Research with Mathematical Models

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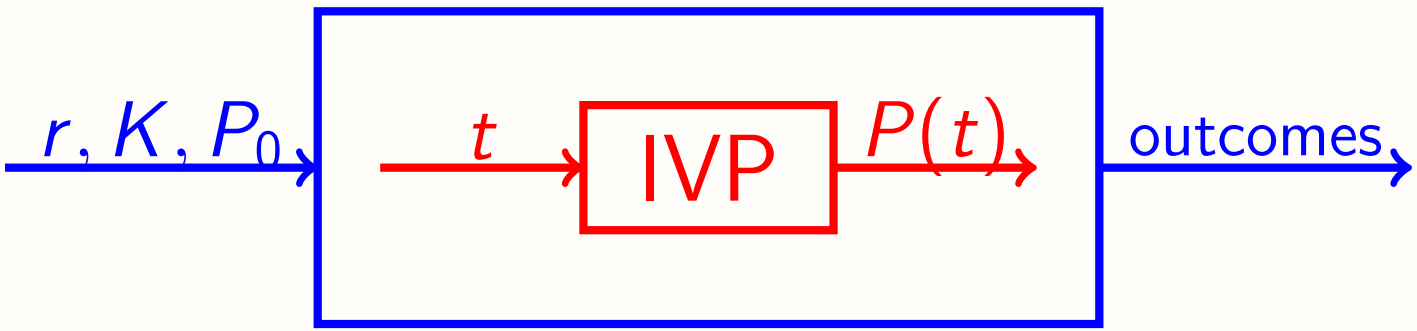
1.1 Models as Functions of Parameters

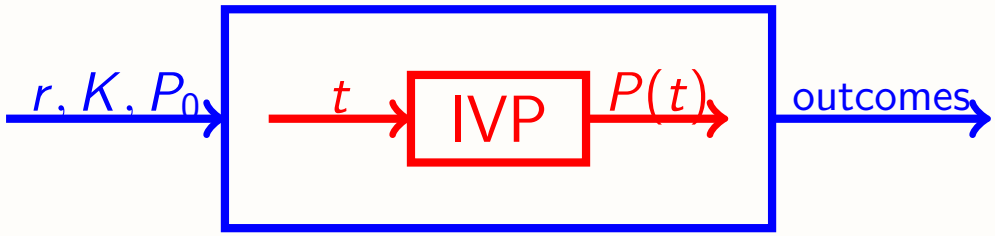
How do we view the model

$$\frac{dP}{dt} = rP\left(1 - \frac{P}{K}\right), \quad P(0) = P_0 > 0, \qquad r, K > 0?$$

- **Narrow** view:
  Initial value problem for $P(t)$, with parameters r, K, and P_0.
- **Broad** view:
  Function that maps parameters r, K, and P_0 to outcomes.



1.1 Models as Functions of Parameters



- **Narrow** view: Math problem with fixed parameters.
  - The narrow view is used to determine the outcomes.
    - Narrow view questions are trivial: "Given $K = 10$, $R = 1$, and $P_0 = 1$, when does the population reach $P = 5$?"
- **Broad** view: Outcomes as functions of parameters.
  - The important questions are in the broad view.
    - Do solutions with any initial condition always approach K?
    - At what point is the population growth the fastest?

1.2 Model Design: Choosing Outcomes

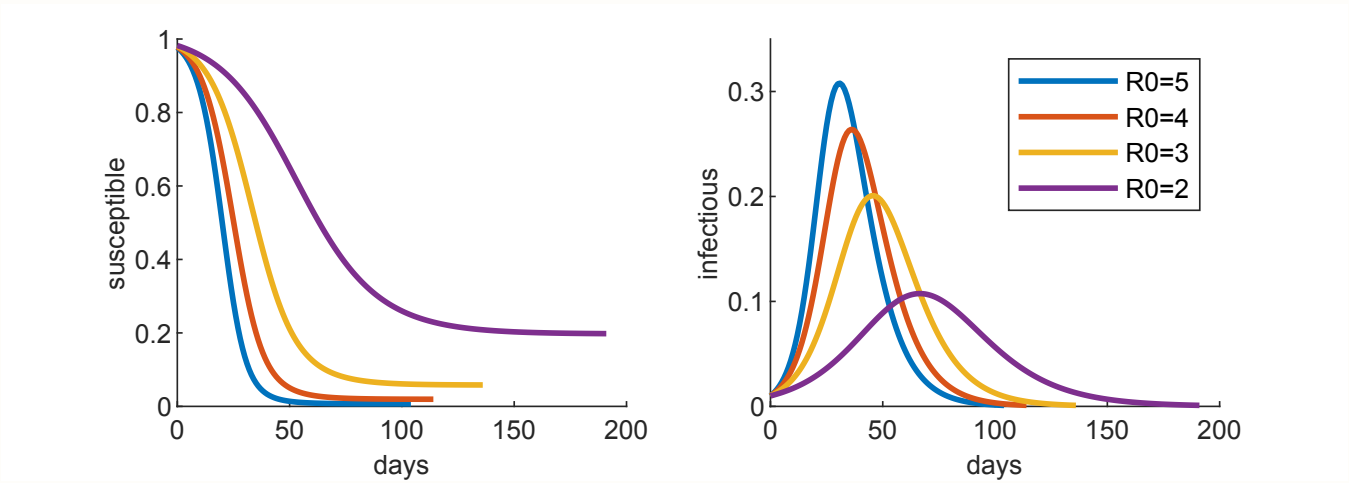
- Maximum number of new infections?
- Maximum number of hospitalizations per million? (compared to an average of 2800 hospital beds per million)
  - Serves as a measure of the stress on the health care system
- Percent deaths? (0.06% is 200,000 people)
  - Serves as a measure of the human cost
- Final fraction of susceptibles?
  - Serves as a measure of the risk of a new outbreak
- Times for any of these events?

