

Modelação matemática e controlo ótimo

Cristiana J. Silva

CIDMA - Centro de Investigação e Desenvolvimento em Matemática e Aplicações,
Departamento de Matemática, Universidade de Aveiro
cjoasilva@ua.pt

Laboratórios de Computação e Visualização Científica
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Apresentação

- **Docente do módulo:** Cristiana João Soares da Silva
- **Contacto:** cjoasilva@ua.pt
- **Página pessoal:**
<https://sites.google.com/site/cristianajssilva/home>
- **Membro:** **Grupo de Sistemas e Controlo**
do
Centro de Investigação e Desenvolvimento em Matemática e Aplicações (CIDMA)
<https://www.cidma.ua.pt/>
Departamento de Matemática

Objetivos:

- Usar a modelação matemática na compreensão de alguns dos mecanismos da transmissão de doenças infecciosas.
- Diferentes modelos matemáticos têm sido usados para tentar prever a evolução do número de pessoas infetadas com o *novo coronavírus* (SARS-CoV-2). Os modelos são apenas uma tentativa de aproximação da realidade (muito complexa).
- Neste módulo iremos estudar modelos matemáticos que permitem descrever casos reais de surtos epidémicos.
- Estes modelos serão a base para a formulação de problemas de controlo ótimo, cujo o objetivo é propor medidas que permitam erradicar epidemias em contextos de escassos recursos.

Mathematical modelling of infectious diseases

Mathematical models have become important tools in analyzing the spread and control of infectious diseases.

Mathematical models are used in comparing, planning, implementing, evaluating, and optimizing various detection, prevention, therapy, and control programs.



H. W. Hethcote, *The mathematics of infectious diseases*, Society for Industrial and Applied Mathematics, 42 (2000), 599–653.

1^o mathematical model for infectious diseases

- In 1760 Daniel Bernoulli proposed a mathematical model for the transmission of smallpox.
- The main objective of Bernoulli was to calculate the gain in life expectancy at birth if smallpox were to be eliminated as a cause of death.

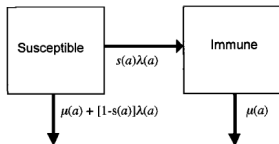


K. Dietz, J.A.P. Heesterbeek, *Daniel Bernoulli's epidemiological model revisited*, Mathematical Biosciences 180 (2002), 1-21.

<http://www.medicine.mcgill.ca/epidemiology/hanley/bios601/competingRisks/DanielBernoulli.pdf>



(Daniel Bernoulli (1700–1782))



Model Bernoulli

Bernoulli was born on 8 February (29 January, Julian Calendar) 1700 in Groningen, the Netherlands as the second son of Johann Bernoulli who was professor of mathematics there. In 1705 the family returned to Basel where Daniel's father took up the chair of his elder brother Jacob. Daniel also wanted to become a mathematician, but his father urged him to take up a commercial apprenticeship. After this failed, Daniel Bernoulli studied medicine in Heidelberg and Strasbourg and graduated in 1721 at the University of Basel with a dissertation entitled *De respiratione* on the mechanics of breathing. After some years in Venice where he studied practical medicine and published his *Mathematical exercises*, he got an offer together with his elder brother Nikolaus to take up positions at the St. Petersburg Academy in 1725. In 1727 began a very productive collaboration with Leonhard Euler. Daniel Bernoulli applied several times for a position in Basel but was unsuccessful because the drawing of lots went against him. Eventually he succeeded in 1733. He first became professor of anatomy and botany and in 1743 took on responsibility for teaching physiology instead of botany and in 1750 he became in addition professor of physics. He was never married and stayed in Basel until his death on 17 March 1782. His major achievements are associated with hydrodynamics and an anticipation of the kinetic theory of gases. He won the prize of the Paris Academy of Sciences ten times with contributions to a wide variety of topics, some of them dealing with marine technology. Sheynin [15] summarizes his work on probability: “... Bernoulli was the first to use systematically differential equations for deducing a number of formulae, one of the first to raise the problem of testing statistical hypotheses ...”. On the occasion of his 300th birthday, the University of Basel organized a special exhibit. He is considered to be one of the greatest scientists of the 18th century.

