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Modeling epidemics from a system-theoretic perspective: the COVID-19 case study

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Introduction

On January 23, 2020, China's central government imposed a lockdown on the city of Wuhan and on the other municipalities of the Hubei province in order to mitigate the health-related concerns caused by the spread of a novel coronavirus which had first been reported as early as December 2019 [1].
By March 11, the World Health Organization had declared the COVID-19 outbreak a pandemic [2].

The virus is now officially addressed to as "SARS-CoV-2"[3] and is documented to cause severe respiratory infections accompanied by a variety of symptoms typical of other common diseases (seasonal flu, for example) like fever, cough, shortness of breath et cetera [4]. Given the relatively high virulence of the pathogen [5], the effort of containing the spread of the infection has quickly become a public health priority worldwide. The virus mainly spreads through close contacts between individuals, in most cases via small droplets naturally produced when talking, sneezing and coughing [6].
As a consequence, the most effective measures to contain a free escalation include improved care for personal hygiene and social distancing.

The aim of this essay is to discuss what could be a mathematical-oriented approach on the problem of flattening the curve of infection by controlling some of the parameters that appear in the differential equations used to model the evolution in time of the epidemic among the population.
To do this, after a brief introduction to the key mathematical tools which are of fundamental importance to understand the problem, we will disclose the most widely adopted models used to make predictions about the behavior of infections; for some of these models, we will focus in depth on their properties from a systems-theory perspective.
Finally, using the data available on official platforms, we will apply the developed ideas to run, through Matlab, a simplified simulation of the COVID-19 outbreak.

Chapter 1

Mathematical background

1.1 State-space models

For a dynamical system Σ described by a differential equation of arbitrary order, we can obtain an alternative description of the system in the so called "state-space representation":

$$\dot{\mathbf{x}}(t) = \mathbf{f}\left(\mathbf{x}(t), \mathbf{u}(t)\right) \tag{1.1}$$
$$\mathbf{y}(t) = \mathbf{h}\left(\mathbf{x}(t), \mathbf{u}(t)\right) \tag{1.2}$$

where

$\mathbf{u}(t)$ is the vector of the inputs,

$\mathbf{y}(t)$ is the vector of the outputs,

and

$\mathbf{x}(t)$ is the vector of the "state variables",

that is the set of variables which, together with $\mathbf{u}(t)$, conveys all the information we need to calculate the state and the output of the system at any given instant t.
Note how, with this representation, we are not trying to visualize the whole dynamics of the system like we would normally do with an n-th order differential equation, but are rather focusing on how each state variable relates to the others.
In the special case of a linear system Σ with n state variables, i inputs and q outputs, its state can be described by these new equations:

$$\dot{\mathbf{x}}(t) = \mathbf{A}\mathbf{x}(t) + \mathbf{B}\mathbf{u}(t) \tag{1.3}$$
$$\mathbf{y}(t) = \mathbf{C}\mathbf{x}(t) + \mathbf{D}\mathbf{u}(t), \tag{1.4}$$

where $\mathbf{A}$, $\mathbf{B}$, $\mathbf{C}$ and $\mathbf{D}$ are square matrices with

$$dim(\mathbf{A}) = n \times n,$$
$$dim(\mathbf{B}) = n \times i,$$
$$dim(\mathbf{C}) = q \times n,$$
$$dim(\mathbf{D}) = q \times i.$$

We can notice how the state-space representation can be seen as a natural "repackaging" of the higher-order differential equation into a system of first-order differential equations. This gives us access to powerful, systematic methods for analyzing and controlling dynamical systems.

1.2 Equilibria, linearization and Lyapunov's direct method

We will now limit ourselves to consider a system Σ' which is described by a set of autonomous differential equations, that is in absence of forcing inputs:

$$\dot{\mathbf{x}}(t) = \mathbf{f}\left(\mathbf{x}(t)\right), \tag{1.5}$$

where the function $\mathbf{f}\left(\mathbf{x}(t)\right)$ may be non-linear.

1.2.1 Equilibria

Given such system, we say that $\widetilde{\mathbf{x}}$ is an "equilibrium point" for Σ' if

$$\mathbf{f}(\widetilde{\mathbf{x}}) = \mathbf{0} \quad \forall t \geq 0.$$

Also, $\widetilde{\mathbf{x}}$ is said to be:

- **simply stable** if $\forall \mathcal{E} > 0 \; \exists \; \Delta > 0 : \left\|\mathbf{x}(0) - \widetilde{\mathbf{x}}\right\| \leq \Delta \implies \left\|\mathbf{x}(t) - \widetilde{\mathbf{x}}\right\| \leq \mathcal{E}$;
- **asymptotically stable** if it is simply stable and such that
  $\exists \Delta > 0 : \left\|\mathbf{x}(0) - \widetilde{\mathbf{x}}\right\| \leq \Delta \implies \lim_{t\to\infty} \mathbf{x}(t) = \widetilde{\mathbf{x}}$.

1.2.2 Linearization

When the system we are dealing with is non-linear, we can get a linear approximation around an equilibrium and study its behavior in a neighborhood of that point.
By recalling the expression of the first-order Taylor expansion for a multi-variable function $g(\mathbf{t})$ around a fixed point $\widetilde{\mathbf{t}}$:

$$g(\mathbf{t}) \approx g(\widetilde{\mathbf{t}}) + \nabla g(\widetilde{\mathbf{t}}) \cdot (\mathbf{t} - \widetilde{\mathbf{t}}),$$

where

$$\nabla g(\widetilde{\mathbf{t}}) = \left(\frac{\partial g}{\partial t_1}(\widetilde{t_1}), \cdots\cdots, \frac{\partial g}{\partial t_n}(\widetilde{t_n}) \right),$$

and by noticing that $\mathbf{f}(\cdot)$ is a vector-valued function, we get

$$\begin{cases} f_1 \approx f_1(\widetilde{\mathbf{x}}) + \nabla f_1(\widetilde{\mathbf{x}}) \cdot (\mathbf{x} - \widetilde{\mathbf{x}}) \\ \\ f_2 \approx f_2(\widetilde{\mathbf{x}}) + \nabla f_2(\widetilde{\mathbf{x}}) \cdot (\mathbf{x} - \widetilde{\mathbf{x}}) \\ \vdots \qquad\qquad \vdots \qquad\qquad \vdots \\ f_n \approx f_n(\widetilde{\mathbf{x}}) + \nabla f_n(\widetilde{\mathbf{x}}) \cdot (\mathbf{x} - \widetilde{\mathbf{x}}) \end{cases}$$

and, by definition,

$$\begin{pmatrix} \nabla f_1 \\ \vdots \\ \vdots \\ \nabla f_n \end{pmatrix} = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \cdots & \frac{\partial f_n}{\partial x_n} \end{pmatrix} = \mathbf{J}_f.$$

