Chapter 1

Classical results in mathematical epidemiology

Epidemics are typical examples of complex phenomena. A mathematical description of an epidemic needs to take into account its non deterministic nature, and, therefore, rely on probabilities. An epidemic process is, essentially, a stochastic process.

In the dawn of mathematical epidemiology, researchers studied the dynamics in time of probabilities regarding the states of individuals. This is the case of the study of life expectancy and smallpox by Daniel Bernoulli, and so is the famous contribution of Kermac y McEndrick with the SIR models. In both cases, the resulting dynamic equations correspond to the Master equation of the given stochastic processes.

1.1 A supersonic intro to Master equation

Introduction to Stochastic Processes and Markov Chains

A **stochastic process** is a mathematical model that describes the evolution of a random system over time. It's a collection of random variables indexed by time, and can be used to model a wide range of phenomena, from the stock market to the weather.

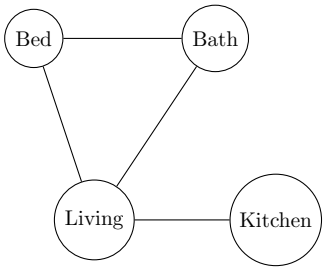
A **Markov chain** is a specific type of stochastic process that has the **Markov property**: the future state of the system only depends on the current state, and not on any of the previous states. This makes Markov chains particularly useful for modeling systems where the future is dependent on the present, but not on the past.

Formally, a Markov chain is a sequence of random variables $X_0, X_1, X_2, \ldots$ that take values in a finite or countable set S, where the probability of moving from one state to another depends only on the current state. That is, for all $n \geq 0$ and all states $i, j \in S$,

$$\mathbb{P}(X_{t+1} = j \mid X_t = i, X_{t-1} = i_{t-1}, \ldots, X_0 = i_0) = \mathbb{P}(X_{t+1} = j \mid X_t = i).$$

Markov chains have many interesting properties and applications, including their use in modeling queueing systems, random walks, and machine learning algorithms.

Example: Drunken man
A drunken man is moving around his own house, which is made of a Bedroom, a Bathroom, a Livingroom and a Kitchen, connected through doors as shown in the diagram:



Everytime he enters a room, he chooses one of the doors in that room at random, and moves throuhg it to the next room. The man starts in his bedroom.

1. What is the shortest path from the bedroom to the kitchen?
2. What is the largest path between bed and kitchen (without cycles)?
3. If the man keeps walking for a very long time, what amount of time he spends in every room?
4. What is the expected time that takes the man to visit the kitchen for the first time?

Master equation

The Master Equation is a fundamental tool in the study of stochastic processes, particularly in probability theory and statistical physics. It describes the time evolution of the probability distribution of a system in terms of transition rates between different states. In its simplest form, the Master Equation takes the form of a first-order differential equation:

$$\frac{d}{dt}P_i(t) = \sum_j W_{ji}P_j(t) - \sum_j W_{ij}P_i(t), \tag{1.1}$$

where $P_i(t)$ is the probability of the system being in state i at time t, and W_{ij} is the transition rate from state j to state i. The first term on the right-hand side of the equation represents the rate of transitions from all other states j to state i, weighted by the probability of being in state j. The second term represents the rate of transitions from state i to all other states j, weighted by the probability of being in state i.

Master equation can be seen as a continuity equation, or a mass conservation equation. In fluid dynamics, for instance, the rate of change of mass in a control volume must be equal to the net rate of mass flow into or out of the control volume. Mathematically, the continuity equation can be written as:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) = \qquad \frac{d}{dt} \int_V \rho \, \mathrm{d}V + \oint_S \rho \mathbf{v} \cdot \mathrm{d}\mathbf{S} = 0$$

where ρ is the fluid density, $\mathbf{v}$ is the velocity vector, $\frac{\partial \rho}{\partial t}$ is the rate of change of density with respect to time, and $\nabla \cdot (\rho \mathbf{v})$ is the divergence of the mass flux density vector.