A THOUSAND AND ONE EPIDEMIC MODELS

HERBERT W. HETHCOTE

*Department of Mathematics
University of Iowa
Iowa City, IA 52242 U.S.A.*

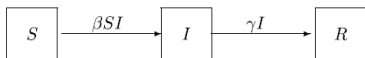
INTRODUCTION

Mathematical models have become important tools in analyzing the spread and control of infectious diseases. Although chronic diseases such as cancer and heart disease receive more attention in developed countries, infectious diseases are the most important causes of suffering and mortality in developing countries. Recently, the human immunodeficiency virus (HIV), which is the etiological agent for acquired immunodeficiency syndrome (AIDS), has become an important sexually-transmitted disease throughout the world. Tuberculosis is again becoming a problem because drug-resistant strains have evolved. Understanding the transmission characteristics of infectious diseases in communities, regions and countries can lead to better approaches to decreasing the transmission of these diseases. Mathematical models are useful in building and testing theories, and in comparing, planning, implementing and evaluating various detection, prevention, therapy and control programs. See Hethcote and Van Ark [30] for a discussion of the purposes and limitations of epidemiological modeling.

Compartmental model: SIR

Firstly proposed by McKendrick (1876-1943) and Kermack (1898-1970) in *Contributions to the mathematical theory of epidemics*, 1927.

<https://mathworld.wolfram.com/Kermack-McKendrickModel.html>



- S : susceptible individuals;
- I : infected/infectious individuals;
- R : recovered individuals;
- β : transmission coefficient;
- γ : recovery coefficient.

Assumption: the infected individuals recover from the infection and gain permanent immunity.

Compartmental model: SIR

Assumption:

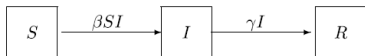
- homogeneous population;
- constant population (no births, deaths, emigration, immigration, etc);
- each individual belongs to only one of the compartments S , I , or R .

The variables $S(t)$, $I(t)$ and $R(t)$ represent the number of individuals in each compartment at time $t \in \mathbb{R}_+^0$.

The SIR model is dynamic!

Compartmental model: SIR - dynamical model

The number of individuals in each class changes over time (but the total population remains constant $N = S(t) + I(t) + R(t)$).



- the number of new infections is given by $\beta S(t)I(t)$;
- the number of removed/recovered individuals from the compartment I is $\gamma I(t)$, $t \in \mathbb{R}_0^+$.

The removed/recovered individuals gain permanent immunity.

SIR - system of ordinary differential equations

$$\begin{cases} \frac{dS(t)}{dt} = -\beta I(t)S(t) \\ \frac{dI(t)}{dt} = \beta I(t)S(t) - \gamma I(t) \\ \frac{dR(t)}{dt} = \gamma I(t) \end{cases} \quad (1)$$

$$N = S(t) + I(t) + R(t)$$

$$\frac{dN}{dt} = \frac{dS(t)}{dt} + \frac{dI(t)}{dt} + \frac{dR(t)}{dt} = 0 \Leftrightarrow N = \text{constant}.$$

SIR - numerical solution using MATLAB

To solve, numerically, the SIR system (1) we need to set values for:

- final time T of the simulation $[0, T]$, with $T \in \mathbb{R}_0^+$;
- initial values of the variables $S(0) > 0$, $I(0) > 0$, $R(0) \geq 0$;
- parameter values β and γ , with $\beta, \gamma \in \mathbb{R}_+^0$.

Consider:

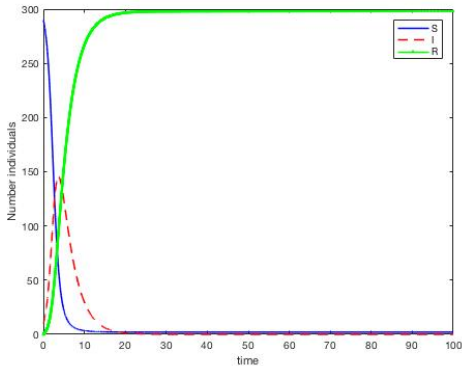
- $T = 100$
- $S_0 = S(0) = 290$; $I_0 = I(0) = 10$; $R_0 = R(0) = 0$;
- $\beta = 0.0055$ and $\gamma = 0.33$.