Let's now introduce

$$\Delta\mathbf{x} = \mathbf{x} - \widetilde{\mathbf{x}}.$$

Taking the derivative of this quantity, we get

$$\dot{\Delta\mathbf{x}} = \dot{\mathbf{x}},$$

as $\widetilde{\mathbf{x}}$ is a constant.
So, we end up with the relation:

$$\dot{\Delta\mathbf{x}} = \dot{\mathbf{x}} = \mathbf{f}\left(\mathbf{x}(t)\right) \simeq \overbrace{\mathbf{f}\left(\widetilde{\mathbf{x}}\right)}^{0} + \mathbf{J}_f(\widetilde{\mathbf{x}}) \cdot (\mathbf{x} - \widetilde{\mathbf{x}}) = \mathbf{J}_f(\widetilde{\mathbf{x}}) \cdot \Delta\mathbf{x}$$

where we dropped the higher-than-first order terms of the Taylor expansion under the assumption that, for $\Delta \to 0$, they would be negligible. The final equation we obtained,

$$\dot{\Delta\mathbf{x}} = \mathbf{J}_f(\widetilde{\mathbf{x}}) \cdot \Delta\mathbf{x},$$

is a linear differential equation ($\mathbf{J}_f(\widetilde{\mathbf{x}})$ is a constant) in state-space representation, where $\mathbf{u}(t) \equiv \mathbf{0}$ and where the current state is the difference between the "real state" and the "state of equilibrium".
This comes useful because, according to the theory of linear differential equations, the solution can be written as a linear combination of terms of the form $e^{\lambda_j t}$, where $\{\lambda_j\}$ is the set of the eigenvalues of the Jacobian. By leveraging on Lyapunov's stability theory, which will be presented later, one could prove that:

- if all eigenvalues of $\mathbf{J}_f(\widetilde{\mathbf{x}})$ have negative real part, then $\widetilde{\mathbf{x}}$ is a *stable* equilibrium point;
- if even only one eigenvalue has positive real part, then $\widetilde{\mathbf{x}}$ is an *instable* equilibrium point;
- if some of the eigenvalues have zero real part while the others have all negative real part we can not conclude anything, due to the fact that the linear approximation that we derived does not keep count of the higher-order terms in the Taylor expansion that in this case are necessary to determine the stability of the equilibrium.

This analysis of equilibria based on linearization we have just presented is commonly referred to as "Lyapunov's indirect method".

1.2.3 Lyapunov's direct method

There also exists a more general tool to investigate the nature of equilibria which works well in a broader range of situations.
The criterion is based on the arbitrary construction and study of the behavior of a scalar function -which has a (local) minimum around the equilibrium of interest- as the system's state evolves.
It can be thought as an "energy" function: it can be proven that if it decreases along the trajectories of the system (i.e. the system "dissipates energy"), the system will (asymptotically) converge to that equilibrium.
More formally:

Theorem (Lyapunov's stability). *Given an autonomous system of the form*

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}),$$

having an equilibrium point at $\widetilde{\mathbf{x}} = \mathbf{0}$ (we can always fall back into this scenario by performing a preliminary shift of the axis), with $\mathcal{D}$ a neighborhood of $\widetilde{\mathbf{x}}$, consider the function

$$V : \mathbb{R}^n \to \mathbb{R}, \quad V \in \mathcal{C}^1(\mathcal{D})$$

such that:

- $V(0) = 0$ *and* $V(\mathbf{x}) > 0$ *for* $\mathbf{x} \in \mathcal{D} \setminus \{0\}$*;*
- $\dot{V}(\mathbf{x}) = \langle \nabla V \, , \, \mathbf{f} \rangle \leq 0$ *for* $\mathbf{x} \in \mathcal{D} \setminus \{0\}$*,*

then $\widetilde{\mathbf{x}} = 0$ *is simply stable.*

If, additionally, for $\mathbf{x} \in \mathcal{D} \setminus \{0\}$*, it holds that*

$$\dot{V}(\mathbf{x}) < 0,$$

then $\widetilde{\mathbf{x}} = 0$ *is asymptotically stable.*

While the first condition assures us that the function will never be negative (which an energy function can not be), the latter arises from the fact that, as stated above, we want the function to decrease towards its minimum (the equilibrium) as time goes by.
In fact, if we try to compute its derivative along the trajectories of the system, that is with respect to time, we get:

$$\begin{aligned}\frac{d}{dt}V\left(\mathbf{x}(t)\right) &= \sum_{i=1}^{n} \frac{\partial}{\partial x_i} V\left(\mathbf{x}(t)\right) \cdot \frac{d}{dt} x_i(t) \\ &= \langle\, \nabla V \,,\, \dot{\mathbf{x}} \,\rangle \\ &= \langle\, \nabla V \,,\, \mathbf{f}(\mathbf{x}) \,\rangle,\end{aligned}$$

where we used the chain rule generalization for multivariable functions together with (1.5).

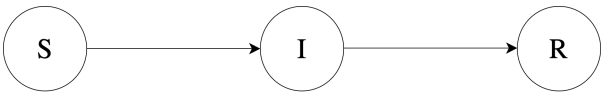
Chapter 2

Compartmental models in epidemiology

2.1 Basic definitions

In the context of infectious diseases, compartmental models are the mathematical tool used to model the evolution of epidemics. The basic idea is to divide the population the pathogen spreads through into categories (compartments): an individual may progress between compartments throughout the life span of the infection. Models can be graphically described by labels representing the compartments connected to each other by arrows which show the flow patterns between them.
Ordinary (sometimes stochastic or partial) differential equations run the models and allow us to gather information about the future outcome of diseases and how different public health interventions can correct the parameters in order to prevent further damage.
We will now present the basic form [10] of three of the most universally used compartmental models in literature; starting from these, various additions can be made to take into account different possible scenarios depending on the characteristics of the disease being examined and the complexity of the context in which it spreads.

2.2 SIR Model



The *SIR* is the oldest and most basic compartmental model.
The population is divided into three categories:

- Susceptibles: those who have not yet caught the disease and are vulnerable to the contagion;
- Infectives: those who are currently ill and, more importantly, are capable of spreading the epidemic to the susceptibles;
- Removed: those who either died from the disease or recovered and gained immunity.

The number of susceptibles, infectives and recovered at time t will be denoted, respectively, by $S(t), I(t)$ and $R(t)$.

Key assumptions

1. The total population $N(t)$ remains constant during the development of the epidemic:

$$N(t) = K, \quad \forall t.$$

From this equation, given that

$$K = N(t) = S(t) + I(t) + R(t), \tag{2.1}$$

will directly follow that

$$\frac{d}{dt}(S + I + R)(t) = 0.$$

This means that births and deaths not correlated to the disease will not be counted; the reason being that often the time scale of the epidemic is at least some orders of magnitude smaller than the "natural" demographic's one.

