$N_{t+1} = g(N_t) + (1 - d) N_t$$

where d is the probability of death

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Recruitment	$g(N_t)$	$\lim_{\mathbf{t}\to\infty} N_t$, positive constant
Beverton-Holt	$r\frac{N_t}{1+bN_t}$	0 if $\mathcal{R}_d = \frac{r}{d} < 1$
Beverton-Holt	$r\frac{N_t}{1+bN_t}$	$\frac{(\mathcal{R}_d - 1)}{b}$ if $\mathcal{R}_d > 1$
Ricker	$rN_t e^{-bN_t}$	0 if $\mathcal{R}_d < 1$
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Ricker recruitment: if $\mathcal{R}_d > e^{\frac{2}{d}}$, then total population undergoes period-doubling bifurcations route to chaos

$r > 0$ is the intrinsic growth rate

$b > 0$ is the scaling parameter

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Disease transmission assumptions

Fraction ϑ of S_t interacting with I_t become exposed with probability $\widehat{\varphi}(\frac{I_t}{N_t}) = (1 - \varphi(\frac{I_t}{N_t}))$, remain susceptible with probability $\varphi(\frac{I_t}{N_t})$, where $\varphi : [0, \infty) \to [0, 1]$ is a nonlinear decreasing smooth concave up function with $\varphi(0) = 1$, i.e., $\varphi'(x) < 0$ and $\varphi''(x) > 0$ for all $x \geq 0$.

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Example: If infections are modeled as Poisson processes, then $\varphi\left(\frac{I_t}{N_t}\right) = \exp\left(-\beta \frac{I_t}{N_t}\right)$ with $\beta > 0$

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Similarly a fraction $(1 - \vartheta)$ of S_t interacting with E_t become exposed with probability $\widehat{\psi}\left(\varepsilon\frac{E_t}{N_t}\right) = \left(1 - \psi\left(\varepsilon\frac{E_t}{N_t}\right)\right)$ with similar assumptions on ψ and $0 < \varepsilon < 1$

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Disease progression assumptions

Per unit time and assuming no death due to disease:

probability E_t progress to I_{t+1} is $\kappa \in (0,1)$
probability I_t recover and progress to R_{t+1} is $\gamma \in (0,1)$
probability of natural death is $d \in (0,1)$ in all classes

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Events are assumed to happen in the following order:

- disease transmission and recovery
- survival (natural death)
- reproduction/recruitment

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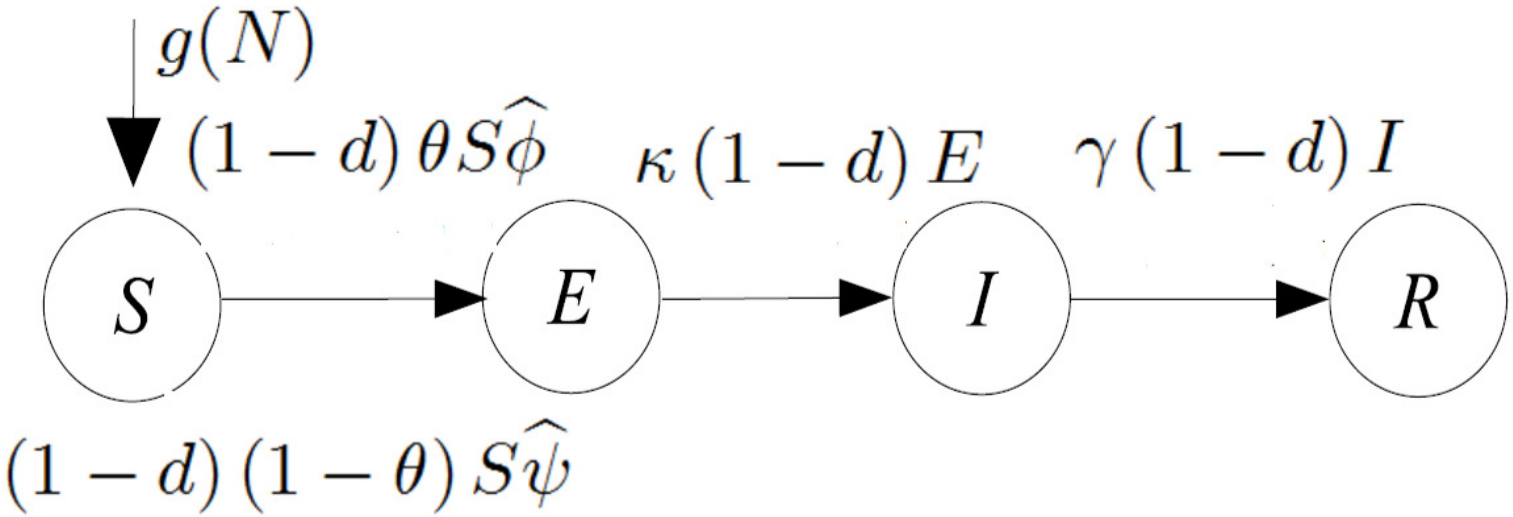
Flow diagram into classes for the *SEIR* model