SIR - MATLAB code

Matlab file *simulation-SIR.m*

```
Editor - /Users/cjoaosilva/Dropbox/1CristianaPosDoc/Investigadoc
simulation_SIR.m  x  +
1  function simulation
2
3      clear all ; close all ; clc ; format short ;
4
5      global beta gamma;
6
7      % - parameters ---
8      beta = 0.0055;
9      gamma = 0.33;
10
11
12      % - final time ---
13      T = 100;
14
15      % -- initial conditions --
16
17      S0 = 290;
18      I0 = 10;
19      R0 = 0;
20
21      x0 = [S0; I0; R0];
22
23      % -- solve system of ODE's ----
24
25      options = odeset('AbsTol',1e-12,'RelTol',1e-12) ;
26      [t, z] = ode45(@sys, [0 T], x0, options);
27
28
29
30
31      % -- solve system of ODE's ----
32
33      options = odeset('AbsTol',1e-12,'RelTol',1e-12) ;
34      [t, z] = ode45(@sys, [0 T], x0, options);
35
36
37      % ----- figures -----
38
39      figure;
40      plot(t, z(:, 1), '-b', t, z(:, 2), '--r', t, z(:, 3), '-g', 'LineWidth',1.5);
41      xlabel('time'); ylabel('Number individuals');
42      legend('S', 'I', 'R')
43
44
45
46
47      % -- System SIR -----
48
49      function zdot=sys(t,z)
50
51      global beta gamma;
52
53      % x = [S=x1; I=x2; R=x3];
54
55      x1=z(1); x2=z(2); x3=z(3);
56
57      zdot = [ - beta.*x1.*x2
58              beta.*x1.*x2 - gamma.*x2
59              gamma.*x2 ] ; % sistema de ode's
```

SIR - MATLAB figure



Norman Bailey's SIR model



N. T. J. Bailey, *The mathematical theory of infectious diseases and its applications*, Hafner Press [Macmillan Publishing Co., Inc.] New York, second ed., 1975.

Assume: the total number of contacts that a susceptible individual could get in contact with, is not the individuals of all three groups but $S + I$.

$$\begin{cases} \frac{dS(t)}{dt} = -\frac{\beta I(t)S(t)}{S(t) + I(t)} \\ \frac{dI(t)}{dt} = \frac{\beta I(t)S(t)}{S(t) + I(t)} - \gamma I(t) \\ \frac{dR(t)}{dt} = \gamma I(t) \end{cases} \quad (2)$$

Norman Bailey's SIR model - analytical solution

Assuming $S, I > 0$, the model (2) is solved by rewriting the first two equations as

$$\begin{cases} \frac{S'}{S} = -\frac{\beta I}{S+I} \\ \frac{I'}{I} = \frac{\beta S}{S+I} - \gamma \end{cases} \quad \text{where } S' \text{ denotes } \frac{dS}{dt}.$$

Subtracting these equations yields

$$\frac{S'}{S} - \frac{I'}{I} = -b + c, \quad \text{i.e.} \quad \frac{I'}{I} = \frac{S'}{S} + b - c.$$

which is equivalent to $(\ln I)' = (\ln S)' + b - c$.

Integrating both sides and taking the exponential, one gets

$$I = S k e^{(b-c)(t-t_0)}, \quad \text{where } k = \frac{I_0}{S_0}.$$



M. Bohner, S. Streipert, D. F.M.Torres, *Exact solution to a dynamic SIR model*, Nonlinear Analysis: Hybrid Systems Volume 32, May 2019, Pages 228-238.

<https://arxiv.org/abs/1812.09759>

Compartmental models with vital dynamics

Consider:

- recruitment rate, Λ , describing, for example, births or immigration;
- natural death rate μ ;
- disease induced death rate d .

Two cases:

- constant total population - assume $\Lambda = \mu$ and $d = 0$;
- variable total population - assume $\Lambda \neq \mu$, $d \geq 0$.