2. The rate at which the number of infectives I increases is constant and proportional to the number of contacts between infectives and susceptibles:

$$\beta\ (>0)\ \textit{is constant,}$$

$$\beta \propto \textit{number of contacts between } I \textit{ and } S.$$

3. Infectives become "removed" (i.e. they either die or recover) at a constant rate:

$$\gamma\ (>0)\ \textit{is constant.}$$

Differential equations
Taking into account these assumptions, the equations that govern our model are as follows[1]

$$\begin{cases} \dfrac{dS}{dt} = -\beta SI & (2.2) \\ \dfrac{dI}{dt} = \beta SI - \gamma I & (2.3) \\ \dfrac{dR}{dt} = \gamma I & (2.4) \end{cases}$$

with initial conditions given by the relations:

$$\begin{cases} S(0) = S_0 & (2.5) \\ I(0) = I_0 & (2.6) \\ R(0) = 0 & (2.7) \end{cases}$$

which, together with (2.1), allow us to write that:

$$S(t) + I(t) + R(t) = S_0 + I_0 \tag{2.8}$$

at any given time.

First of all, we can make some observations about the domain of existence of the model:

- For the problem to make sense, it must be $S(t) \geq 0$ and $I(t) \geq 0\ \forall t$.
  Also, $S(t) \equiv 0 \implies \dot{S}(t) = 0$ and thus S will not decrease further; the same holds for $I(t)$.

[1] Sometimes, βSI is seen divided by a factor of N. That is done in order to normalize with respect to the total population size.

- Being γ defined strictly positive, $R(t)$ is a monotonically increasing function, which means that, because it starts being non-negative, it will stay that forever. If the infection ever fades out, we will have $I(t) \equiv 0 \implies \dot{R}(t) = 0$ and will fall back into the same reasoning of S and I.

This means that, for the SIR model, the set

$$A = \{(S, I, R) \in \mathbb{R}^3_+\}$$

is positive invariant, i.e. the vector field along the boundary does not allow the trajectories to exit the domain ($S \geq 0, I \geq 0, R \geq 0$).

Now, by looking at the equations, we can gather some useful insights about the qualitative properties of the model:

System's equilibrium points and their stability
Solving the system

$$\begin{cases} 0 = -\beta SI \\ 0 = \beta SI - \gamma I = I \cdot (\beta S - \gamma) \\ 0 = \gamma I \end{cases}$$

gives that the equilibrium points[2] are all the pairs $(S, 0, R)$ $\forall S \geq 0$.
The relations in the system are not linear: to get a linear approximation of the system's behavior around the equilibria we have to find the Jacobian matrix of the state-space representation of the system with state-variables S, I and R:

$$\mathbf{J}(S, I, R) = \begin{pmatrix} -\beta I & -\beta S & 0 \\ \beta I & \beta S - \gamma & 0 \\ 0 & \gamma & 0 \end{pmatrix}$$

which, evaluated along the S axis, becomes

$$\mathbf{J}(S, 0, R) = \begin{pmatrix} 0 & -\beta S & 0 \\ 0 & \beta S - \gamma & 0 \\ 0 & \gamma & 0 \end{pmatrix}$$

with eigenvalues $\lambda_1 = \lambda_3 = 0$ and $\lambda_2 = \beta S - \gamma$.
Thus,

1. if $S > \frac{\gamma}{\beta}$, the equilibrium will be unstable;
2. If, on the other hand, $S \leq \frac{\gamma}{\beta}$, nothing can be said (because of the linearization we considered) other that the equilibrium will surely not be asymptotically stable but, at most, only simply stable[3].

Spreading of the disease: the role of r_0
We can first notice by looking at equation (2.2) that the derivative with respect to time of $S(t)$ is negative for all times, thus $S(t)$ is a monotonic decreasing function.
This allows us to write the following inequality:

$$S(t) \leq S_0, \quad \forall t. \tag{2.9}$$

Now, looking at the derivative of the infective population and substituting S_0 for $S(t)$, the disease will spread under the assumption that $\dot{I}(t) > 0$, giving the chain of inequalities:

[2] If we were to take into account vital dynamics, we would also find the so called "endemic equilibrium", which we will discuss in more detail later, in the section dedicated to the SIS model.
[3] We will show with a graphical analysis (figure 2.4) that it is, in fact, simply stable (it could also be proven with Lyapunov's direct method).

$$\frac{dI}{dt} = I \cdot \big(\beta S(t) - \gamma\big) \leq I \cdot (\beta S_0 - \gamma) > 0 \iff S_0 > \frac{\gamma}{\beta} = \frac{1}{q}, \tag{2.10}$$

where we defined

$$q = \frac{\beta}{\gamma} = \frac{\text{rate of } \textbf{increase} \text{ in infectives}}{\text{rate of } \textbf{decrease} \text{ in infectives}} = \text{“contact ratio”}.$$

By manipulating (2.10), dividing by γ and multiplying by β, we can create a new parameter:

$$\mathbf{r_0} = \frac{\beta S_0}{\gamma} = q \cdot S_0 = \text{“basic reproduction number”}. \tag{2.11}$$

This quantity represents the number of people that -on average- an infective person will transmit the disease to while they are infected.
What we could actually do is think of β and γ as explicitly depending on time, as they will change due to the precautions taken to prevent the spread of the infection; this way, we would get a time-dependent version of (2.11): $r(t)$.
Then, we would surely know that

$$\frac{\beta S(t)}{\gamma} = r(t) \leq r_0 = \frac{\beta S_0}{\gamma} \quad \forall t,$$

given what we said in (2.9).
Thus, r_0 is an upper-bound to the time-dependent basic reproduction number $r(t)$.
Now, (2.10) tells us that:

$$\begin{aligned} r_0 > 1 &\implies \text{the epidemic } \textit{will} \text{ start spreading.} \\ r(t) > 1 &\implies \text{the epidemic } \textit{is currently} \text{ spreading} \end{aligned}$$

For context, we will point out that, while the average value for seasonal flu is $r(t) \equiv r_0 \approx 1.3$ [7], on March 22nd, during the first days of the COVID-19 outbreak in Lombardy, it was estimated to be $r_0 \approx 4.9$ [8].

Epidemic curves
By dividing (2.2) by (2.3) we get:

$$\frac{dS}{dI} = \frac{\beta S}{\gamma - \beta S},$$

which, after separating variables (imposing $S \neq 0$ in order to divide), gives the differential relation:

$$\frac{\gamma - \beta S}{\beta S}\, dS = dI,$$

that can be directly integrated:

$$\int_{S_0}^{S(t)} \frac{\gamma}{\beta S} - 1 \, dS = \int_{I_0}^{I(t)} dI,$$

finally giving

$$\frac{\gamma}{\beta} \ln\big[S(t)\big] - S(t) = I(t) - I_0 - S_0 + \frac{\gamma}{\beta} \ln(S_0). \tag{2.12}$$

Equation (2.12) allows us to write $I(\cdot)$ as a function of S:

$$I(S) = \frac{\gamma}{\beta} \ln\left(\frac{S}{S_0}\right) - S + I_0 + S_0, \tag{2.13}$$

and thus plot the phase portrait of the trajectories in the $S - I$ plane without knowing the explicit dependence of $I(\cdot)$ nor of $S(\cdot)$ on time (the plot should be drawn in a 3-dimensional space, but we will omit R as its behavior passively follows from that of the other two variables):

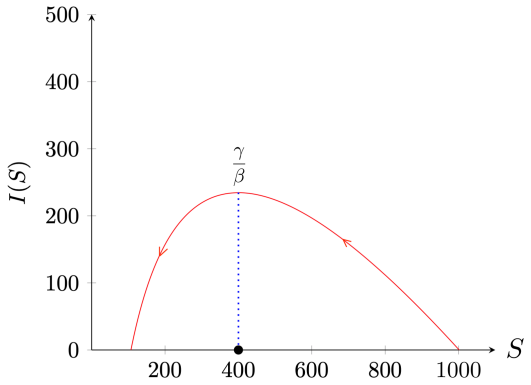


Figure 2.1: As t increases, the curve is travelled from right to left as $\frac{dS(t)}{dt} < 0 \ \forall t$. Here, we assumed $\frac{\gamma}{\beta} = 400$, an initial population of $K = S_0 = 1000$ and $I_0 = 1$.