1.2 Model Design: Asking and Addressing Questions

- Models must be designed to answer specific questions.
  - If we want to know the impact of COVID-19 on health care resources, we need to modify the SEIR model to track hospitalizations and/or ICU patients.
- Some common question types:
  - Is a specific claim supported by modeling or not?
  - What effect does parameter x have on outcome y?
- Strategies for addressing questions
  - Run simulations for several values of a parameter and compare simulation plots.
  - Calculate an outcome y for a large set of values of parameter x and plot y vs x.

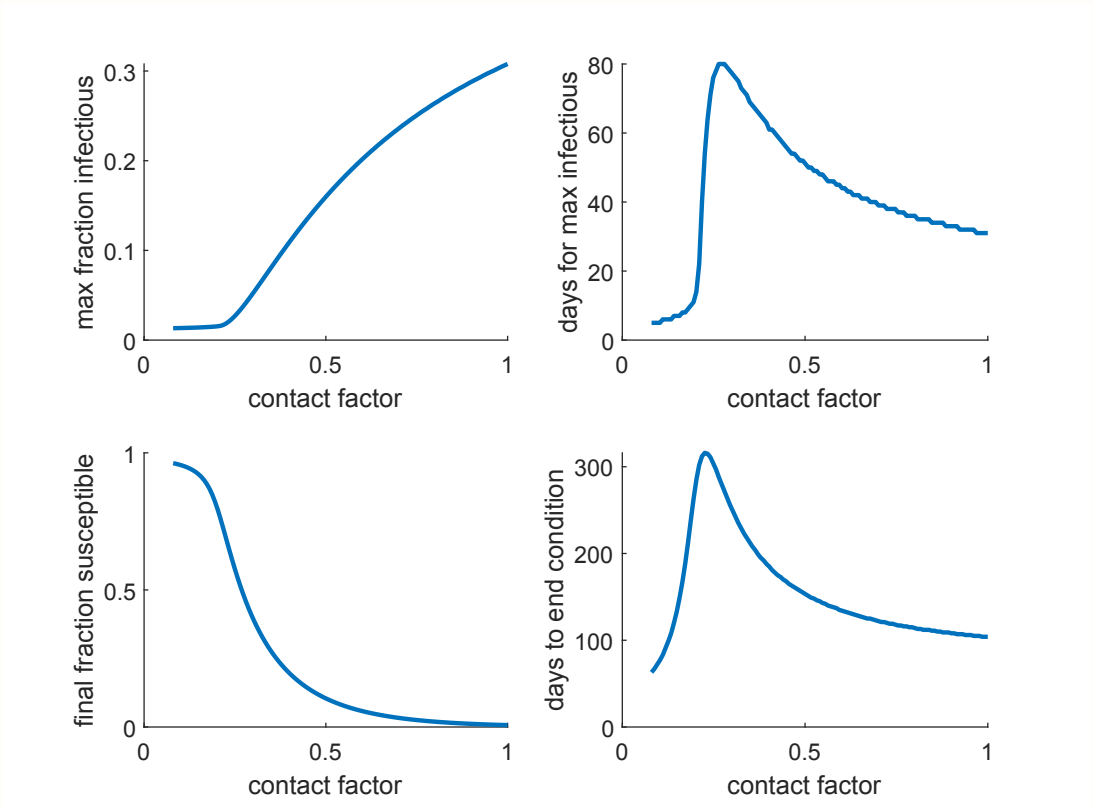
1.2 Simulations

- Simulations require known parameter values.
  - Plots show model behavior.
  - Results only guaranteed to apply to the specific parameter set.
  - Multiple simulations can *help* us understand the generality of the results and the effects of the parameters.



1.2 Parameter Studies

- Parameter studies systematically explore the impact of a parameter on one or more outcomes.
  - They show outcome vs parameter, not individual simulation results.



1.3 Reporting Results and Answering Questions

- Graphs must be informative and not misleading.
  - No negative values for populations or parameters.
  - Axes must be labeled.
  - Sometimes multiple curves on the same axes are more informative than multiple graphs.
  - Measured data should be plotted as points; simulation results should be plotted as dot-to-dot 'curves'.

- Answers to *math* questions are often numbers or formulas. **Modeling questions require verbal answers**, supplemented with visual aids.
  - 'The graph goes up and then comes down' is merely a *description*. An *explanation* connects to the real world scenario and **offers a reason** for the observed results.

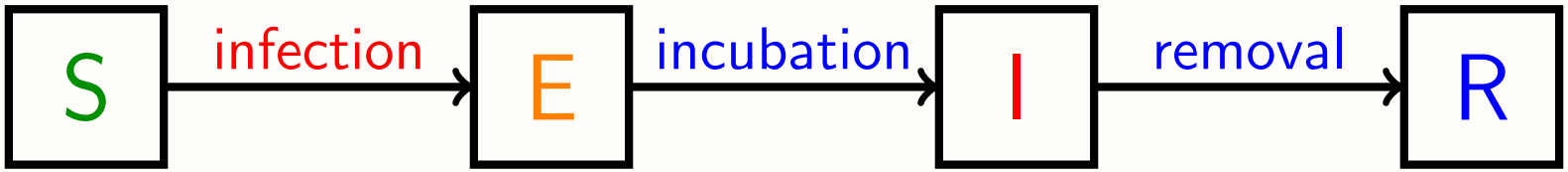
2.1. Class Structure

- Individuals in a population are divided into classes. These can vary from one model to another. Examples:
  - **S**: *Susceptible* – can be infected
  - **E**: *Exposed* – infected but not infectious
  - **I**: *Infectious* – can transmit the disease to susceptibles
  - **R**: *Removed* – no longer infectious
- Sometimes the names are misleading.
  - '*Exposed*' should be '*Latent*'
  - *Removed* includes people who are still sick and may include people who are deceased
- Models are designated by the class structure: SIR, SIS, SEIR, SEAIR, SEAIRHD etc

2. Processes

- Processes move individuals from one class to another.
  - Some models have processes that bring individuals into or out of the system.