Mathematical model for HIV/AIDS - SICA model

Divide the total population N in:

↗ **S**: susceptible;

↗ **I**: HIV-infected individuals with no clinical symptoms of AIDS;

→ **C**: HIV-infected individuals under treatment for HIV infection;

↘ **A**: HIV-infected individuals with AIDS clinical symptoms.

$$\begin{cases} \dot{S}(t) = \Lambda - \lambda(t)S(t) - \mu S(t), \\ \dot{I}(t) = \lambda(t)S(t) - (\rho + \phi + \mu)I(t) + \alpha A(t) + \omega C(t), \\ \dot{C}(t) = \phi I(t) - (\omega + \mu)C(t), \\ \dot{A}(t) = \rho I(t) - (\alpha + \mu + d)A(t), \end{cases}$$

where

$$N(t) = S(t) + I(t) + A(t) + C(t)$$

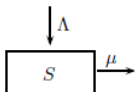
and

$$\lambda(t) = \frac{\beta}{N(t)} (I(t) + \eta_C C(t) + \eta_A A(t)).$$

SICA model

The susceptible population is increased by the recruitment of individuals (assumed susceptible) into the population, at a rate Λ .

All individuals suffer from natural death, at a constant rate μ .



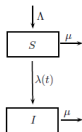
$$\begin{cases} \dot{S}(t) = \Lambda - \mu S(t), \\ \dot{I}(t) = -\mu I(t) \\ \dot{C}(t) = -\mu C(t), \\ \dot{A}(t) = -\mu A(t), \end{cases}$$

SICA model

Susceptible individuals acquire HIV infection, following effective contact with people infected with HIV at a rate λ , given by

$$\lambda(t) = \frac{\beta}{N(t)} (I(t) + \eta_C C(t) + \eta_A A(t)),$$

where β is the effective contact rate for HIV transmission.



$$\begin{cases} \dot{S}(t) = \Lambda - \lambda(t)S(t) - \mu S(t), \\ \dot{I}(t) = \lambda(t)S(t) - \mu I(t) \\ \dot{C}(t) = -\mu C(t), \\ \dot{A}(t) = -\mu A(t), \end{cases}$$

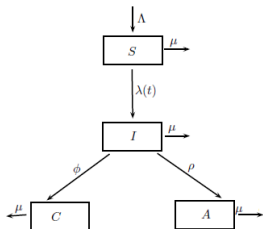
The modification parameters:

- $\eta_A \geq 1$ - individuals with AIDS symptoms are more infectious than HIV-infected individuals (pre-AIDS);
- $\eta_C \leq 1$ - partial restoration of immune function of individuals with HIV infection that use correctly ART.

SICA model

HIV-infected individuals (with no AIDS symptoms) progress:

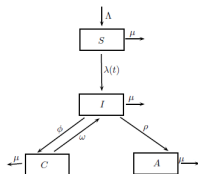
- to the AIDS class A at a rate ρ ;
- to the class of individuals with HIV infection under treatment C at a rate ϕ .



$$\begin{cases} \dot{S}(t) = \Lambda - \lambda(t)S(t) - \mu S(t), \\ \dot{I}(t) = \lambda(t)S(t) - \rho I(t) - \phi I(t) - \mu I(t) \\ \dot{C}(t) = \phi I(t) - \mu C(t), \\ \dot{A}(t) = \rho I(t) - \mu A(t), \end{cases}$$

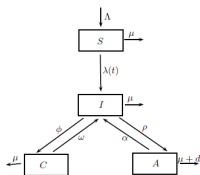
SICA model

Individuals in the class C leave to the class I at a rate ω .



$$\begin{cases} \dot{S}(t) = \Lambda - \lambda(t)S(t) - \mu S(t), \\ \dot{I}(t) = \lambda(t)S(t) + \omega C(t) - (\rho + \phi I(t) + \mu)I(t) \\ \dot{C}(t) = \phi I(t) - \omega C(t) - \mu C(t), \\ \dot{A}(t) = \rho I(t) - \mu A(t), \end{cases}$$

HIV-infected individuals with AIDS symptoms are treated for HIV at the rate α and suffer induced death at a rate d .



$$\begin{cases} \dot{S}(t) = \Lambda - \lambda(t)S(t) - \mu S(t), \\ \dot{I}(t) = \lambda(t)S(t) - (\rho + \phi + \mu)I(t) + \alpha A(t) + \omega C(t), \\ \dot{C}(t) = \phi I(t) - (\omega + \mu)C(t), \\ \dot{A}(t) = \rho I(t) - (\alpha + \mu + d)A(t), \end{cases}$$

SICA model - basic reproduction number R_0

R_0 : the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection.