In other words, the continuity equation states that the change in the amount of fluid within a control volume is equal to the net flow of fluid across the boundaries of that control volume. This principle is based on the law of conservation of mass, which states that mass cannot be created or destroyed, only transferred or transformed.

1.2 Daniel Bernoulli and smallpox

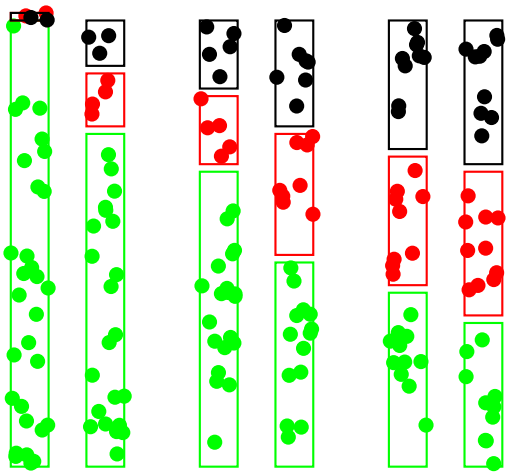
Daniel Bernoulli's study of the effect of smallpox in life expentancy and the possibility of innoculation as a vaccination strategy, a debated argument in the Royal Academy of Science in Paris, in the second half of the XVIII century.

Effect of innoculation in Smallpox, Royal Academy of Science, Paris, 1760, published in 1766

Scope: calculate the gain in life expectancy at birth if smallpox were to be eliminated as a cause of death. The model assumes a fixed amount of infections every year, so, it is not a model for the infection. Still, it deals with relevant questions in epidemiology.

The model of Bernoulli studied the age dynamics of the entire population in a country, as classified in three groups: susceptibles, immunes and dead[1]. Susceptible was everyone that had not been in conctact with the disease. Immune was everyone that had passed the disease. Dead were those that died, either from the disease or from other causes. Smallpox could either cause death, or cause life-long immunity. So, it is considered one of the SIR family of models, but rather, in this case, SR model.

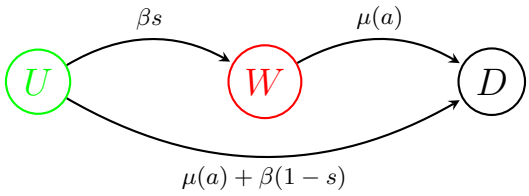
[1] As you can see, there is no characterization of those that are currently infected. The reason for this is that the study considered large time scales, such that the actual infectious period was neglible in that scale, and people were considered to transition immediately between susceptible to immune.



Bernoulli imagined that people born in year $a = 0$, could go through the states (un-infected, immune, dead) with certain probabilities [2] The dynamics relied on the following dynamic parameters:

- $\mu(a)$ the rate of death of all causes except smallpox, for an individual of age a
- β is the **force of infection**: the rate at which susceptible individual get infected
- $c = 1 - s$ the fraction of individuals infected that dies of smallpox.

The Markov chain is described graphically as this:



The relevant quantities (dynamic variables) of the model depend on the age of the persons a. They are:

- $u(a)$ the probability for an individual of being alive and susceptible (un-infected) at age a
- $w(a)$ the probability for an individual of being alive and immune at age a
- $d(a)$ is the probability of being dead at age a, but since probabilities add up to 1, and there are only three posible states, $d(a) = 1 - u(a) - w(a)$.

[2] The transitions between this states were described as a Markov chain, although Markov contribution came centuries later.