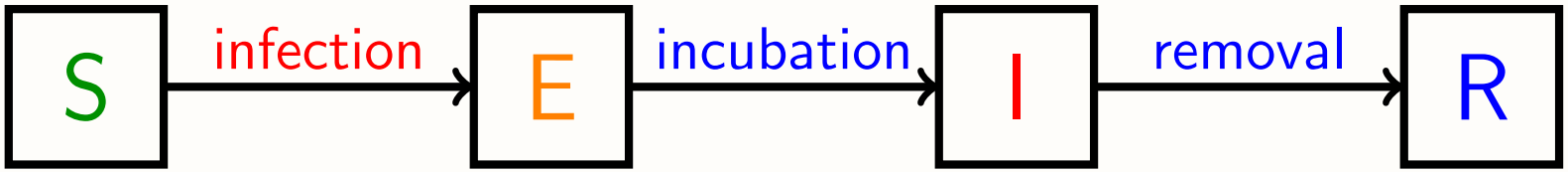
- Example: Basic SEIR model



- Rate of change of S is $-$ **infection**
- Rate of change of E is **infection** $-$ **incubation**
- Rate of change of I is **incubation** $-$ **removal**
- Rate of change of R is **removal**

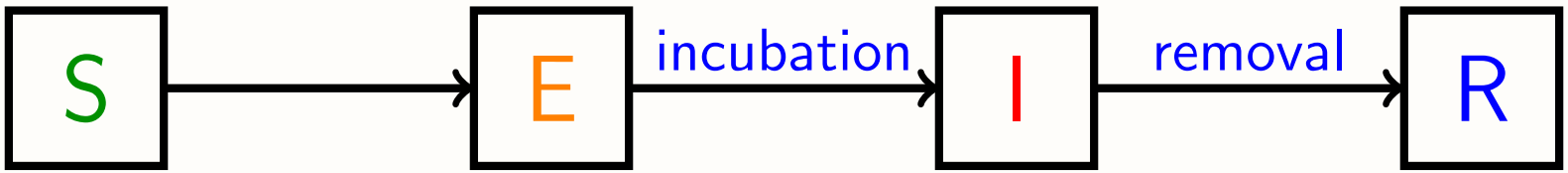
2. Processes – Two Types

- Processes are either **transmissions** or **transitions**.



  - **Transmissions** require interaction with another class.
    - Susceptibles are infected by Infectives.
  - **Transitions** happen without any interaction.
    - Incubation of Latent (E) individuals and removal of Infectious individuals happen spontaneously.

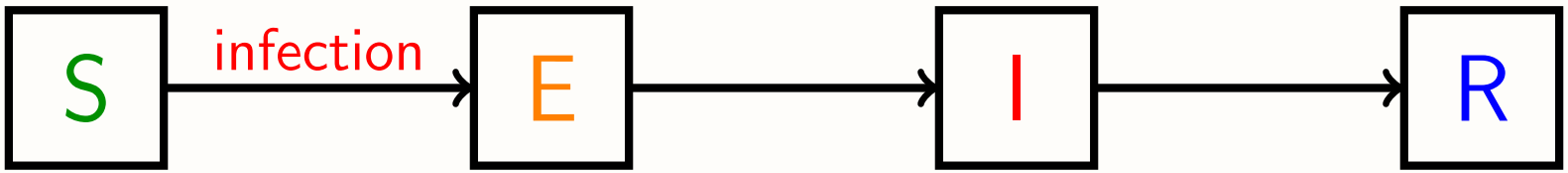
2.2 Processes – Transitions



- Transition rates are usually assumed to be proportional to the **leaving** class
  - incubation rate = constant $*$ $E = \eta E$
  - removal rate = constant $*$ $I = \gamma I$

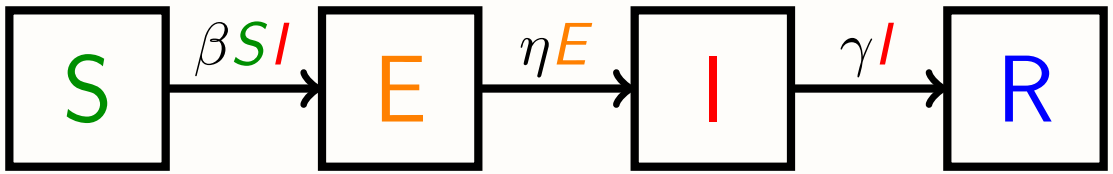
- **Rate constants are reciprocals of average time in class.**
  - Average removal time 10 days $\rightarrow \gamma = 0.1$

2.2 Processes – Transmissions



- Transmission rates are proportional to the **leaving** class size
  - infection rate $=$ force of infection $*$ $S = \lambda S$
- The force of infection is proportional to the **transmitting** class total(s) (just $I$for SEIR)
  - force of infection $=$ constant $*$ $I = \beta I$
- The infection rate is $\beta I * S = \beta S I$

2.2 Summary – SEIR epidemic model



$$S' = -\beta S I$$

$$E' = \beta S I - \eta E$$

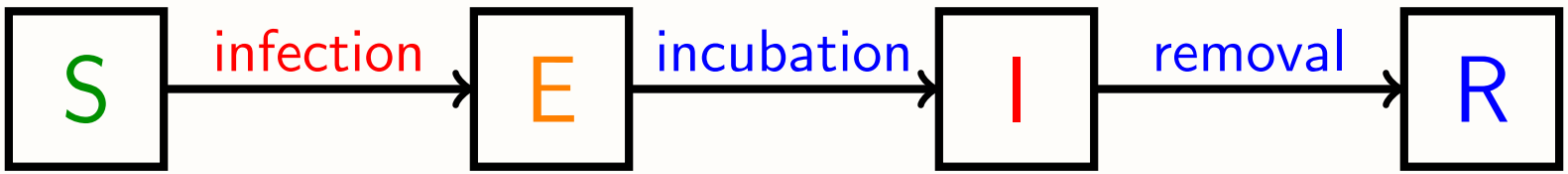
$$I' = \eta E - \gamma I$$

$$R' = \gamma I$$

- Let $N = S + E + I + R$. Then $N' = 0$, so N is constant.
  - The R equation is not needed because $R = N - S - E - I$.

