Infectious Disease Modeling

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What does it mean to model

and why it is important...

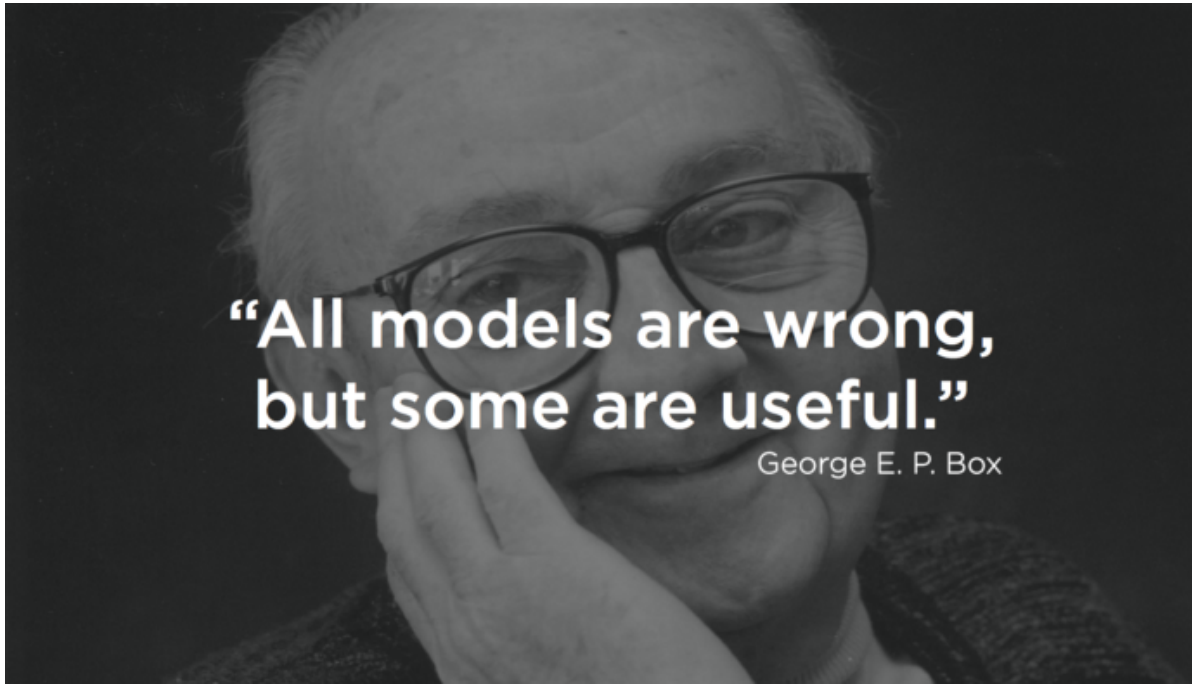
Models are "useful" simplification of reality

Why useful?

- understand phenomena
- decompose their components
- make predictions

Quantitative models (mathematical/statistical) have the advantage to allow **numerical predictions** that can be verified and fitted with **real data**.

> **Models are as good as the prediction they make**



Two approaches

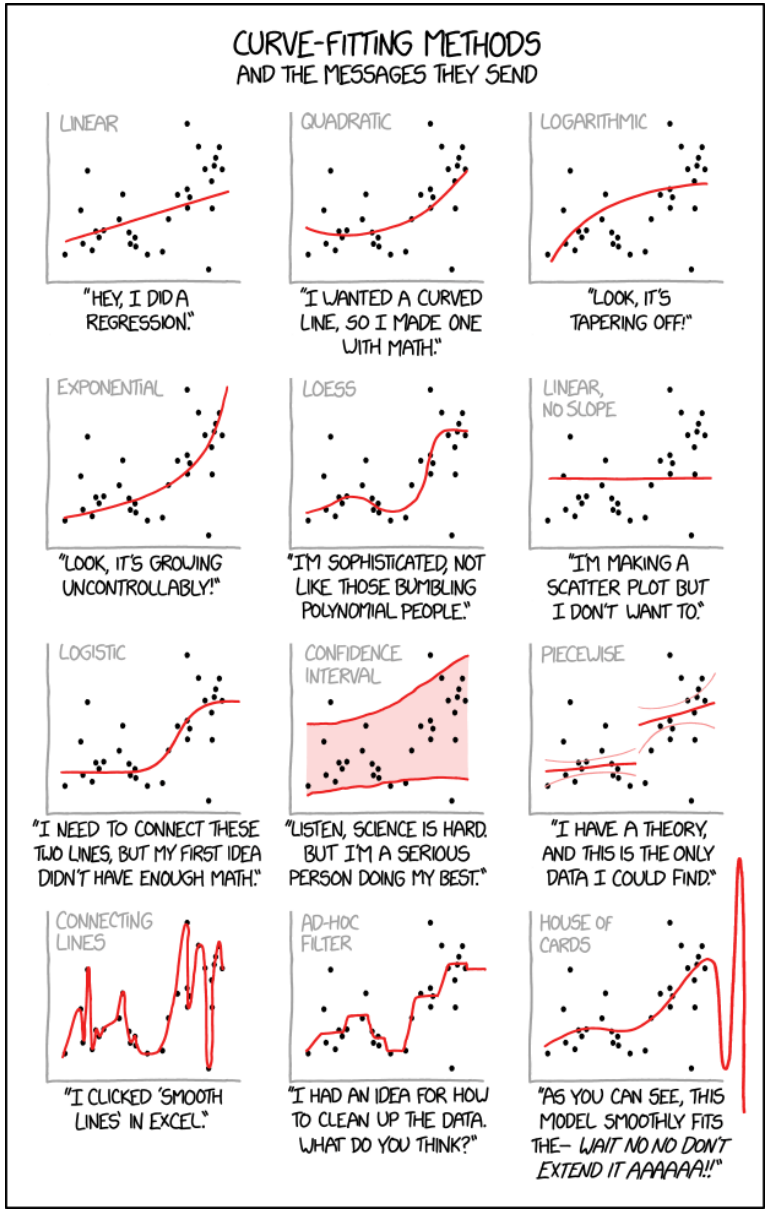
Top-down

Start from the data and build a model that fit them well.