From the picture we can see that the function $I(S)$ has a maximum at $S = \frac{\gamma}{\beta}$, which brings us to the next observation:

Maximum number of infectives $I_{\mathbf{MAX}}$
Even if it is clear by the graphical representation above, we can find the maximum of the function $I(S)$ analytically by studying the sign of the derivative:

$$\frac{dI(S)}{dS} = \frac{\gamma}{\beta S} - 1 > 0 \iff S < \frac{\gamma}{\beta} = \frac{1}{q}.$$

Thus, after plugging $S = \dfrac{\gamma}{\beta}$ into (2.13), we get:

$$I_{\text{MAX}} = S_0 + I_0 - \frac{1}{q}\left[1 + \ln(\underbrace{qS_0}_{r_0})\right].$$

This is what the function looks like:

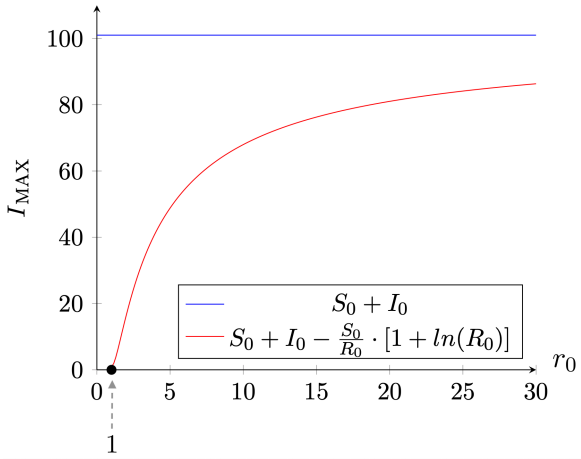


Figure 2.2: As r_0 increases, so does the number of maximum infectives. Notice how the plot only makes sense for $r_0 > 1$: if an infected is inserted in a population of susceptibles but $r_0 \leq 1$, the epidemic will immediately fade out and there will be no outbreak ($I_{MAX} = I_0$). We will discuss this eventuality in detail in a few moments.

Time evolution and first approximation
Figure (2.3) shows three epidemic curves on the S-I plane built by picking different initial conditions S_0 and I_0:

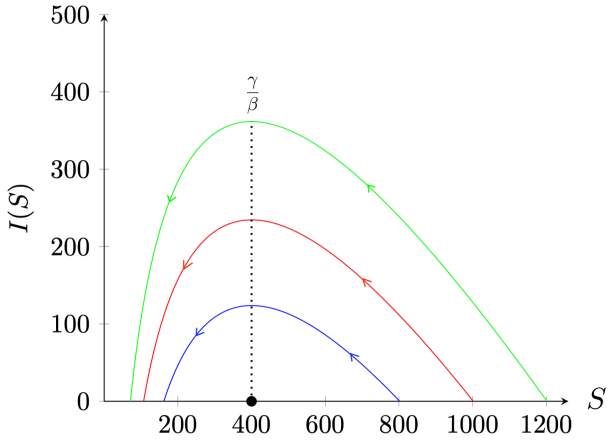


Figure 2.3: Blue curve: $\frac{\gamma}{\beta} = 400$, $S_0 = 800$, $I_0 = 1$; red curve: $\frac{\gamma}{\beta} = 400$, $S_0 = 1000$, $I_0 = 1$; green curve: $\frac{\gamma}{\beta} = 400$, $S_0 = 1200$, $I_0 = 1$;

Notice how, by multiplying both β and γ by some constant h, the model will keep the same family of curves. What will change is the velocity at which the trajectories are travelled: if $h > 1$, the epidemic will grow faster.
An explicit form of the evolution can be obtained when, during the first instants, $S_0 \simeq K > \frac{\gamma}{\beta}$:
equation (2.2) can be approximated as

$$\frac{dI}{dt} = \beta SI - \gamma I = (\beta S - \gamma)I \simeq (\beta K - \gamma)I = \gamma(r_0 - 1)I$$

and directly integrated:

$$\int_{I_0}^{I(t)} \frac{dI}{I} = \int_0^t \beta K - \gamma \, dt,$$

giving

$$I(t) = I_0 e^{(\beta K - \gamma)t} = I_0 e^{\gamma(r_0 - 1)t}, \tag{2.14}$$

which shows that the initial growing rate of an epidemic with $r_0 > 1$ is exponential.

To summarize what we found:

1. **Spread of the disease in relation to the initial population**
   The maximum number of infectives is always hit when the number of susceptibles reaches the threshold $\frac{\gamma}{\beta}$: if $S_0 = K$ and if we (unrealistically) assumed that γ and β stayed constant throughout the life span of the epidemic (that would mean that no measures were taken to limit the spread of the infection, the contact rate between individuals remained the same, and the pathogen itself did not biologically evolve),

   - if K were such that $K < \frac{\gamma}{\beta}$ (i.e. $r_0 < 1$), the insertion of a small initial number of infectives I_0 would cause their immediate decrease: the pair $\big(S(t), I(t)\big)$ would tend to the point $\big(S(\infty), 0\big)$ which would be the closest to $(K, 0)$ the smallest the perturbation I_0. That is, the equilibrium at $(K, 0)$ is stable.

   - If, on the opposite, $K > \frac{\gamma}{\beta}$ (i.e. $r_0 > 1$), a small number of infectives I_0 would be enough to trigger the spread of the disease until the susceptibles reached the threshold value $\frac{\gamma}{\beta}$. After that, the epidemic would slow down to eventually die out in $\big(S(\infty), 0\big)$. In this case the equilibrium is unstable.

Together, the two conditions above mean that when the initial population is smaller in number than the value $\frac{\gamma}{\beta}$, an initial trace of infection can be removed more quickly than it can spread to the susceptibles.