2.3 Time Frames – Epidemic

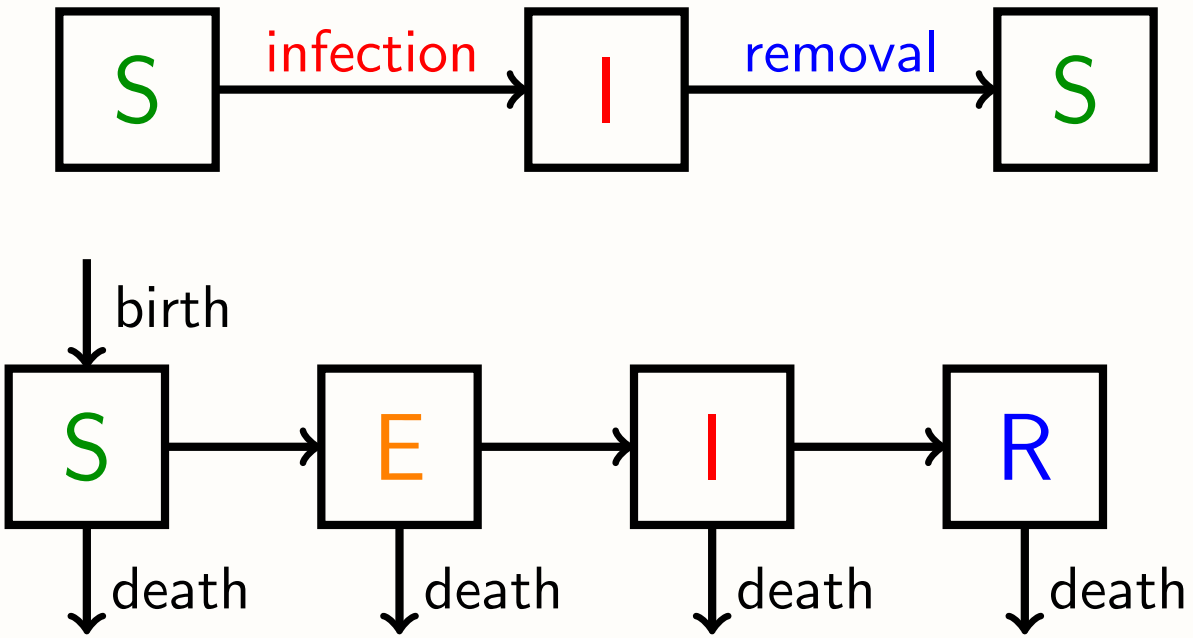
- **Epidemic** models have no means for replenishment of susceptibles.
  - These do not have births or natural deaths, so they are intended only for short time intervals (up to a few years).



- Including deceased individuals as 'Removed' makes the total population constant, which simplifies the model.

2.3 Time Frames – Endemic

- **Endemic** models have some means for replenishment of susceptibles.
  - The focus of analysis is on determining long term behavior.



2.4. Basic Reproduction Number

- **Basic reproduction number** $\mathcal{R}_0$:
  the average number of secondary infections caused by one primary infective in a fully susceptible population.
  - $\mathcal{R}_0 > 1$ is needed to start an epidemic.

- The total number is the average rate times the average time.

- Calculation of average transmission rate:
  - Recall that the **transmission rate** is βSI
  - Transmission rate **per infective**: βS
  - Rate per infective in a **fully-susceptible population**: βN

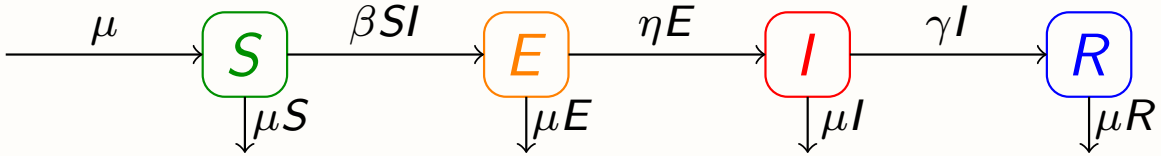
2.4. Basic Reproduction Number

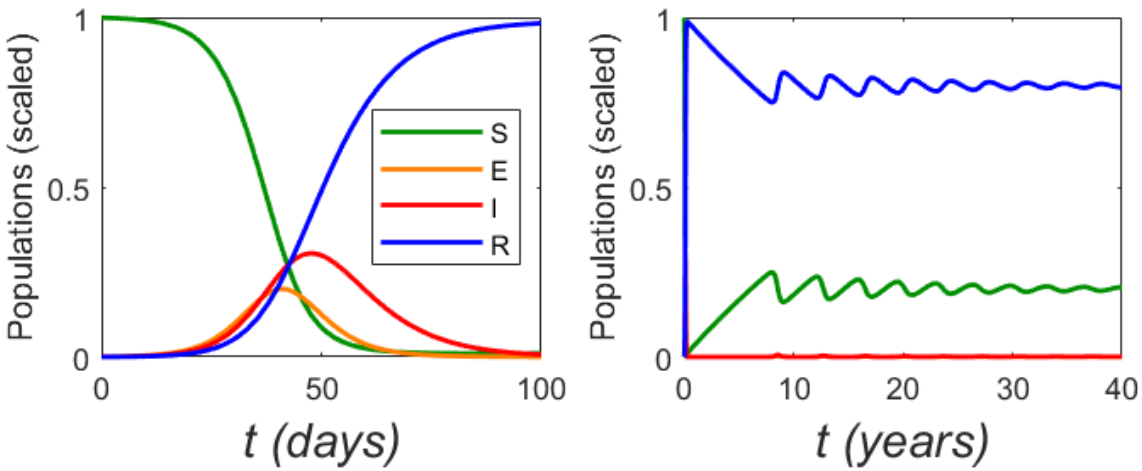
- **Basic reproduction number** $\mathcal{R}_0$:
  transmission rate per infective in a fully susceptible population multiplied by average time in the Infectious class.
- Average transmission rate: βN
- Calculation of average time:
  - Recall that the **removal rate** is γI.
  - The average time is $1/\gamma$.

$$\mathcal{R}_0 = \beta N \cdot \frac{1}{\gamma} = \frac{\beta N}{\gamma}.$$

- Other diseases (like COVID-19) can be more complicated.