Easier to build, rely more on statistical/data science skill than domain knowledge.

May not generalize well outside observed data and may have not a natural interpretation.

Examples: hypothesis testing, regression modeling, machine learning.



Two approaches

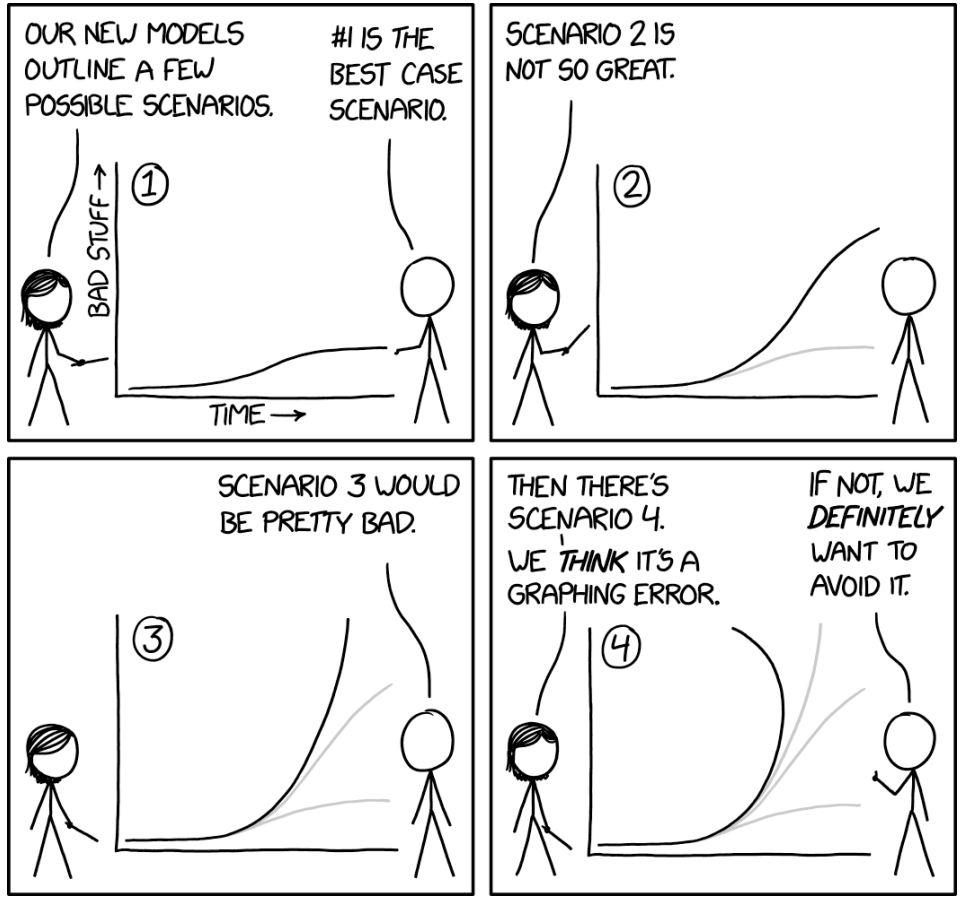
bottom-up

Build a model according to a theory and check it against the data. Data can also be used to fit the model parameters.

Harder to build in a meaningful way, require both mathematical skill and domain knowledge.

If well built can generalize well and the paramters usually have a natural interpretation. But nature is hardly so simple and well behaved (we will talk about this)

Examples: weather forecast, physics models, infectious disease modeling.



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Modeling infectious diseases

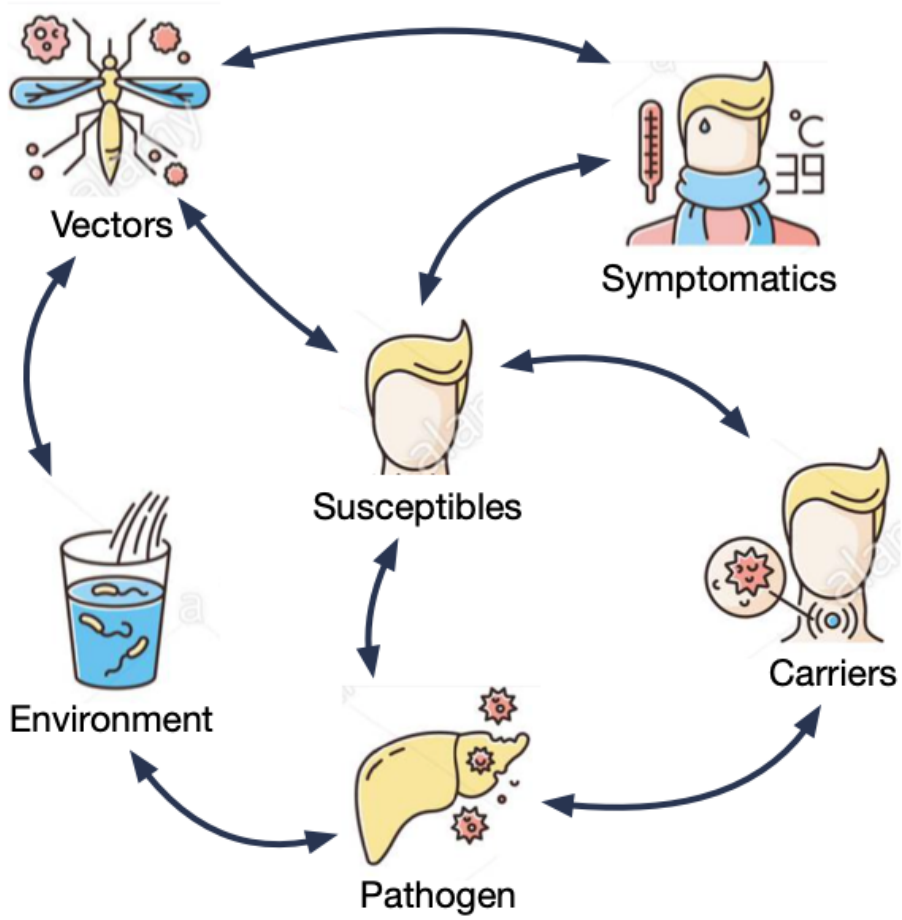
Why infectious diseases?