Considering the rates at which individuals can move from one state to the other, we can compute the contributions of each state in the Master equation. The dynamical system derived by Bernoulli is given by:

$$\begin{aligned} \frac{\mathrm{d}u}{\mathrm{d}a} &= -(\beta + \mu(a))u(a) \\ \frac{\mathrm{d}w}{\mathrm{d}a} &= \beta(1-c)\mu(a)u(a) - \mu(a)w(a) \end{aligned}$$

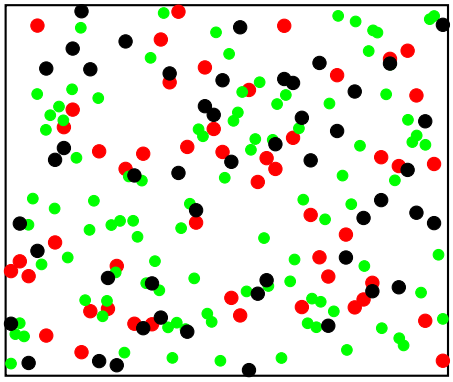
The interest of Bernoulli was comparing the total amount of persons alive at a given age $u(a) + w(a)$ in the case where $c = 0$ (people do not die of smallpox), and $c \neq 0$.

These equations are recognized as one of the first modern mathematical approaches to mathematical epidemiology. Their solution and Bernoulli conclusions is out of the scope of the present course (if interested see [**?**]). However, its interpretation and derivation are useful to introduce some probabilistic methods and epidemic concepts.

The Master Equation provides a powerful framework for analyzing a wide range of phenomena, including chemical reactions, population dynamics, and the behavior of complex systems. By solving the Master Equation, one can obtain the time-dependent probability distribution of the system, which can be used to calculate various statistical quantities of interest, such as the mean and variance of observables. The Master Equation can also be used to study the long-time behavior of the system, such as the emergence of steady-state solutions and the behavior of fluctuations around these solutions.

1.3 SIR compartmental models

The SIR (Susceptible-Infectious-Recovered) model is a widely used mathematical framework for studying the spread of infectious diseases in populations. It was first introduced by Kermack and McKendrick in a seminal paper published in 1927. They used a system of differential equations to describe the time evolution of the number of individuals in each compartment, and derived an expression for the critical threshold of the disease, above which an epidemic occurs.



A first idealization of what actually happens in an epidemic, is to think of society as a gas of individuals. Each individual can be in one of the following states:

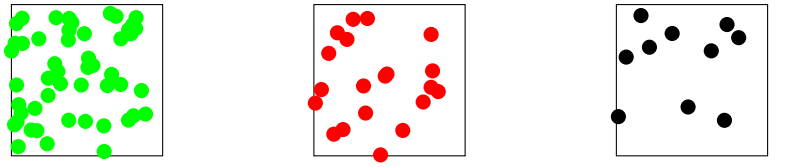
- **Susceptible** individuals, who are at risk of becoming infected;
- **Infectious** individuals, who are capable of transmitting the disease to susceptible individuals;
- **Recovered** individuals, who have either recovered from the disease and are immune, or have died from the disease, and are removed.

Under well mixed assumptions, this individuals-particles move around and interact with each other, occasionally. The process of contagion can be seen as a catalytic chemical reaction, in which the interaction of an Infectious individual with a Susceptible, can induce the latter to turn into infectious with a certain probability:

$$\begin{aligned} S + I &\xrightarrow{\beta} 2I \\ I &\xrightarrow{\mu} R \end{aligned}$$

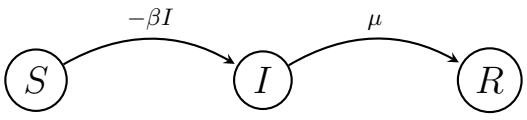
Simulation of this process in a computer, relies on Monte Carlo methods, more precisely in action diffusion equations and Gillespie algorithm, that we will study later.

A mean field probabilistic description can be made, by considering the population to be classified into three different compartments, according to their state:



Compartment S Compartment I Compartment R

The evolution of the epidemic correspond to the process of changing individuals between compartments, with certain probabilities, as represented in the following diagram:



A key difference with the work of Bernoulli is that the **force of infection:** $\beta I(t)$ (the rate at which susceptible individuals contract the disease) is not fixed in time, but proportional to the amount of people infected in the population. This is typical for human-human transmitted diseases in a well mixed population, where the probability of getting infected depends on the chances of meeting

an infectious individual. This probability is proportional to the current amount of individuals in that state.