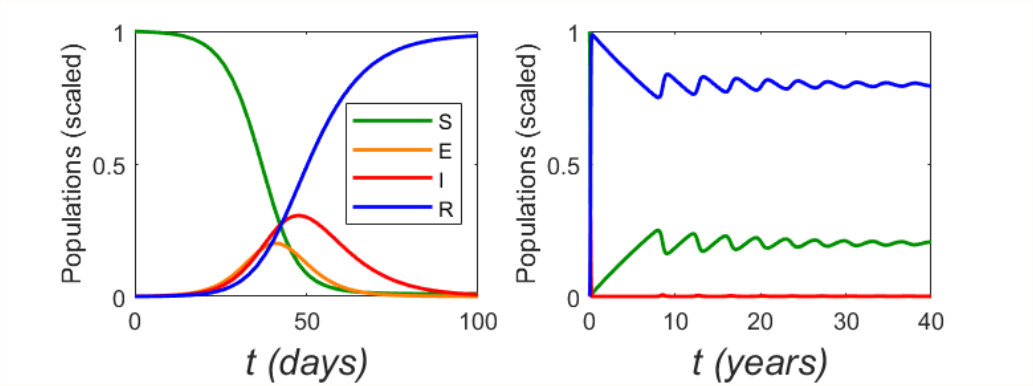
2.5 Typical Disease Model Behavior





- The plot on the left shows the initial epidemic.
  - With the chosen parameters, $E + I \approx 0.5$ at peak.
- After the epidemic, S slowly grows to about 0.25.
  - This triggers a new wave.
- Eventually, the disease becomes an endemic childhood disease.

2.5 Two Time Scales



- The fast time scale (days) shows the epidemic phase.
  - Demographic changes are negligible.
  - Plots on the fast time scale show no clue to endemic behavior.
  - Infectious population fractions are significant.
- The slow time scale (years) shows the long-term behavior.
  - Both demographics and disease processes are important.
  - On the slow scale, the epidemic behavior appears at $t = 0$.
  - Infectious populations are very small.

3.1 Autonomous Systems

- An **autonomous system** is a system of differential equations in which the derivatives are functions of the state of the system, and not the time:

$$S' = -\beta SI$$

$$I' = \beta SI - \gamma I$$

$$R' = \gamma I$$

- Seasonality makes a system **non-autonomous**:

$$S' = -\left(\beta + \delta \sin \frac{2\pi t}{365}\right) SI$$

$$I' = \left(\beta + \delta \sin \frac{2\pi t}{365}\right) SI - \gamma I$$

$$R' = \gamma I$$

3.1 Equilibria of Autonomous Systems

- An **equilibrium point** for an autonomous system is a point where the derivatives are all 0.

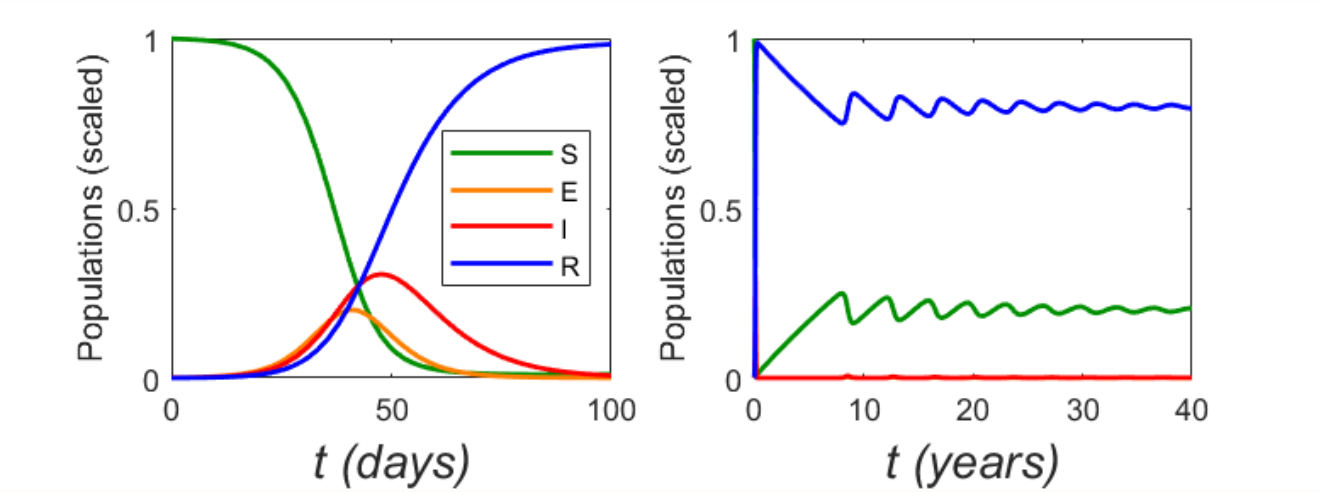
$$0 = S' = 1 - S - \mathcal{R}_0 SI$$

$$0 = I' = (\mathcal{R}_0 S - 1)I$$

  - There is a disease-free equilibrium (DFE) that has $I = 0$ and an endemic disease equilibrium (EDE) that has $I > 0$.
    - The DFE is $I^* = 0, \quad S^* = 1.$
    - The EDE is $S^* = \mathcal{R}_0^{-1}, \quad I^* = 1 - \mathcal{R}_0^{-1}.$
  - The DFE always exists; the EDE requires $\mathcal{R}_0 > 1$.

3.1 Stability of Equilibria

- Each equilibrium point in the state space corresponds to an equilibrium solution of the system.
- Equilibria can be (asymptotically) stable or unstable, depending on regions in the parameter space.
  - Over time, most systems tend toward a stable equilibrium.
  - The EDE for the endemic SEIR model is stable whenever it exists ($\mathcal{R}_0 > 1$).