Growing public health problem.

Complex behavior in time, hard to model and predict with top-down approaches.

Mostly mono-factorial etiology (the pathogen) and a limited number of actors. This makes easier to develop solution, if the models are appropriate.

A lot of hidden complexity.



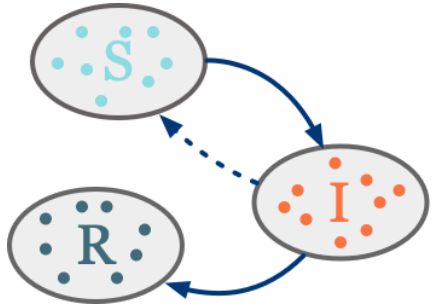
Common models

Agent-based model

Each agent is modeled individually, and interact between themselves and the environment following specific rules. The interactions can change their disease status. Very flexible, easier to model but computationally intensive (good for small scale simulations). Analytical solutions usually not available.

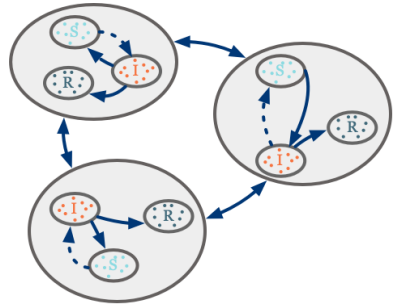
Network model

Also in these models individual agents and their properties are modeled, but there's no environment and the focus is on the connections (fixed or dynamic) that allows infection events.
Less flexible, allow more mathematical abstraction; analytical solutions for simple models but usually simulation analysis are needed.



Compartimental model

The population is grouped into homogeneous "compartments" and the average dynamics with which these compartments exchange individuals are modeled.
Much less flexible, higher mathematical abstraction needed to compensate flexibility; many more assumptions (can be relaxed); computationally less demanding.

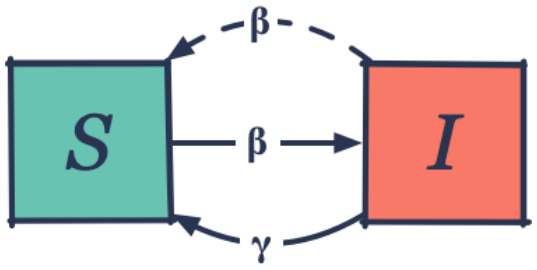


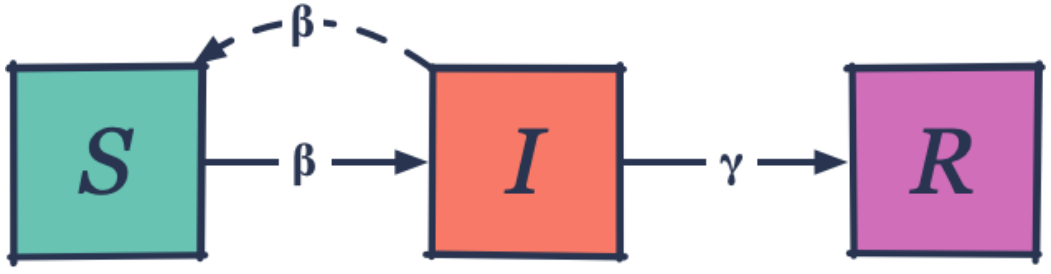
Metapopulation model

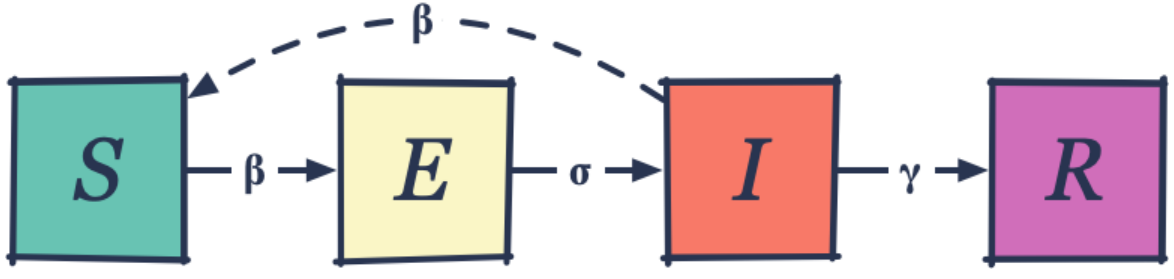
A mixed model. Population is grouped into clusters (e.g., cities, countries) in which different epidemic dynamics can be modeled. The cluster exchange individuals (e.g. travels)
Can be modeled as a mix of abstraction and simulations.