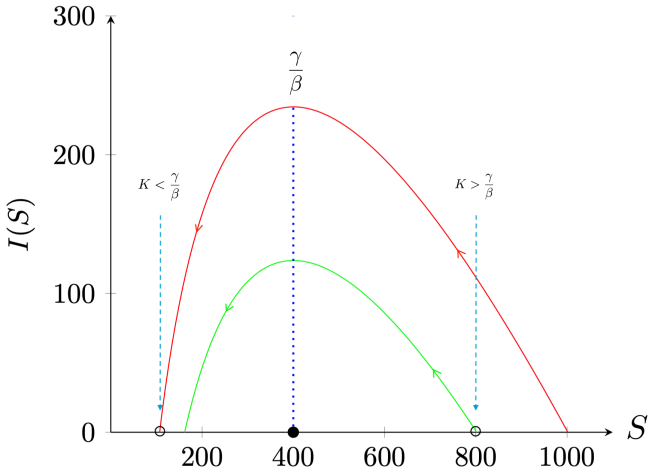


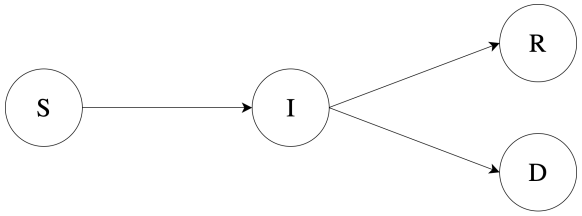
Figure 2.4: Behavior of the epidemic based on the starting population K.

2. **Escaped individuals**
   By looking at equation (2.13), it is clear that the curve $I(S)$ crosses the $I = 0$ axis only for positive values of S: the epidemic will eventually end due to the lack of infectives (too few to keep the spreading) rather than susceptibles.
   In other words, there is always a number of individuals who will escape the contagion.

2.2.1 Two modified versions of the SIR model

We will now present a brief overview of two variations of the model we have studied so far. We will not go into detail as the differences with the SIR are few and not of significant relevance to us.

SIRD Model



It is a very natural extension of the SIR, in which the "removed" compartment is in turn divided into the "recovered" and "deceased" compartments, and is thus described by the set of ODEs:

$$\begin{cases} \frac{dS}{dt} = -\beta SI & (2.15) \\ \frac{dI}{dt} = \beta SI - \gamma I - \delta I & (2.16) \\ \frac{dR}{dt} = \gamma I & (2.17) \\ \frac{dD}{dt} = \delta I & (2.18) \end{cases}$$

with initial conditions:

$$\begin{cases} S(0) = S_0 \\ I(0) = I_0 \\ R(0) = 0 \\ D(0) = 0 \end{cases}$$

For the $SIRD$, the "basic reproduction number" is defined as:

$$r_0 := \frac{\beta}{\gamma + \delta}.$$

We will later be using this model as a mathematical tool to run some computer-based simulations.

SEIR Model

For some diseases, when a susceptible comes in contact with an infective, they do not immediately become contagious themselves, but rather spend a period of time while they have contracted the infection but are not yet "fully" able to transmit it.
To model this scenario, we add a new compartment E representing these subjects.
As we said, while in the *exposed* compartment, individuals have lower "infective capacity", which brings us to assume that an exposed will, during the unit time dt, infect $\mathcal{E}\beta S$, with $0 < \mathcal{E} < 1$.
The set of ordinary differential equations that will define our model will then be:

$$\begin{cases} \frac{dS}{dt} = -\beta SI - \beta S\mathcal{E}E & (2.19) \\ \frac{dE}{dt} = \beta SI + \beta S\mathcal{E}E - \alpha E & (2.20) \\ \frac{dI}{dt} = \alpha E - \gamma I & (2.21) \\ \frac{dR}{dt} = \gamma I & (2.22) \end{cases}$$

where once again, assuming that the number of births and deaths unrelated to the disease is negligible, the following condition holds:

$$\frac{d}{dt}(S + E + I + R)(t) = 0,$$

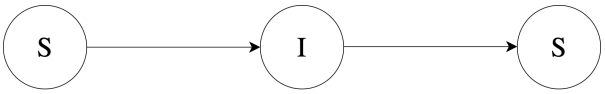
and thus

$$S(t) + E(t) + I(t) + R(t) = K \quad \forall t.$$

When talking about the SIR model, we defined r_0 as "the number of people that -on average- an infective person will transmit the disease to while they are infected".
To fit the idea in this new context, we need to think that an infected placed in a population of susceptibles will spend a certain time being exposed, and a second time being fully infected and contagious;
for this reason, we will define:

$$r_0 := \frac{\mathcal{E}K\beta}{\alpha} + \frac{K\beta}{\gamma}.$$

2.3 SIS Model



Unlike in the SIR model, healed individuals do not earn immunity upon recovery, but rather become susceptible again (they can not die), as is the case for some common infections like cold or influenza.

Key assumptions
Except for the property we have just mentioned, the hypothesis are identical to those of the SIR model:

1. The total population $N(t)$ remains constant during the outbreak of the epidemic:

$$N(t) = K \quad \forall t.$$

2. The rate at which the number of infectives I increases is constant and proportional to the number of contacts between infectives and susceptibles:

$$\beta\ (> 0)\ is\, constant,$$

$$\beta \propto number\, of\, contacts\, between\, I\, and\, S.$$

3. Infectives heal and become susceptibles again at a constant rate:

$$\gamma\ (> 0)\ is\, constant.$$

Differential equations
The equations that govern this model are:

$$\begin{cases} \dfrac{dS}{dt} = -\beta SI + \gamma I & (2.23) \\ \dfrac{dI}{dt} = \beta SI - \gamma I & (2.24) \end{cases}$$

Now, from the fact that the total population stays constant,

$$S(t) + I(t) = N(t) = K \quad \forall t, \tag{2.25}$$

and thus:

$$\frac{d}{dt}(S + I)(t) = 0.$$

Following the exact same line of reasoning used in the case of the SIR, it can be proven that the set

$$B = \{(S, I) \in \mathbb{R}^2_+\}$$

is invariant for the model, thus the only solutions we will consider to be valid will be the pairs with a positive number of susceptibles and infected.

Equilibrium points

After imposing

$$\begin{cases} 0 = -\beta SI + \gamma I \\ 0 = +\beta SI - \gamma I \end{cases}$$

we get the equilibria

$$(S, 0) \quad \text{and} \quad \left(\frac{\gamma}{\beta}, K - \frac{\gamma}{\beta}\right). \tag{2.26}$$

This latter is referred to as "endemic equilibrium" and describes a situation in which susceptibles and infected co-exist together[4].
We will now use Lyapunov's direct method to first prove its simple, and later asymptotic, stability.