The dynamic variables for this model are:

- $S(t)$, the fraction of the population susceptible to contracting the disease
- $I(t)$ the fraction that is currently infected and infectious
- $R(t) = 1 - S(t) - I(t)$ the fraction that is recovered or deceased.

The Master equations for the dynamic parameters reads

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI \\ \frac{dI}{dt} &= \beta SI - \mu I \\ \frac{dR}{dt} &= \mu I \end{aligned} \tag{1.2}$$

where, the parameters

- β is the transmission rate or the rate at which susceptible individuals become infected.
- μ is the recovery rate or the rate at which infected individuals recover and become immune.

The first equation describes the rate at which susceptible individuals become infected. It assumes that the rate of transmission is proportional to the product of the number of susceptible individuals and the number of infectious individuals, with the proportionality constant β.

The second equation describes the rate at which infected individuals recover. It assumes that the rate of recovery is proportional to the number of infectious individuals, with the proportionality constant μ. The term βSI represents the rate at which susceptible individuals become infected, and the term μI represents the rate at which infected individuals recover.

The third equation describes the rate at which individuals recover from the disease and become immune. It assumes that the rate of recovery is proportional to the number of infectious individuals, with the proportionality constant μ.

These equations are a set of coupled first-order ordinary differential equations, which means that the values of S, I, and R change over time according to the values of β, μ, and the initial conditions. The SIR model is a simple but powerful tool for studying the dynamics of infectious diseases and predicting the impact of interventions such as vaccination and social distancing.

1.3.1 Short time limit

In the early stages of an epidemic, when the number of infected individuals is small compared to the total population size, the SIR model can be approximated by a linear differential equation. Suppose that the initial number of infected individuals is small compared to the total population size, i.e., $I(0) \sim 1/N$, where N is the total population size. Then, the number of susceptible individuals can be approximated as $S(t) \simeq 1$, and the number of recovered individuals can be approximated as $R(t) \sim 1/N$.

Under these assumptions, the dynamics of the infected compartment can be approximated by the following linear differential equation:

$$\frac{dI}{dt} = \beta S(t) I(t) - \mu I(t), \tag{1.3}$$

where β is the transmission rate, μ is the recovery rate, and $I(t)$ is the fraction of infected individuals at time t. During the initial epidemic phase, when few cases still exists compared to the population size, we can approximate $S(t) = S(0) = 1$, and write the linear equation:

$$\frac{dI}{dt} = \lambda I(t), \qquad \text{where } \lambda = \beta - \mu. \tag{1.4}$$

The solution to this linear differential equation is an exponential function of the form:

$$I(t) = I(0) \exp(\lambda t). \tag{1.5}$$

The exponential solution of the SIR model in the low prevalence linear phase shows that the number of infected individuals changes exponentially, growing when $\beta > \mu$, and decreasing when $\beta < \mu$. This exponential growth phase is characteristic of the beginning of an epidemic, when the number of infected individuals is small compared to the total population size and the epidemic has not yet reached a significant proportion of the population.

The basic reproduction number R_0, is the expected number of new infections created by every single infected individual, in the early exponential phase of an epidemic. Since μ is the recovery rate, $\tau = 1/\mu$ is the expected duration of the infection on an individual. Since β is the rate of new cases, $R_0 = \beta\tau = \beta/\mu$ is the average number of new cases created by an infected individual during the period in which it is actively infectious. Notice that the criteria $\lambda \lessgtr 0$ is equivalent to $R_0 \lessgtr 1$.

1.3.2 Infinite time limit

Properties of SIR equations. Since the total amount of studied subjects remain invariant, only their categories changes, $S(t) + I(t) + R(t) = 1$. This can also be proven by adding (1.2). Furthermore, since

$$S'(t) + I'(t) = -\mu I(t)$$

is a decreasing non negative function, it converges to a limit $S_\infty + I_\infty$ in $t \to \infty$. Moreover, it is easy to see that I_∞ can only be zero, so $S + I \to S_\infty$.