3.2 The Jacobian Matrix

- Near each equilibrium, the system is represented by a different matrix, called the Jacobian.
- The Jacobian is the matrix of partial derivatives of the DE functions.

$$X' = \Gamma(bSY - \rho X)$$

$$Y' = \Gamma(\rho X - Y)$$

$$S' = 1 - S - bSY$$

$$J(X, Y, S) = \begin{pmatrix} -\rho\Gamma & bS\Gamma & bY\Gamma \\ \rho\Gamma & -\Gamma & 0 \\ 0 & -bS & -(1 + bY) \end{pmatrix}$$

3.2 The Jacobian Matrix

$$J = \begin{pmatrix} -\rho\Gamma & bS\Gamma & bY\Gamma \\ \rho\Gamma & -\Gamma & 0 \\ 0 & -bS & -(1+bY) \end{pmatrix}$$

$$J_{DFE} = \begin{pmatrix} -\rho\Gamma & b\Gamma & 0 \\ \rho\Gamma & -\Gamma & 0 \\ 0 & -b & -1 \end{pmatrix}$$

$$J_{EDE} = \begin{pmatrix} -\rho\Gamma & \Gamma & bY\Gamma \\ \rho\Gamma & -\Gamma & 0 \\ 0 & -1 & -(1+bY) \end{pmatrix}$$

where $Y = 1 - \mathcal{R}_0^{-1}$

- Tip 1: Better to have extra symbols than messier formulas.

3.2 Stability Example

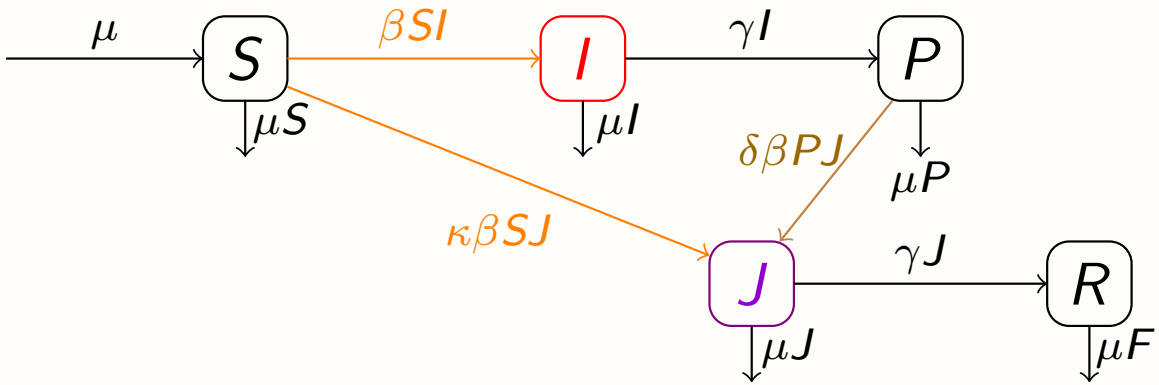
$$J_{DFE} = \left(\begin{array}{cc|c} -\rho\Gamma & b\Gamma & 0 \\ \rho\Gamma & -\Gamma & 0 \\ \hline 0 & -b & -1 \end{array}\right)$$

- Stability requires all eigenvalues to have negative real part.
- The block structure decouples the eigenvalue problem.
  - One eigenvalue is $-1 < 0$.
  - The other submatrix has trace $-(\rho+1)\Gamma < 0$ and $\det J = \rho\Gamma^2(1-b)$. Stability (for 2×2 matrices) requires negative trace and positive determinant.
    - The DFE is stable if and only if $b < 1$.

4.1 A Research Problem Inspired by COVID-19

- Biological question: Why did the omicron COVID-19 variant displace the delta variant so quickly?
  1. It could be more contagious.
  2. It could have advantages that offset being less contagious.
- Research Question: What features would a less contagious disease need to outcompete a more contagious one?
- Research Plan: Add a second variant to the **simplest** endemic disease model.
  - Make the new variant less contagious to (S)usceptibles.
  - But give it some compensatory advantage.
    - Inspiration from COVID-19: Maybe immunity to the original variant doesn't protect against the new variant.

4.1 Variant Competition Model



- Population is constant with equal birth and death rates (μ).
- Both variants have the same mean recovery time ($1/\gamma$).
- The invader (J) is less contagious to Susceptibles ($\kappa < 1$).
- Recovery from I confers at most partial immunity against J.
  - $\delta \leq \kappa < 1$.

4.1 Variant Competition Model Equations (T is time)

$$\begin{aligned}
\frac{dI}{dT} &= -(\gamma+\mu)I + \beta SI \\
\frac{dJ}{dT} &= -(\gamma+\mu)J + \kappa\beta SJ + \delta\beta PJ \\
\frac{dS}{dT} &= \mu(1-S) - \beta SI - \kappa\beta SJ \\
\frac{dP}{dT} &= \gamma I - \mu P - \delta\beta PJ \\
1 &= S + I + J + P + R
\end{aligned} \tag{1}$$

- Parameters and Scaling:

$$\epsilon = \frac{\mu}{\gamma+\mu} \ll 1, \quad b = \frac{\beta}{\gamma+\mu} > 1, \qquad t = \mu T \Rightarrow \frac{d}{dT} = \mu\frac{d}{dt}.$$

  - ϵ is the ratio of disease duration $1/(\gamma+\mu)$ to lifespan $1/\mu$.
  - b is the basic reproduction number for the resident (I).
  - $t = \mu T$ selects the slow time scale.

4.1 Scaling Example: The S Equation

$$\frac{dS}{dT} = \mu(1 - S) - \beta SI - \kappa\beta SJ$$

$$\epsilon = \frac{\mu}{\gamma+\mu} \ll 1, \quad b = \frac{\beta}{\gamma+\mu} > 1, \qquad t = \mu T \Rightarrow \frac{d}{dT} = \mu\frac{d}{dt}.$$

- Substitute $\mu\frac{d}{dt}$ for $\frac{d}{dT}$:

$$\mu\frac{dS}{dt} = \mu(1 - S) - \beta SI - \kappa\beta SJ$$

- Divide by μ $\left(\text{note } \frac{\beta}{\mu} = \frac{b}{\epsilon}\right)$:

$$\frac{dS}{dt} = (1 - S) - \epsilon^{-1} bS(I + \kappa J)$$

4.1 Rescaling Infectious Populations

$$\frac{dS}{dt} = (1 - S) - \epsilon^{-1} bS(I + \kappa J)$$

- This scaling is fine for simulations.
- For analysis, long-term behavior with $\epsilon \to 0$ and other parameters/variables $O(1)$ should make sense.
  - Here, $\epsilon \to 0$ reduces the S equilibrium equation to
    $$bS(I + \kappa J) = O(\epsilon) \quad \Rightarrow \quad I, J = O(\epsilon).$$
  - I and J should be rescaled with $I = \epsilon Y$ and $J = \epsilon Z$.
    $$\frac{dS}{dt} = (1 - S) - bS(Y + \kappa Z)$$
    - This correctly implies that all terms are equally important.