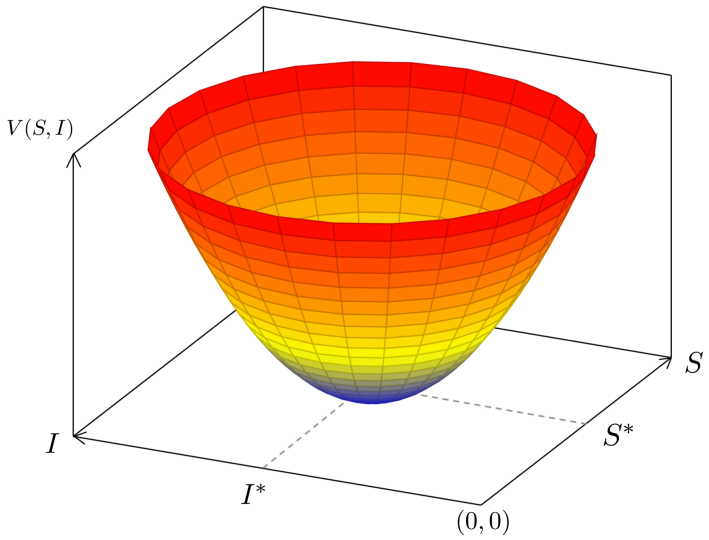
Proposition. *The endemic equilibrium is asymptotically stable.*

Simple stability. First, let E^* be the point $E^* = (S^*, I^*) = \left(\frac{\gamma}{\beta}, K - \frac{\gamma}{\beta}\right)$.

Let us start by considering a "typical" quadratic Lyapunov function:

$$V(S, I) = \frac{1}{2}\left(S - S^*\right)^2 + \frac{1}{2}\left(I - I^*\right)^2, \tag{2.27}$$

that is a simple elliptic paraboloid defined over the positive quadrant of the $S - I$ plane:



We have that:

- $V(S, I) > 0 \quad \forall\, (S, I) > 0$;
- $V\left(S^*, I^*\right) = 0$, thus the equilibrium is the point in which the function has its global minimum.

To show that V is monotonically decreasing, we first compute its total derivative with respect to time:

$$\begin{aligned} \frac{d}{dt} V\left(S(t), I(t)\right) &= \nabla V(S, I) \cdot \left(\dot{S(t)}, \dot{I(t)}\right) \\ &= \left(S - S^*\right)\left(\gamma I - \beta SI\right) + \left(I - I^*\right)\left(\beta SI - \gamma I\right). \end{aligned}$$

[4] We will later show that, in the case of a starting population of $S_0 = K$ individuals, this state will only be "reasonably" reached when $r_0 > 1$.

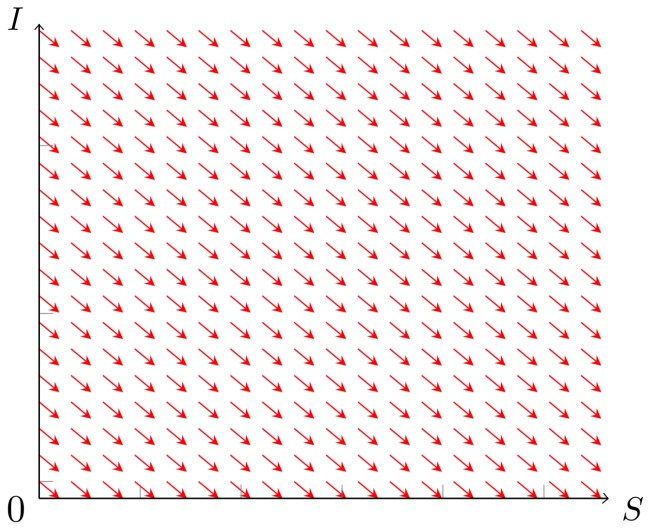
Now, by recalling that $S^* = \dfrac{\gamma}{\beta}$, we can obtain $\gamma = \beta S^*$; also we can use (2.25) to write $I(t) = K - S(t)$ and $I^* = K - S^*$.
The derivative thus becomes (we will omit the time dependence of $S(\cdot)$ and $I(\cdot)$):

$$\begin{aligned}
\dot{V}\left(S(t), I(t)\right) &= (S - S^*)\left[\beta S^*(K - S) - \beta S(K - S)\right] + \left[K - S - (K - S^*)\right]\left[\beta S(K - S) - \beta S^*(K - S)\right] \\
&= \left[(S - S^*) \cdot \beta(K - S) \cdot (S^* - S)\right] + \left[(S^* - S) \cdot \beta(K - S) \cdot (S - S^*)\right] \\
&= -\beta(K - S)(S - S^*)^2 - \beta(K - S)(S - S^*)^2 \\
&= -2\beta(K - S)(S - S^*)^2 \\
&= -2\beta I(S - S^*)^2 \\
&\leq 0 \quad \forall S,\ \forall I.
\end{aligned}$$

□

Unfortunately, given the fact that the point E^* represents a "family" of equilibria -each one only reachable by a particular solution starting with some specific initial conditions- there is nothing we can do to prove the asymptotic stability by following this track.
What we can and will do, instead, is to make an observation about the geometry of the problem to gain insight about the shape of the solutions; we will then prove that, by limiting ourselves to one of the "leaves" of the $S - I$ plane picked by fixing the value of K, the trajectories will asymptotically approach E^*:

Asymptotic stability. The model is described by a set of two differential equations, which "spatially" put us on a plane.
What we can notice, though, is that, under the assumption mentioned above that the population stays constant, we have that $S(t) = K - I(t)$.
In fact, by dividing (2.24) by (2.23) we get $\dfrac{dI}{dS} = -1$, which generates such slope field:



Indeed, the trajectories will look like segments with edges $(K, 0)$ and $(0, K)$. This allows us to "shrink" the problem to one dimension: we can write S as a function of I (or vice versa).
Because of this, we can build a Lyapunov function which is only dependent on I, for example

$$V(I(t)) = \frac{1}{2}\left(I - I^*\right)^2,$$

which has derivative

$$\begin{aligned}
\dot{V}\left(I\left(t\right)\right) &= \frac{dV(I)}{dI} \cdot \frac{dI(t)}{dt} \\
&= (I - I^*) \cdot (\beta SI - \gamma I) \\
&= (I - I^*) \cdot (\beta SI - \beta S^* I) \\
&= (I - I^*) \cdot \left(\beta \left(K - I\right) I - \beta \left(K - I^*\right) I\right) \\
&= (I - I^*) \cdot \left(\beta I \left(I^* - I\right)\right) \\
&= -\beta I (I - I^*)^2 \\
&< 0 \quad \forall I \neq 0, \, \forall I \neq I^*
\end{aligned}$$

where, once again, we used the fact that $\gamma = \beta S^*$. □

Qualitative analysis
We will now verify that the results that we will find by directly solving the equations will confirm what we have just proved about the asymptotic stability (thus, the attractiveness) of the endemic equilibrium.