Compartimental Models

Many alternative fomulations







Susceptible-Infectious models

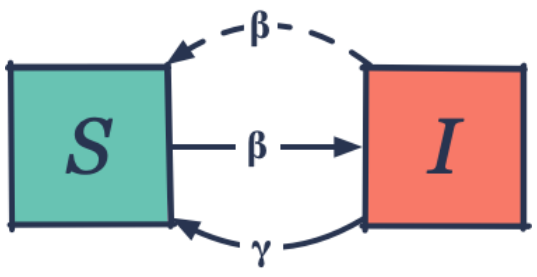
> First proposed by Kermack & McKendrick (1927), they are the foundation for modeling infectious diseases.

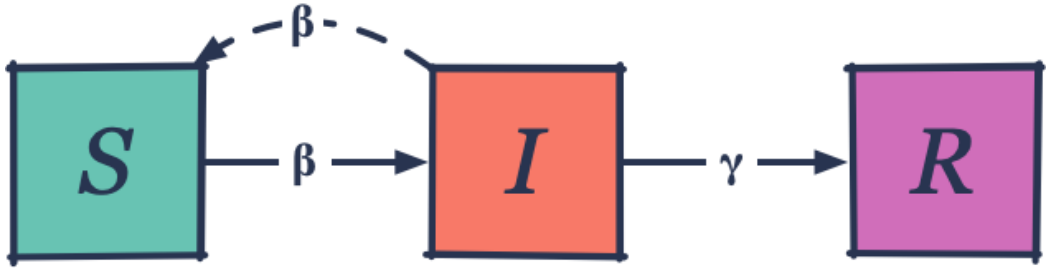
Describes an epidemic in term of the disease status (compartments) of fraction of the population, for example Susceptible (S), Infectious (I), Recovered (R).

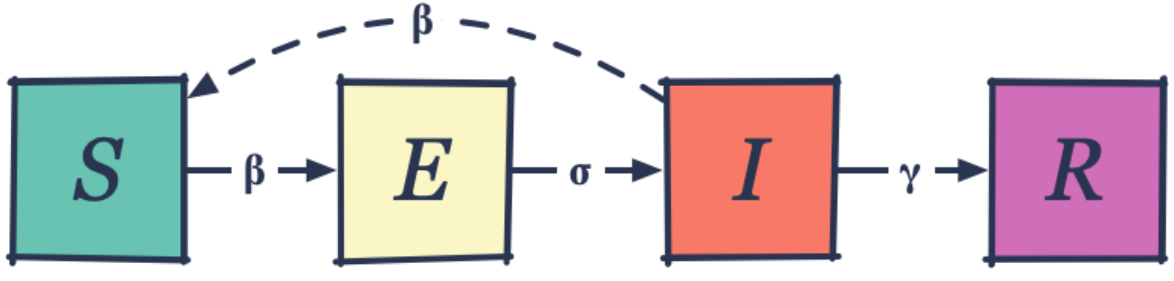
The individuals passes from between compartments according to specific rates.

Based on the assumption of:

- **Homogeneous Mixing**: Everyone is potentially in contact with everyone else in the population with a given rate.
- **Mass Action**: The population size is not relevant, only the proportional partition in compartments -> works well only for large populations.







Susceptible-Infectious models

Mathematically are solved through **ordinary differential equations**.

There several modeling choices.

According to time definition:

- **Continouos-time models**: time is considered as a continouos flow.
- **Discrete-time models**: time is considered as a sequence of events of a given duration.

According to the transmission mechanics:

- **Deterministic**: no random effects, paramters are fixed and equal for everyone in the population. Given the same starting conditions, the epidemic trajectory is fixed.
- **Stochastic**: there is random variation at the individual level and/or at parameter level. Infectious event are discrete and random

General SIR model

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

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

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

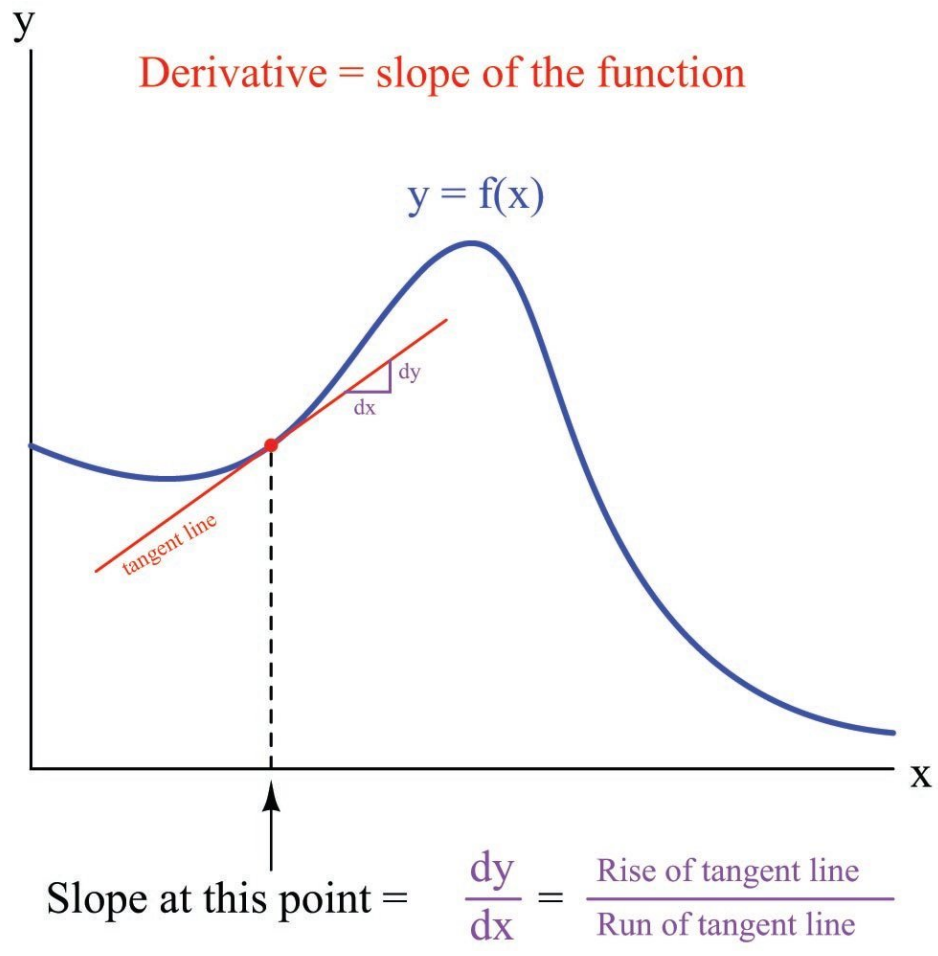
The SIR models is a system of differential equations that defines the change in time (dt) of the population in the compartments S, I, R according to rates β, γ.