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Model equations

Assume that the total population is asymptotically constant and $\lim_{t\to\infty} N_t \equiv S_\infty > 0$

For the limiting system, take proportions

$$s_t = \frac{S_t}{S_\infty},\ e_t = \frac{E_t}{S_\infty},\ i_t = \frac{I_t}{S_\infty},\ \text{and}\ r_t = \frac{R_t}{S_\infty}$$

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Since $s_t = 1 - e_t - i_t - r_t$, the model reduces to

$$\begin{aligned} e_{t+1} &= (1-d)\, s_t \left(\theta\widehat{\varphi}\left(i_t\right) + (1-\theta)\,\widehat{\psi}\left(\varepsilon e_t\right)\right) + (1-\kappa)\,(1-d)\, e_t \\ i_{t+1} &= \kappa\,(1-d)\, e_t + (1-\gamma)\,(1-d)\, i_t \\ r_{t+1} &= \gamma\,(1-d)\, i_t + (1-d)\, r_t \end{aligned}$$

with disease-free equilibrium (DFE) $(e, i, r) = (0, 0, 0)$

Does the disease die our or persist, can $\mathcal{R}_0$ be calculated?

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Some remaining questions

How to

- incorporate more realistic assumptions:
  For COVID-19 some individuals are asymptomatic (infected but never develop symptoms), some are presymptomatic (infected develop symptoms later)
- estimate parameters from data (e.g. transmission term)
- incorporate more realistic assumptions about the infectious period (ODEs assume that it is exponentially distributed)

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- estimate parameters from data (e.g. transmission term)
- incorporate more realistic assumptions about the infectious period (ODEs assume that it is exponentially distributed)
- identify $\mathcal{R}_0$ for ODE & discrete-time systems (LA)
- account for movement of humans, e.g. metapopulations (LA)

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- estimate parameters from data (e.g. transmission term)
- incorporate more realistic assumptions about the infectious period (ODEs assume that it is exponentially distributed)
- identify $\mathcal{R}_0$ for ODE & discrete-time systems (LA)
- account for movement of humans, e.g. metapopulations (LA)
- prove global stability of DFE or endemic equilibrium (algebraic and combinatorial methods to determine Lyapunov functions)
- incorporate control strategies (LA)

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Some remaining questions

How to

- incorporate more realistic assumptions:
  For COVID-19 some individuals are asymptomatic (infected but never develop symptoms), some are presymptomatic (infected develop symptoms later)
- estimate parameters from data (e.g. transmission term)
- incorporate more realistic assumptions about the infectious period (ODEs assume that it is exponentially distributed)
- identify $\mathcal{R}_0$ for ODE & discrete-time systems (LA)
- account for movement of humans, e.g. metapopulations (LA)
- prove global stability of DFE or endemic equilibrium (algebraic and combinatorial methods to determine Lyapunov functions)
- incorporate control strategies (LA)

Thank you!

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