4.1 Final (Rescaled and Approximate) Model

$$\begin{aligned} Y' &= \Gamma Y(-1 + bS) \\ Z' &= \Gamma Z(-1 + bQ) \\ S' &= 1 - S(1 + bX) \\ P' &= Y - P - \delta bPZ \end{aligned} \tag{2}$$

where

$$X = Y + \kappa Z, \quad Q = \kappa S + \delta P, \quad \Gamma = \epsilon^{-1}. \tag{3}$$

- Y is the resident and Z is the invader.
- Tip 2: Better to have extra symbols than messier formulas!

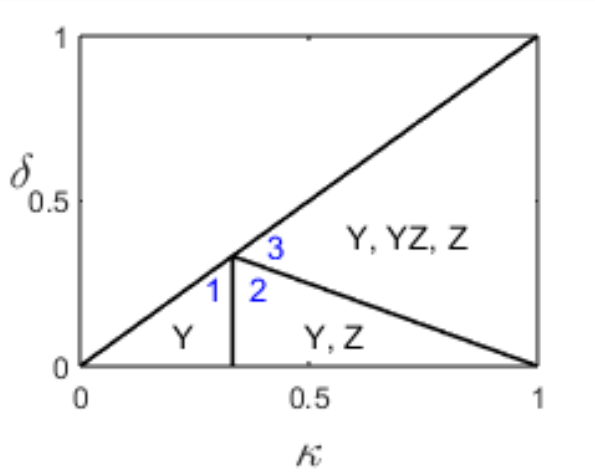
4.2 Mathematical Agenda

- Our research began with a biological question. This led to a model. For the analysis, we need a mathematical agenda.
- We have three principal parameters, b, κ, δ.
  - Larger b makes both variants more contagious in general.
  - Larger κ decreases the advantage of I for infecting S.
  - Larger δ decreases the value of immunity from I against J.
- Mathematical question: How do the values of κ and δ affect the competition between variants?
- Strategy: Pick a value of b. Determine the regions in the $\kappa\delta$ plane that produce different outcomes.
  1. Identify possible end states in different regions of the $\kappa\delta$ plane.
  2. Determine which are stable in each region.

4.2 Endemic Equilibria (all require $b > 1$)

- There are three possible endemic equilibria
  1. A resident-only equilibrium (EDE-Y)
  2. An invader-only equilibrium (EDE-Z)
  3. A coexistence equilibrium (EDE-YZ)

- The plot shows existence regions for $b = 3$.
  - The letters indicate which equilibria exist in each region.

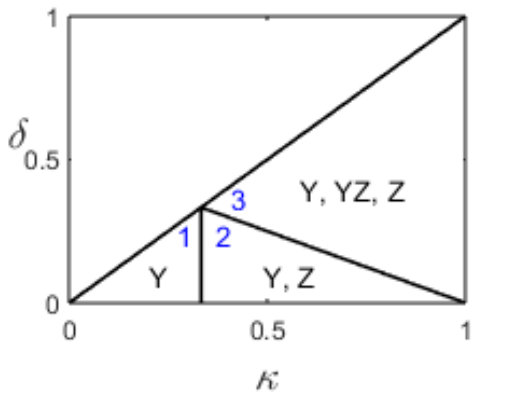


4.2 Details for EDE-YZ

- Define $w = bW$ for $W \in \{Y, Z, S, P\}$.
- The equations decouple to give $s, p > 0$ and

$$\delta z = \delta(b-1) - (1-\kappa), \qquad y = (b-1) - \kappa z.$$

- $z < 0$ in regions 1 and 2. $y > 0$ in all regions $\Rightarrow$
  - EDE-YZ exists in region 3.



4.2 The Jacobian

The Jacobian for the YZSP system is

$$J = \begin{pmatrix} -(1-s)\Gamma & 0 & y\Gamma & 0 \\ 0 & -(1-q)\Gamma & \kappa z\Gamma & \delta z\Gamma \\ -s & -\kappa s & -\bar{x} & 0 \\ 1 & -\delta p & 0 & -\Sigma \end{pmatrix}, \qquad (4)$$

where

$$x = y + \kappa z, \quad q = \kappa s + \delta p, \quad \Sigma = 1 + \delta z, \quad \bar{w} = w + 1 \ (\forall w).$$

- Tip 3: Better to have extra symbols than messier formulas!!

4.2 Stability for the DFE

- The Jacobian for the disease-free equilibrium simplifies to

$$J_{DFE} = \begin{pmatrix} -(1-b)\Gamma & 0 & 0 & 0 \\ 0 & -(1-\kappa b)\Gamma & 0 & 0 \\ -b & -\kappa b & -1 & 0 \\ 1 & 0 & 0 & -1 \end{pmatrix}$$

- The matrix is lower triangular $\Rightarrow$ the eigenvalues are

$$(b-1)\Gamma, \quad (\kappa b - 1)\Gamma, \quad -1, \quad -1.$$

- The DFE is stable when $b < 1$ (recall $\kappa < 1$).
  - The basic reproduction numbers are b for Y and $\kappa b < b$ for Z.