The progression from S to I depends on: prevalence of infected, the underlying population contact structure, and the probability of transmission given contact. These factors are described by the parameter β: the rate of a **successful infectious contact**.

The progression from I to R is parameterized by γ and describes the **rate of recovery** from the infection.

> The parameters `(\beta, \gamma)` are considered **fixed** and **equal on average** for the whole population (Deterministic Model).

Differential equations



A **function** $y = f(x, \dots)$ describes the value of y (dependent variable, output) for various values of on or many x (indepentent variables, predictors, arguments, inputs). E.g. the position y of a car after a certain time x.

The **derivative** $\frac{dy}{dx}$ describe how y is changing when x has a certain value. E.g. the velocity of the car at time x.

This change may not be fixed (example of fixed derivative?), but may be a function of the input and/or output $\frac{dy}{dx} = g(x, y, \dots)$ themselves. This is a **differential equation**. E.g. the velocity changes on mountain roads, slopes, traffic jams, etc...

A group of interconnected differential equation is called a **system of differential equations**, like the SIR model.

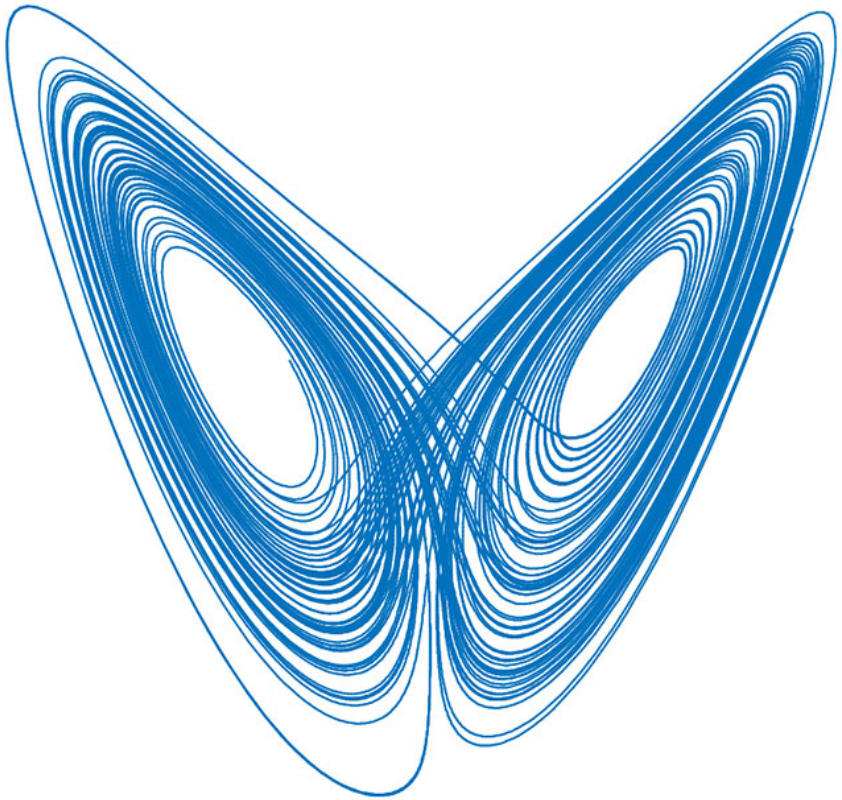
Differential equations

Differential equations are used to describe **dynamical systems**, that is systems that evolve in **time**.

Solving a dynamical systems means find the **state of the system at a given time**. These systems can be solved in two ways:

- **Analytical solution**: also called close-form, there is a set of mathematical operations that given a time t, allows you to get the status of the system $\mathcal{S}_t$ at that time. This is possible only for very simple systems. E.g., how distant would get a car going at constant velocity or a velocity simply known at every point.

- **Numerical solution**: the only way to know $\mathcal{S}_t$ is to simulate the system time step by time step $\mathcal{S}_t = f(\mathcal{S}_{t-1})$. Usually the only way to solve complex or chaotic systems.



Let's go back to the SIR model

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

To simplify calculation we assume a fixed population of size N, and S, I, R as **fractions of this population**, not number of individuals.

βSI: The **rate of infection** of individuals at risk. It depends from how many risk contact an average person has (β), adjusted by the ratio of infectious individuals among these contacts (I), and by the rate of susceptible individuals (S) still available.

γI: the **recovery rate** at the population level. It determines how fast the proportion of infected in the population drops due to people recovering.

What is actually β?

A way to define it is the product of the (average) **number of contacts** κ by the **probability of a efficacious contact** π i.e. $\beta = \pi\kappa$. Actually this is a simplification of $\beta = -\kappa\log(1-\pi)$ given that $\log(1-\pi) \approx -\pi$ se π è vicino a zero. But where does this come from?