C. Fraser, C. A. Donnelly, S. Cauchemez; et al. *Pandemic Potential of a Strain of Influenza A (H1N1): Early Findings*, Science. 324 (5934): 1557–1561 (2009).

<https://science.sciencemag.org/content/324/5934/1557>

Basic reproduction number of the SICA model:

$$R_0 = \frac{\beta (\xi_2 (\xi_1 + \rho \eta_A) + \eta_C \phi \xi_1)}{\mu (\xi_2 (\rho + \xi_1) + \phi \xi_1 + \rho d) + \rho \omega d},$$

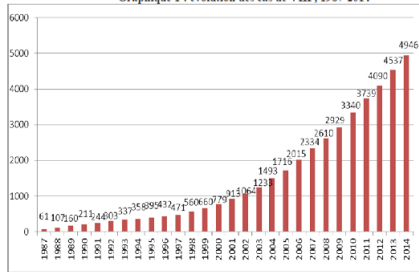
where $\xi_1 = \alpha + \mu + d$, $\xi_2 = \omega + \mu$, $\xi_3 = \rho + \phi + \mu$.

HIV/AIDS: case study for Cape Verde



En termes de notifications de cas, de 1987 à 2014, le total de cas cumulatifs d'infection VIH et SIDA monte à 4946 personnes infectées avec le VIH. De ce total, 1766 ont développé la maladie du SIDA et 1066 ont décédés.

Graphique 1 : évolution des cas de VIH , 1987-2014



source : SVELDNS/MS

CCS-SIDA Rapport de Progrès sur la riposte au SIDA au Cabo Verde - 2015


República de Cabo Verde
Comité de Coordenação do Combate a Sida
Secretariado Executivo



Rapport de Progrès de la riposte VIH / SIDA
Cabo Verde - 2015



C. Postal 835 - Praia - República de Cabo Verde
 Telefone (238) 2600343 Fax: (238) 2618576
 E-mail: Artur.Corneia@ccssida.gov.cv
Maria.M.Ferreira@ccssida.gov.cv

HIV/AIDS: case study for Cape Verde

- Assume: $(\eta_C, \eta_A) = (0.04, 1.35)$; estimated $\beta = 0.695$.

Symbol	Description	Value	References
N	Total population	variable	
$N(0)$	Initial population	323972	World Bank
Λ	Recruitment rate	10724	World Bank
μ	Natural death rate	1/69.54	World Bank
ϕ	HIV treatment rate for I_H individuals	1	Silva & Torres (2015)
ρ	Rate at which individuals leave I_H class to A	0.1	Silva & Torres (2015)
α	AIDS treatment rate	0.33	Silva & Torres (2015)
ω	Rate at which individuals leave C_H class	0.09	Silva & Torres (2015)
d	AIDS induced death rate	1	UNAIDS

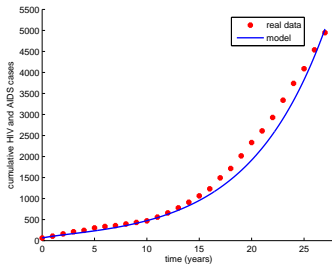
Note: data from World Bank was considered the average from 1987 to 2014.

HIV/AIDS: case study for Cape Verde

Table: Cumulative cases of infection by HIV/AIDS and total population in Cape Verde in the period 1987–2014.