Let us assume to start with a population only constituted by susceptibles, where $S_0 = K$.
The model will be descripted by a logistic equation:

$$\frac{dI}{dt} = I(\beta K - \gamma) - \beta I^2, \tag{2.28}$$

where we can put $c := \beta K - \gamma$ and define $\widetilde{K} := c/\beta = K - \gamma/\beta$ to be the "carrying capacity", i.e. the maximum possible size, imposed by the limited resources of the environment, reachable by the population. If we once again define $\mathbf{r_0} := \beta/\gamma =$ *"basic reproduction number"*, we can distinguish two different cases:

1. $r_0 = 1 \, (\text{i.e.} \, c = 0) \implies \dfrac{dI}{dt} = -\beta I^2$, which can be solved by separation of variables:

$$\frac{dI}{I^2} = -\beta \, dt$$

and then integration:

$$\int_{I_0}^{I(t)} \frac{1}{I^2} \, dI = -\beta \int_0^t dt,$$

giving

$$I(t) = \frac{I_0}{1 + \beta I_0 t}.$$

Thus the number of infectives decreases like an hyperbole and the number of susceptibles $S(t) = K - I(t)$ approaches that of the total population.
Formally,

$$\lim_{t \to \infty} S(t) = K \quad \text{and} \quad \lim_{t \to \infty} I(t) = 0.$$

This makes sense as the equilibrium with no infective individuals is the other equilibrium we found earlier in (2.26) and is a sub-case of the endemic one (when $\frac{\gamma}{\beta} = K$). It is, however, trivial and not of particular interest.

2. $r_0 \neq 1 \implies$ the solution of the logistic equation will have the form

$$I(t) = \frac{I_0 \widetilde{K} e^{ct}}{\widetilde{K} - I_0(1 - e^{ct})} \tag{2.29}$$

and therefore:

- if $r_0 < 1$ (i.e. $c < 0$), for (2.24) $I(t)$ will have negative derivative and thus will be decreasing for each t, while for (2.25):

$$\lim_{t\to\infty} S(t) = \widetilde{K} \quad \text{and} \quad \lim_{t\to\infty} I(t) = 0.$$

This second result makes "formal" sense but is not physically possible: if c is negative, so is $\widetilde{K}$; this means that this equilibrium is not reachable in practice as, of course, the number of susceptibles can not be negative.
What we can conclude, anyway, is that, if $r_0 \leq 1$, the disease will not spread.

- if $r_0 > 1$ (i.e. $c > 0$) we get

$$\lim_{t\to\infty} I(t) = \widetilde{K} \quad \text{and} \quad \lim_{t\to\infty} S(t) = \frac{\gamma}{\beta}. \tag{2.30}$$

This last case is the only one to make practical sense: in the scenario in which the disease explodes ($r_0 > 1$), it will eventually converge to the endemic equilibrium, which is what we proved earlier with Lyapunov's direct method.

Chapter 3

Controlling an epidemic

3.1 Flattening the curve: control variables

From the mathematical models we have discussed so far, it is clear that the two parameters β and γ play a central role in the progress of epidemics. We will now give a less intuitive, more formal definition of what they are and what they mean:

3.1.1 The role of β

We defined β to be the "transmission rate constant", that is the number of an infective's daily "contagious" contacts.
More accurately,

$$\beta = \tau \cdot c\,,$$

where

$$\tau = \text{probability of infection given a contact between a susceptible and an infective,}$$

and

$$c = \text{average daily rate of contacts between susceptibles and infectives.}$$

Of course, the probability τ of infection may be very hard to control as it is usually directly correlated to the virulence of the pathogen; on the other hand, the parameter c can be drastically reduced by applying contagion-preventing measures and social distancing policies.

3.1.2 The role of γ

Until this point, we have assumed that γ is the "removal rate", i.e. the rate at which infectives recover or die (or, in the case of the SIS model, become susceptibles again). We will now give a probabilistic interpretation of the this quantity.
The term $\gamma\, dt$ can be seen as the probability that an individual that is infective at time t leaves the infectives compartment during the interval $[t, t + dt]$.
Let's now denote with $p(t)$ the probability that a person that was infective at $t = 0$ is still contagious at instant t.
To find an explicit expression of $p(t)$ we can follow this line of reasoning: we know from basic probability theory that, given two independent events A and B,

$$P(A \cap B) = P(A) \cdot P(B).$$

This means that, under the assumption that the event of being infective at time t is independent from the event of being removed during the interval $[t, t + dt]$, an individual infectious at t has probability to be infective at time $t + dt$:

$$p(t + dt) = p(t)(1 - \gamma dt),$$

from which follows that

$$\frac{dp}{dt} = -\gamma p(t),$$

which has solution $p(t) = e^{-\gamma t}$.
So, the probability for an infective to be removed at some instant in the interval $[0, t]$ will be the cumulative distribution $1 - e^{-\gamma t}$, to which corresponds the density function $\gamma e^{-\gamma t}$.
Thus, $\left(\gamma e^{-\gamma t} dt\right)$ is the probability of someone being contagious at time $t = 0$ (and still infectious at time t) to be removed during the interval $[t, t + dt]$; and the mean value of the instant of transition to the *removed* compartment, that is the mean time of permanence in the *infectives*, is

$$\int_0^{+\infty} t\gamma e^{-\gamma t} dt = \frac{1}{\gamma}.$$

The expression we derived is useful in formalizing the control-based aspect of the problem:
by increasing γ, the infected individual will spend an average shorter time being infectious and this will lower the probability of infecting others.
Increasing γ means improving healing strategies: better drugs, shorter hospitalization periods and more overall efficient therapy techniques.

3.2 The COVID-19 case study

Predicting the behavior of a spreading disease is, given the complexity of the phenomenon, a very hard task.
First of all, if we wanted to take into account all the factors that come into play, it would be necessary to include some probabilistic tools to consider the stochastic nature of human interactions, which can also be deeply dependent both on space and time.
Furthermore, the biggest weakness of our model would is that the parameters that govern the equations are not time-sensitive: all the ratios we have introduced are not very useful if they are not allowed to vary over time. The way their dependency on time is embedded to the models by epidemiologists is through the analysis of statistical data which is fed to algorithms that perform regression for the fitting and validation of the model.
What we can and will do with our limited set of tools is running a very simple simulation -set in Lombardy over a period of two years- with fixed parameters which will be, when possible, recovered from official data; this way, we will be able to see what the predictions for the epidemic looked like in the very first stages of the outbreak ($\sim$ early March 2020).
Also, if we will not focus on the "numerical values" of the curves per se, but rather on their shape, we will see that they look very similar to the ones made available by the Italian government on official platforms [12].

3.2.1 Software simulations

As we said, softwares can be used to run simulations where the model is solved by means of numeric integration. We will considered a $SIRD$ model, implemented in Matlab[1], with the following parameters:

- $r_0 = 4.9$, as it was estimated to be in Lombardy in March of 2020 [8];
- $\delta = 0.02$, as it was estimated to be in Lombardy in March of 2020 [11];
- $I_0 = 100$, chosen arbitrarily among a reasonable, realistic range of values;

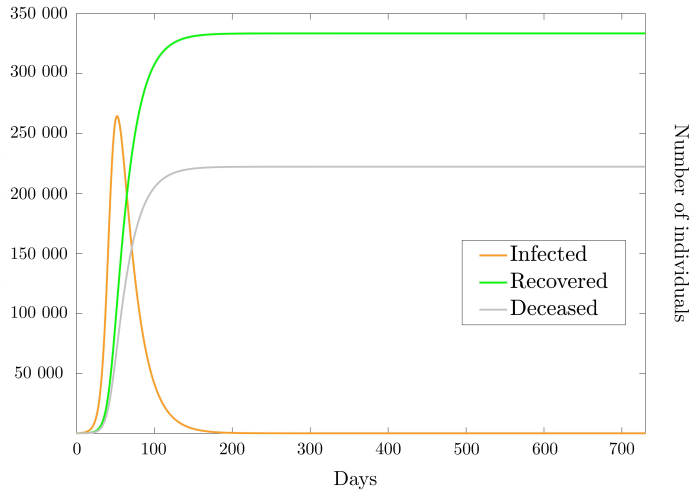
One very important thing to realize is that the model heavily depends on the initial conditions which determine both the amplitude and the time location of the peak in the number of infected individuals.
In particular, the value of S_0 is very often unknown to the epidemiologists, and in real simulations approximating S_0 with the total size of the population living in a geographical region may a be a gross

[1] see the *Appendix* for the full code.