Consider p as the probability of getting infected by an infectious individual. The probability of NOT getting infected is $1 - p = (1 - \pi)$. What is the probability of not getting infected by κ infectious individuals?

$$1 - p = \prod_{i=1}^{k}(1 - \pi_i) \approx (1 - \pi)^k$$

(the probability of "independent" events it's their probabilities' product).

If not all contact are infectious we can write the former as:

$$1 - p = (1 - \pi)^{kI}$$

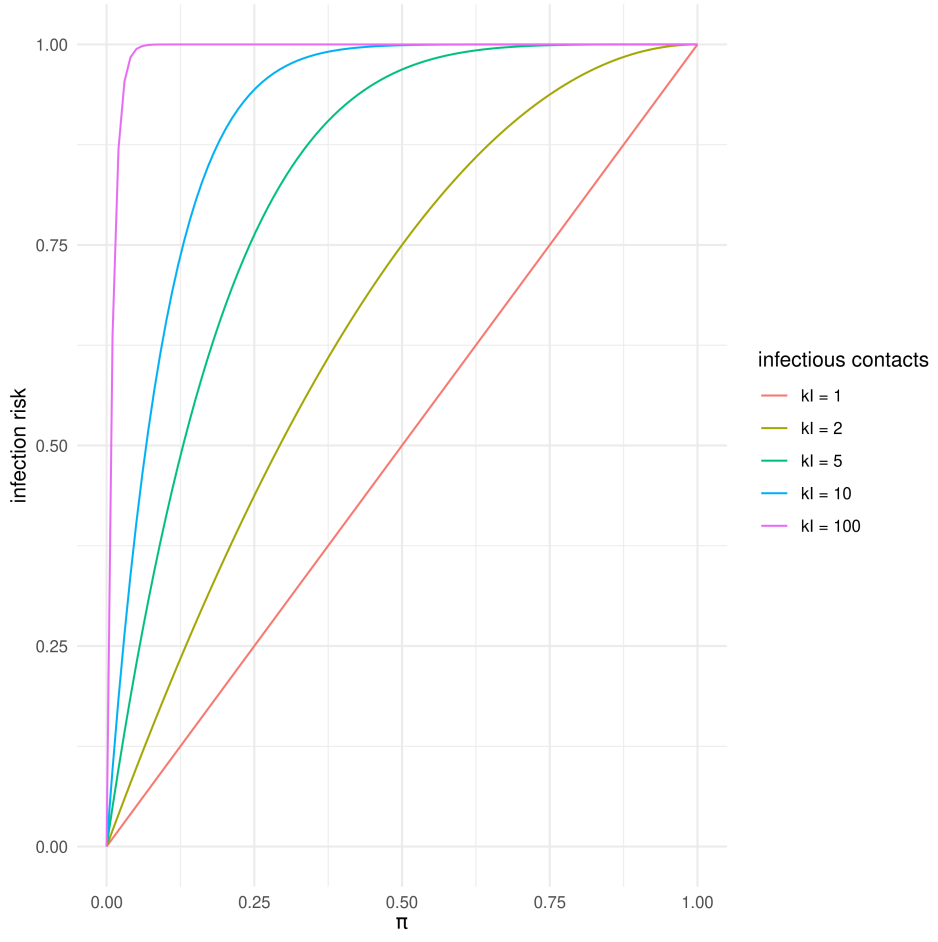
with I being the fraction of infected in the population, and therefore the individual risk of infection as:

$$p = 1 - (1 - \pi)^{kI}$$

What is actually β?

What does $p = 1 - (1 - \pi)^{kI}$ tell us? The probability of getting infected every given time is related to:

- the number of infectious contact kI;
- the probability of infection given contact π;



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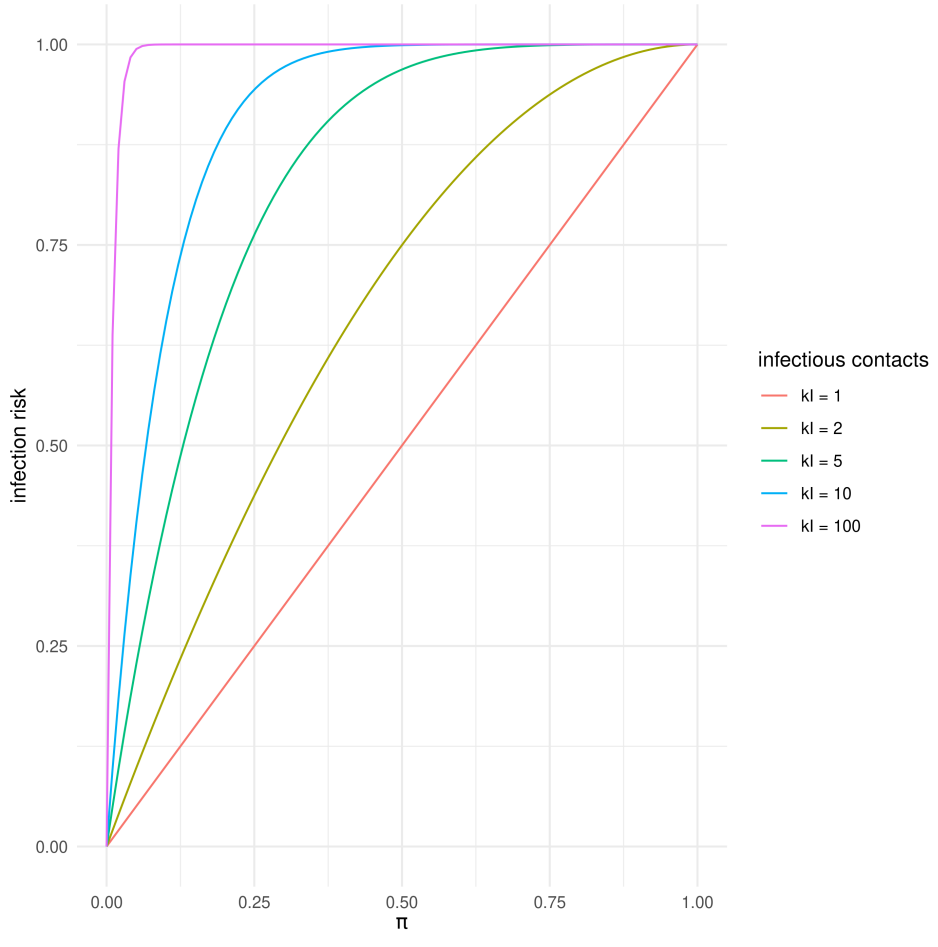
> Epidemics can be controlled either by **reducing the number of contacts** (e.g. social distancing, closures, lockdowns) or by **decreasing the risk of contagion** given a contact (masks, hand hygiene, physical distancing).