Year	1987	1988	1989	1990	1991	1992	1993
HIV/AIDS	61	107	160	211	244	303	337
Population	323972	328861	334473	341256	349326	358473	368423
Year	1994	1995	1996	1997	1998	1999	2000
HIV/AIDS	358	395	432	471	560	660	779
Population	378763	389156	399508	409805	419884	429576	438737
Year	2001	2002	2003	2004	2005	2006	2007
HIV/AIDS	913	1064	1233	1493	1716	2015	2334
Population	447357	455396	462675	468985	474224	478265	481278
Year	2008	2009	2010	2011	2012	2013	2014
HIV/AIDS	2610	2929	3340	3739	4090	4537	4946
Population	483824	486673	490379	495159	500870	507258	513906

HIV/AIDS: case study for Cape Verde

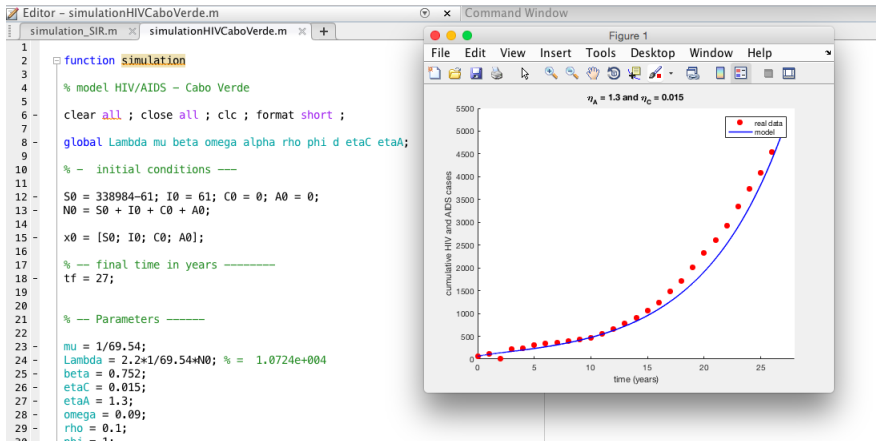


$$(\beta, \eta_C, \eta_A) = (0.752, 0.015, 1.3), R_0 = 4.0983$$

Remark: The parameter β was estimated. The l_2 norm of the difference between the real data and the cumulative cases of infection by HIV/AIDS given by model (1) gives, an error of 0.03% of individuals per year with respect to the total population of Cape Verde in 2014.

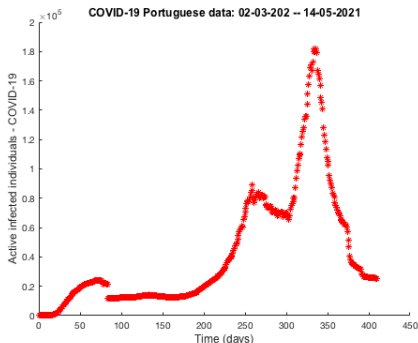
HIV/AIDS: case study for Cape Verde - MATLAB

Matlab file: simulationHIVCaboVerde.m



A SAIRP model for COVID-19 in Portugal

Active infected individuals with COVID-19 in Portugal from March 2, 2020 until April 15, 2021.

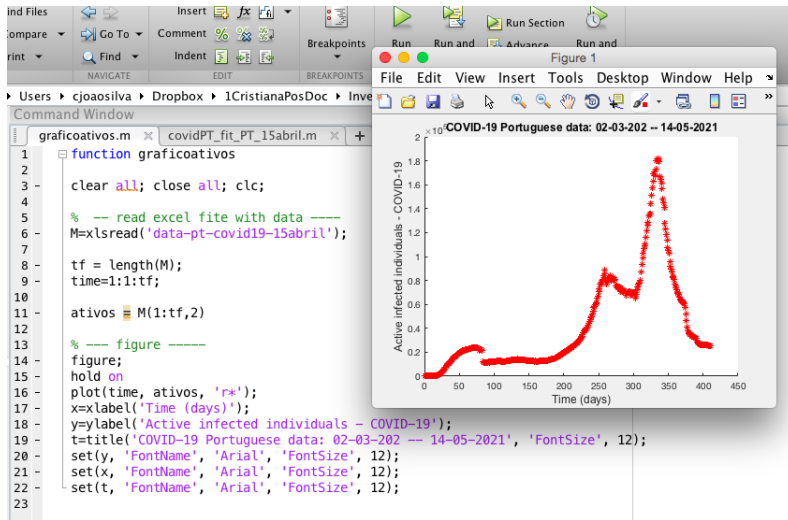


Data: example where to get the information
<https://github.com/dssg-pt/covid19pt-data>