Integration of the previous equation results in

$$1 - S_\infty = \mu \int_0^\infty I(t)\mathrm{d}t$$

The first number $S_0 + I_0 = 1$ comes from assuming that all the population is originally in the states S or I.

Dividing the equation for $S'(t)$ by $S(t)$, we get

$$\frac{\mathrm{d}\log S(t)}{\mathrm{d}t} = -\beta I(t) \quad \text{that integrating} \quad \log(S_\infty/S_0) = -\beta \int_0^\infty I(t)\mathrm{d}t$$

This results in a relation for the final amount of susceptible individuals

$$\log(S_0/S_\infty) = \frac{\beta}{\mu}(1 - S_\infty) = R_0(1 - S_\infty)$$

that is called the *final size relation* for the epidemic. If the variables are kept extensive $\tilde{S}(t) = NS(t), \tilde{I}(t) \ldots$, the final relation reads

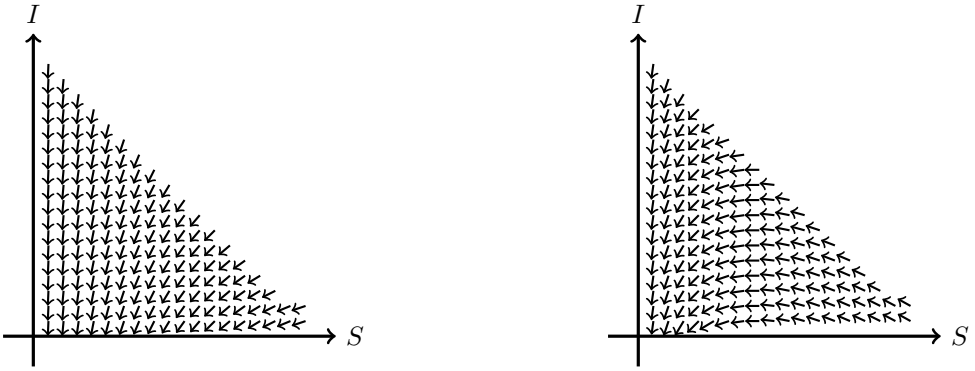
$$\log(\tilde{S}_0/\tilde{S}_\infty) = R_0(1 - \frac{\tilde{S}_\infty}{N}) \tag{1.6}$$

which is a useful relation between the basic reproduction number and the final size of the epidemic.

The total number of infected people in the population is given by $N - \tilde{S}_\infty$, and the fraction $1 - S_\infty$ or $1 - \frac{\tilde{S}_\infty}{N}$ is called the *attack rate*, although it is not a rate, but a fraction.

Another conclusion from (1.6) is that $S_\infty > 0$, and so, in every epidemic there is always a fraction of the population that will not be infected.

While the recovery rate μ is generally simple to estimate from studies on infected individuals. However the contact rate $\tilde{\beta} = \beta/N$ is much harder. Direct calculation of β, or of $R_0 = \beta/\mu$ can be difficult, while a post facto analysis of the epidemic through serological studies, can provide estimation for S_∞, and through (1.6), to R_0 and β.



A similar procedure as the one we carried, but taken up to time t instead of ∞, results in a parametric relation between $S(t)$ and $I(t)$:

$$I(t) + S(t) - \frac{\mu}{\beta}\log S(t) = 1 - \frac{\mu}{\beta}\log S_0 \tag{1.7}$$

This trajectories correspond to the flux lines in the diagram of I vs S, using the vector defined by the right hand side of (1.2), normalized.

The maximum number of infectives at any time is the number of infectives when the derivative of I is zero, that is, when $S = \mu/\beta$. This maximum is obtained by replacing this value into (1.7) as

$$I_{max} = I_0 + S_0 - \frac{\mu}{\beta}\log S_0 - \frac{\mu}{\beta} + \frac{\mu}{\beta}\log\frac{\mu}{\beta}$$

1.4 And beyond