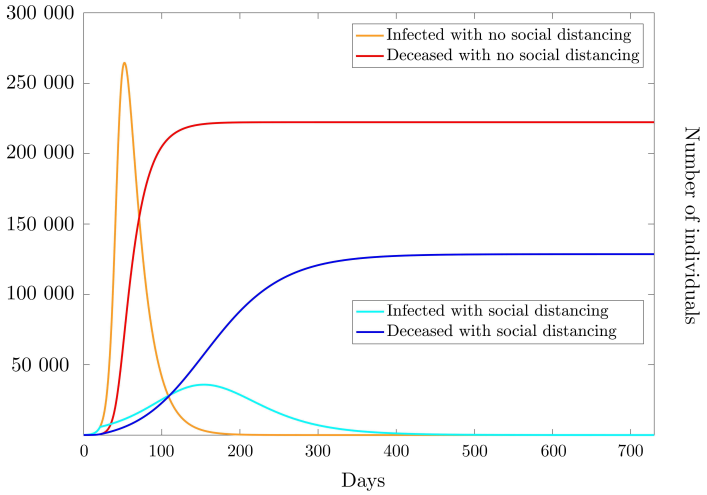
and imprecise over-estimation.
We used the results from the work by Calafiore et al. [11] and supposed, for Lombardy, to be

$$S_0 \simeq 0.05 \cdot N \simeq 560\,000.$$

This are the curves that we got after running the simulation:



By looking at the graph, we can see that without the introduction of any measures to prevent the spread of the disease, the damage would be drastic: in a region with ∼10 000 000 of people, about 220 000 would die (around 2%).
We also implemented the scenario of the introduction, by the government, of social-distancing measures and mask-wearing obligations; below is the comparison between the number of total infections/deaths in the case of no preventive measures taken and in the case of implementation -with a delay of three weeks from the outbreak[2]- of regulations able to reduce by 70% the rate of infection β:



From the figure it is clear how social-distancing policies not only almost halve the number of casualties (∼100 000 less deceased), but do actually have an even deeper impact on the number of infected: this is what experts mean when talking about "flattening the curve".
From the 21st day, the new infection curve (in light blue) starts to draw a very different picture from the old one (in orange): the peak of active cases is reduced and delayed, allowing more time for the healthcare capacity to increase and better cope with patient load; indeed, as we said, the biggest threat societies face during an epidemic is the risk of the healthcare system collapsing on itself.

[2]More specifically, we mean three weeks after the first 100 cases of infection were reported.

Conclusions

We have seen how the mathematical tools help us with the hard task of modeling and forecasting the spread of infectious diseases in epidemiology.
We have also acknowledged how, just like it happens in physics, with the effort of describing a deeply complex system comes the trade-off between the accuracy of the description and the complexity of the model used.
In the specific case of our work on COVID-19, we decided to settle for a basic model only able to describe a simplified version of the problem but that could, however, still exhibit some of the crucial features of the behavior of the epidemic.
With all of this in mind, we can see that the simulations we ran have drawn a very clear picture of the situation: until the introduction of a widely-available vaccine, the only realistically effective measure to protect the community from mass-infection, the healthcare system from collapsing and to minimize the number of casualties is the adoption of strict measures to introduce social distancing and compulsory mask-wearing; even partially-alternative solutions, such as those proposed by the U.K [13] and Sweden [14], which aimed at achieving herd immunity almost entirely relying on individual responsibility, do not seem to have worked so far.

Appendix

Matlab code

```
N = 560000; I0 = 100;
beta = 0.245/N; gamma = 0.03; delta = 0.02;
T = 730; dt = 1/24;
delay_soc_dist = 21; eff_soc_dist = 0;
[S,I,R,D] = sird_model(beta,gamma,delta,N,I0,T,dt,delay_soc_dist,eff_soc_dist);
tt = 0:dt:T-dt;
figure(); %first figure (with eff_soc_dist = 0;
plot(tt,I,'color',[.99 .62 .15],'LineWidth',2); hold on;
plot(tt,R,'g','LineWidth',2);hold on;
plot(tt,D,'color', [.76 .76 .76],'LineWidth',2); hold on;
%axis properties:
xlim([0 730]); xlabel('Days'); ylabel('Number of individuals');
legend('Infected','Recovered','Deceased');
figure(); %second figure
plot(tt,I,'color',[.99 .62 .15],'LineWidth',2); hold on;
plot(tt,D,'r','LineWidth',2); hold on; %infections and deaths with eff_soc_dist = 0
eff_soc_dist = 0.7;
[S,I,R,D] = sird_model(beta,gamma,delta,N,I0,T,dt,delay_soc_dist,eff_soc_dist);
plot(tt,I,'c',tt,D,'b','LineWidth',2);
%axis properties:
xlim([0 730]); legend('Infected with no social distancing','Deceased with no social ...
    distancing','Infected with social distancing', 'Deceased with social distancing');

function z = step(tt,dt,delay_soc_dist) %step function to implement social distancing
    if (tt*dt ≥ delay_soc_dist)
        z = 1;
    else
        z = 0;
    end
end

function [S,I,R,D] = sird_model(beta,gamma,delta,N,I0,T,dt,delay_soc_dist,eff_soc_dist)
    S = zeros(1,T/dt);
    S(1) = N;
    I = zeros(1,T/dt);
    I(1) = I0;
    R = zeros(1,T/dt);
    D = zeros(1,T/dt);

    for tt = 1:(T/dt)-1 %numeric integration
        dS = (-(1-eff_soc_dist*step(tt,dt,delay_soc_dist))*beta*I(tt)*S(tt)) * dt;
        dI = ((1-eff_soc_dist*step(tt,dt,delay_soc_dist))*beta*I(tt)*S(tt) - ...
            gamma*I(tt)- delta*I(tt)) * dt;
        dR = (gamma*I(tt)) * dt;
        dD = (delta*I(tt))*dt;

        S(tt+1) = S(tt) + dS;
        I(tt+1) = I(tt) + dI;
        R(tt+1) = R(tt) + dR;
        D(tt+1) = D(tt) + dD;
    end
end
```

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