A SAIRP model for COVID-19 in Portugal

Excel file: data-pt-covid19-15abril.xls

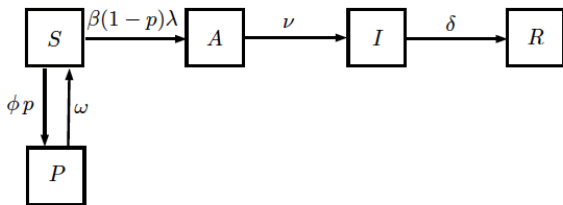
Matlab file: graficoativos.m



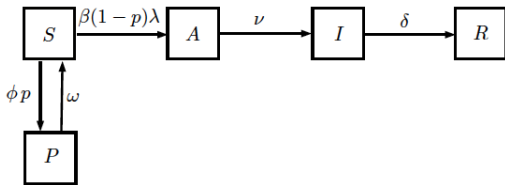
A SAIRP model for the transmission dynamics of SARS-CoV-2

Assume a homogeneous population subdivided into five compartments:

- S , susceptible (uninfected and not immune);
- A , infected but asymptomatic (undetected);
- I , active infected (symptomatic and detected/confirmed);
- R , removed (recovered and deaths by COVID-19);
- P , *protected/prevented* (not infected, not immune, but that are under protective measures).



SAIRP model: parameters



Parameter/	Description
β	Infection transmission rate
θ	Modification parameter
p	Fraction of susceptible S transferred to protected class P
ϕ	Transition rate of susceptible S to protected class P
$\omega = wm$	
w	Transition rate of protected P to susceptible S
m	Fraction of protected P transferred to susceptible S
$\nu = vq$	
v	Transition rate of asymptomatic A to active/confirmed infected I
q	Fraction of asymptomatic A infected individuals
δ	Transition rate from active/confirmed infected I to removed R

SAIRP model with vital dynamics and constant parameters

Model:

$$\begin{cases} \dot{S}(t) = \Lambda - \beta(1-p)\frac{(\theta A(t)+I(t))}{N(t)}S(t) - \phi pS(t) + \omega P(t) - \mu S(t), \\ \dot{A}(t) = \beta(1-p)\frac{(\theta A(t)+I(t))}{N(t)}S(t) - \nu A(t) - \mu A(t), \\ \dot{I}(t) = \nu A(t) - \delta I(t) - \mu I(t), \\ \dot{R}(t) = \delta I(t) - \mu R(t), \\ \dot{P}(t) = \phi pS(t) - \omega P(t) - \mu P(t). \end{cases}$$

Total population, $N(t) = S(t) + A(t) + I(t) + R(t) + P(t)$, with $t \in [0, T]$ representing the time (in days) and $T > 0$.

Model with piecewise constant parameters

The human behavior and the governmental public health decision makers can change the dynamics of the SAIRP model.

Consider parameters determined by piecewise constant functions.

Subdivide the time line $[0, +\infty)$ into a finite number of n intervals

$$[T_0, T_1) \cup [T_1, T_2) \cup \cdots \cup [T_n, +\infty),$$

with disjoint unions, and introduce a piecewise constant function α defined on each time interval as

$$\alpha(t) = \alpha_i, \quad t \in [T_i, T_{i+1}), \quad 0 \leq i \leq n,$$

with $T_0 = 0$, $T_{n+1} = +\infty$ and $\alpha_i \in \mathbb{R}^9$.

Existence of pseudo-periodic solutions: example

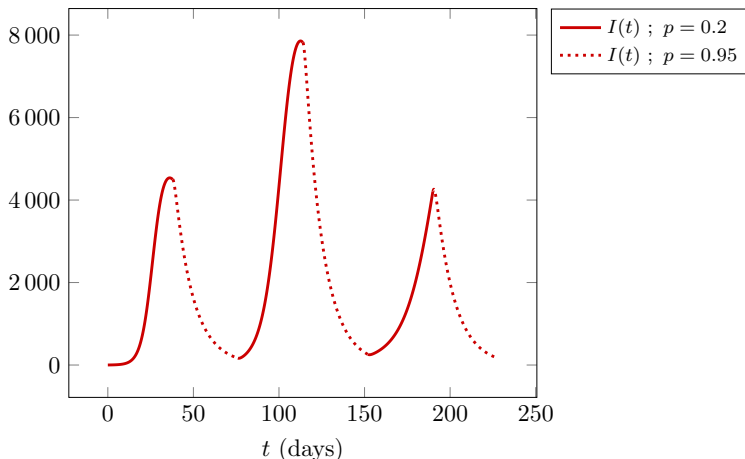


Figure: Here I denotes the number of active infected individuals and p the fraction, $0 < p < 1$, of susceptible individuals S that is transferred to the protected class P .