What is actually β?

Defining $\beta = -\kappa \log(1-\pi)$ we can rewrite the risk formula $p = 1 - (1-\pi)^{kI}$ as:

$$p = 1 - e^{-\beta I}$$

taking the derivative in time (ie. the change of risk in time) we get the **force of infection** λ:

$$\frac{dp}{dt} = \beta I = \lambda$$

> The **force of infection** represents the transmission rate per individual.

When multiplied by the fraction of still susceptible individuals λS gives the growth of the cumulative number of cases in the epidemic.

What is actually γ?

> It represent the recovery rate of infected individuals.

It derives from the average length of the infectious period which is $\frac{1}{\gamma}$. This latter value can be collected by clinical data or serology studies.

γ increases if patients are treated with a pharmacological/clinical solution that either remove the pathogen or makes it non infectious.

Reproductive numbers

We can consider λS as how fast the epidemic grows and γI how fast it dies out. The ratio of these two parameters is the **effective reproductive number** $\mathcal{R}_t$:

$$\mathcal{R}_t = \frac{\lambda S}{\gamma I} = \frac{\beta S I}{\gamma I} = \frac{\beta S}{\gamma}$$

> The **effective reproductive number** describes the **trend of the epidemic**. It can be interpreted as the number of susceptible an infectious individual can infect before recovering.

If this number is above 1 the number of cases increases faster than they recover and we observe an exponential growth. $\mathcal{R}_t$ in these situations:

- the **force of infection was decreased** (e.g. by public health interventions or change in behavior)
- the **fraction of susceptibles has decreased** (natural immunity or vaccination)
- **the recovery rate** was increased by a pharmacological/clinical solution.

Reproductive numbers

If we consider the beginning of the epidemic when all the population is susceptible (S ≈ 1) and we insert one single infected case we get the **basic reproductive number** $\mathcal{R}_0$:

$$\mathcal{R}_0 = \frac{\beta}{\gamma}$$

> The **basic reproductive number** represents the **invasive potential** of a given pathogen in given, homogeneous population.

It can be interpreted as the number of susceptible an infectious individual can infect before recovering, in a totally susceptible population.

Epidemic Threshold (1)

The epidemic starts to decline when $\frac{dI}{dt} \leq 0$, that is, infected people start to decrease. This can be rewritten as:

$$\frac{dI}{dt} \leq 0 \implies$$

$$\beta SI - \gamma I \leq 0 \implies$$

$$\implies I(\beta S - \gamma) \leq 0$$

That is the epidemic dies off if:

- $I = 0$, there are no infectious people anymore;
- $\beta S - \gamma \leq 0$, the recovery rate is faster than the creation of new cases.

Epidemic Threshold (2)

For which value of S does $\beta S - \gamma \leq 0$?

$$\beta S - \gamma \leq 0 \implies$$

$$\implies \beta S \leq \gamma \implies$$

$$\implies S \leq \frac{\gamma}{\beta} \implies$$

$$\implies S \leq \frac{1}{\mathcal{R}_0}$$

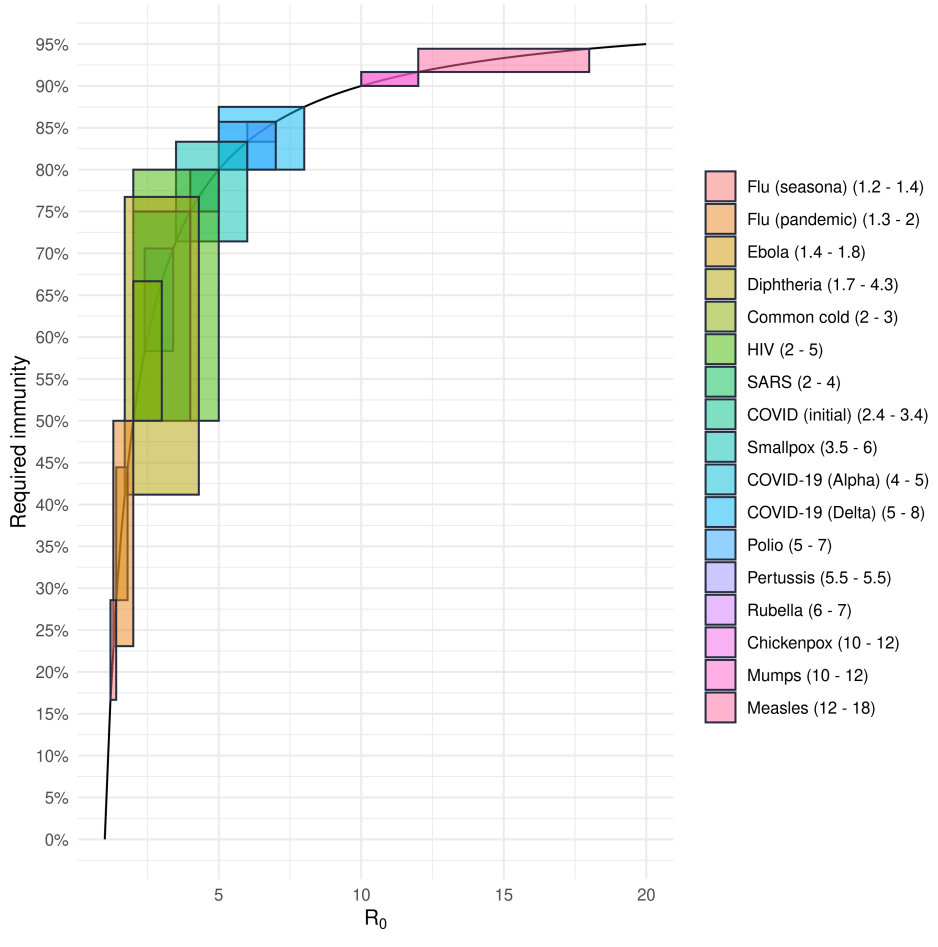
> The epidemic stops if the fraction of susceptible is lower than $\frac{1}{\mathcal{R}_0}$