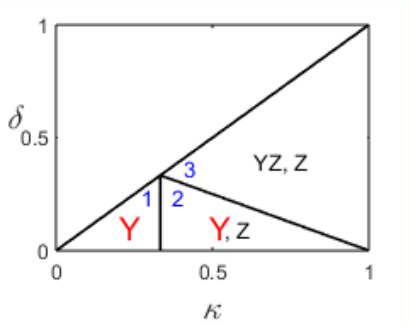
4.2 Stability for EDE-Y

J_Y is similar to the block matrix

$$\left(\begin{array}{c|cc|c} -(1-q)\Gamma & 0 & 0 & 0 \\ \hline 0 & 0 & y\Gamma & 0 \\ -\kappa & -1 & -b & 0 \\ \hline -\delta p & 1 & 0 & -1 \end{array}\right)$$

$$p = b - 1 > 0$$
$$q = \kappa + \delta p$$

- Two of the eigenvalues are $(q-1)\Gamma$ and -1.
  - Stability requires $q < 1$, which rules out region 3.
- More work shows Y is stable in regions 1 and 2.

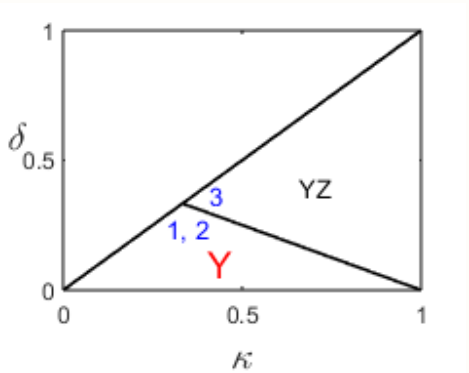


4.2 Stability for EDE-Z – eigenvalue λ_1

- J_Z can be written in block form:

$$J_Z = \left(\begin{array}{c|c} -(1-s)\Gamma & 0 \\ \hline \cdots & J_{234} \end{array}\right), \quad J_{234} = \begin{pmatrix} 0 & \kappa z\Gamma & \delta z\Gamma \\ -\kappa s & -\bar{x} & 0 \\ -\delta p & 0 & -\Sigma \end{pmatrix}$$

- $\lambda_1 = (s-1)\Gamma = \cdots > 0 \quad \Rightarrow \quad$ EDE-Z is never stable.



  - The resident always persists for this model ($b > 1$). ☹
  - But maybe the variant can also. 😐

4.2 Stability for EDE-YZ

The Jacobian for EDE-YZ is

$$J_{YZ} = \begin{pmatrix} 0 & 0 & y\Gamma & 0 \\ 0 & 0 & \kappa z\Gamma & \delta z\Gamma \\ -1 & -\kappa & -b & 0 \\ 1 & -\delta p & 0 & -\Sigma \end{pmatrix}$$

- There is no decoupling. ☹

1. How do we manage a 4×4 characteristic polynomial?
   - The char. poly. theorem! ☺ With asymptotics! ☺ ☺
2. How do we find Routh-Hurwitz stability conditions for a 4×4 characteristic polynomial?
   - The Routh array! ☺ With asymptotics! ☺ ☺

4.2 Stability Results for EDE-YZ

- A LOT of algebra eventually yields a single stability requirement for EDE-YZ:

$$b\Sigma\zeta^2 > \delta\xi(b+\Sigma)^2,$$

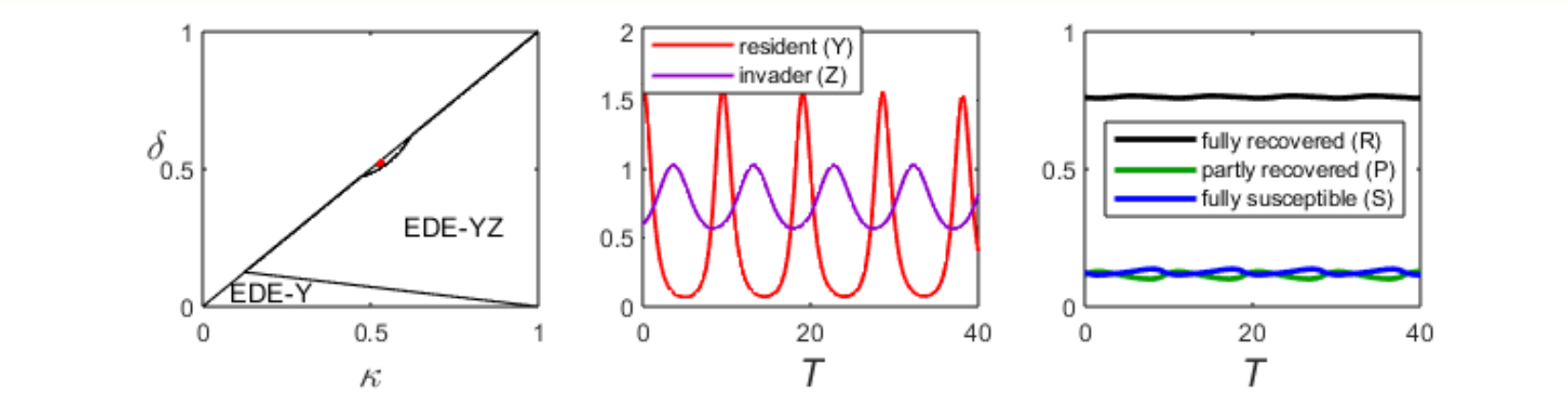
where

$$\Sigma = \delta x + \kappa, \quad \zeta = \delta x - (\kappa+\delta)\pi, \quad \xi = \kappa\pi(1+\pi),$$
$$\delta p = 1-\kappa, \quad x = b-1, \quad \delta z = \delta x - \delta p, \quad \pi = (\delta p)(\delta z).$$

  - Given a value of b, we can plot the stability region in the $\kappa\delta$ plane.

- Tip 4: Better to have extra symbols than messier formulas!!!

4.2 The End of the Story



- Hacker's Challenge: Without the plot on the left, try to find a limit cycle like the one here.
  - With $b = 8$ (shown here), the probability is 0.007. With $b = 3$, it is only 0.003.

4.3 Conclusions

1. We did not achieve the goal of finding a scenario in which a less infectious variant could replace a more infectious one. 
2. We did find some surprising results. 
3. For our next try, we need to give the variant an additional advantage.
   - Loss of immunity for the fully recovered does the job. 
4. **It is much better to have extra symbols than messier formulas.**