Initial conditions and important dates - Portuguese COVID-19 data

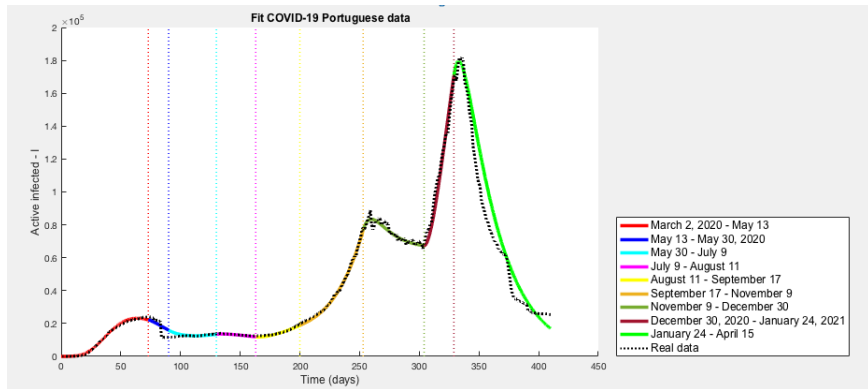
Initial condition	Value	Reference
$N = S_0 + A_0 + I_0 + R_0 + P_0$	10295909	INE
S_0	10295894/ N	DGS
I_0	2/ N	DGS
A_0	(2/0.15)/ N	DGS
R_0	0	DGS
P_0	0	DGS

Some important dates:

- March 2, 2020 – first confirmed 2 infected cases were reported, in Portugal;
- March 12, 2020 – declared State of Emergency - first confinement;
- May 2, 2020 – emergency status was canceled (duration of 45 days);
- October 14, 2020 – State of Calamity;
- November 6, 2020 – State of Emergency - partial confinement;
- January 21, 2021 – close of schools of all education levels.

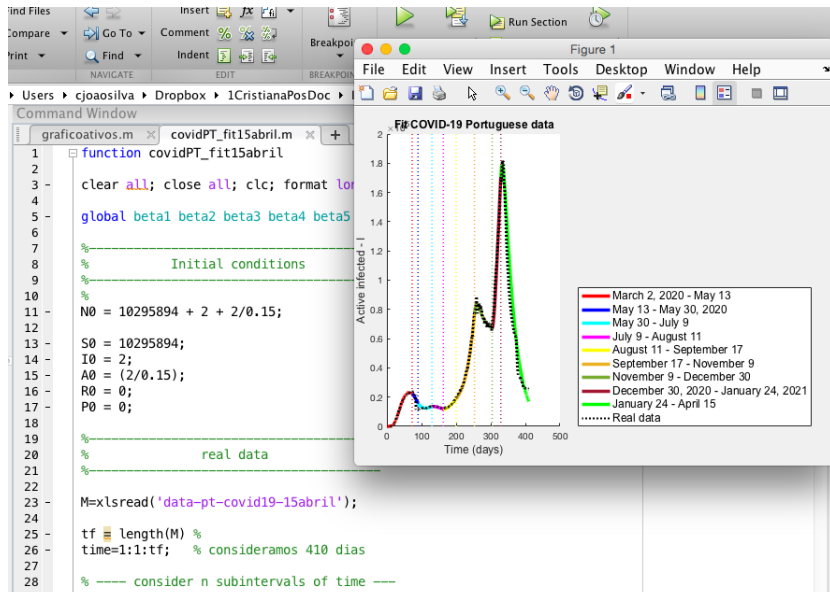
SAIRP model - fitting active infected cases in Portugal

From March 2, 2020 until April 15, 2021



SAIRP model - fitting active infected cases in Portugal

Matlab file: covidPT_fit15abril.m



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See slides LCVC-part2 for Optimal control applied to epidemiological models!