Immunity

The epidemic threshold helps dictating public health targets.

> To stop the epidemic a population must reach a **level of immunity** equal to:
>
> $$1 - \frac{1}{\mathcal{R}_0}$$

This can happen either by **natural immunity** or by **vaccination**, assuming no reinfection and sterilizing vaccines.



Final epidemic size

It can be demonstrated that total fraction of susceptible in time varies as:

$$S_{(t)} = S_{(0)} e^{-R_{(t)} \mathcal{R}_0}$$

and that at the end of the epidemic the final number of affected (and recovered) will be:

$$R_{(\infty)} = 1 - S_{(0)} e^{-R_{(\infty)} \mathcal{R}_0}$$

This function can only be solved numerically.

- The epidemic **never hits 100%** of the population and the transmission breaks due to the **drop in infectious people** more than susceptible ones.
- The cumulative fraction of affected depends from the **initial conditions** $(S_{(0)})$ and from the **pathogen invasiviness** $(\mathcal{R}_0)$.

Model with demographics

Demographics (1)

The model can be extended including the population birth and death rates ν, μ. This is a so called **open popualation**.

$$\frac{dS}{dt} = \nu - \beta SI - \mu S$$

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

$$\frac{dR}{dt} = \gamma I - \mu R$$

In this formulation, the I compartment loses people not only for the recovery rate but also for the natural mortality.

The basic reproduction number becomes:

$$\mathcal{R}_0 = \frac{\beta}{\gamma + \mu}$$

Demographics (2)

In presence of birth and deaths, if the population is stable (i.e. $\nu = \mu$) the epidemic either dies off $(\mathcal{R}_0 < 1)$ or it reaches an **equilibrium state** $(\mathcal{R}_0 > 1)$, characterized by:

$$(S^*, I^*, R^*) = \left(\frac{1}{\mathcal{R}_0}, \frac{\mu}{\beta}(\mathcal{R}_0 - 1), 1 - \frac{1}{\mathcal{R}_0} - \frac{\mu}{\beta}(\mathcal{R}_0 - 1)\right)$$

When demographics are considered end disease-related mortality is ignored, at the equilibrium $\mathcal{R}_0$ can be used to estimate the **mean age of infection**:

$$A \approx \frac{1}{\mu(\mathcal{R}_0 - 1)}$$

Consequently, the age of first infection and the life expectancy $L = \frac{1}{\mu}$ allow to estimate $\mathcal{R}_0$ at equilibrium:

$$\mathcal{R}_0 = \frac{L}{A}$$

Demographics (3)

The epidemic reaches the equilibrium through **oscillations**, whose period is:

$$T = 2\pi\sqrt{AD}$$

with A being the mean age of infection and $D = \frac{1}{\gamma+\mu}$ the average length of the infection period.

Regime for $\frac{1}{\mu} = 70$ years, $\beta = 520$ per year, and $frac1\gamma = 7$ days, giving $\mathcal{R}_0 = 10$. Initial conditions were $S_{(0)} = 0.1$ and $I_{(0)} = 2.5 \times 10^{-4}$.

Demographics (summary)

The basic reproductive number is **lower when considering demographics** due to the **natural death of infected individuals**.

In presence of demographics the epidemic **reaches an equilibrium** through an **oscillatory dynamic** of the infection prevalence.

The age of first encounter with the disease **decreases with** $\mathcal{R}_0$.

$\mathcal{R}_0$ can be estimated through the **age of first encounter and the life expectancy** once the epidemic equilibrium is reached

Host heterogeneity and contact mixing

Heterogeneity

Until now we assumed that:

- the transmission rate is equal for every individual;
- every individual can have a contact with everyone else in the population.

Including **heterogeneity** in the model relaxes the first assumption.

Heterogeneity sources

Sources of heterogeneity (and what they change):

- Age (β, γ)
- Behavior (β)
- Living environment (β)
- Drugs (β, γ) (examples?)
- Other examples?

Two-group SIS

A very well studied examples were different STI risk group during the early HIV era. Let's assume a high risk group H and a low risk group L and no lifelong immunity (SIS model). The model becomes:

$$\frac{dI_H}{dt} = \beta_{HH} S_H I_H + \beta_{HL} S_H I_L - \gamma I_H$$

$$\frac{dI_L}{dt} = \beta_{LH} S_L I_H + \beta_{LL} S_L I_L - \gamma I_L$$

β can be described with a **transmission matrix**:

$$\beta = \begin{pmatrix} \beta_{HH} & \beta_{HL} \\ \beta_{LH} & \beta_{LL} \end{pmatrix}$$

> With G risk groups, β take the form of $G \times G$ **Who Acquires Infection From Whom** matrix.