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A TIME-DEPENDENT SEIR MODEL TO ANALYSE THE EVOLUTION OF THE SARS-COV-2 EPIDEMIC OUTBREAK IN PORTUGAL

A PREPRINT

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ABSTRACT

Background: The analysis of the SARS-CoV-2 epidemic is of paramount importance to understand the dynamics of the coronavirus spread. This can help health and government authorities take the appropriate measures and implement suitable politics aimed at fighting and preventing it.
Methods: A time-dependent dynamic SIR model inspired in a model previously used during the MERS outbreak in South Korea was used to analyse the time trajectories of active and hospitalized cases in Portugal.
Results: The time evolution of the virus spread in the country was adequately modelled. The model has changeable parameters every five days since the onset of mitigation measures. A peak of about 13,000 active cases is estimated somewhere around April. Hospitalized cases could reach a peak of about 2,300 cases, of which 500-600 in ICU units.
Conclusion: With appropriate measures, the number of active cases in Portugal can be controlled at about 13,000 people, of which about 2,300 hospitalized and 500-750 in ICU units. This seems manageable by the country's national health service with an estimated 1,140 ventilators.

1 Introduction.

There is already abundant information on SARS-CoV-2 [1–5]. In the most severe cases, the virus SARS-CoV-2 infection can lead to the development of acute respiratory distress syndrome (ARDS) causing respiratory failure, septic shock, multiorgan failure, and even death [6]. Studies suggest that the case fatality rate of the virus is of about 3.5% in mainland China [7]. However, this value seems to be much higher in Italy [8], suggesting its strong dependence on demographics [9]. The WHO declared Europe as the new epicentre of the disease on the 13th of March of 2020[[10]. The rapid growth of the number of active cases presenting severe symptoms has saturated the health services in most countries in the continent, especially in Italy [11]. Governments throughout Europe have implemented severe measures to prevent and mitigate the spread of the virus. Yet, as of the 6th of April there were as many as 646,340 confirmed cases on the European continent, resulting in 49,227 deaths [2, 3].

In this study, a time-dependent SEIR model [12, 13] was used to analyse the evolution of current active and hospitalised cases in Portugal. The model takes into account mitigation and self-protective measures implemented by the government and the population, from the 18th of March 2020 onwards. The use of time-dependent models has been proposed before as they provide a chance to readjust the parameters as time passes and the conditions in which the epidemic is spreading change [14].

This study shows that although sometimes blunt [15], an SEIR model can accurately predict the trajectory of the curve of infected and hospitalized cases, and may be suitable to be used in the future for a consistent analysis of the data, and the repercussions of mitigation and control measures, which can be taken into account in these models.

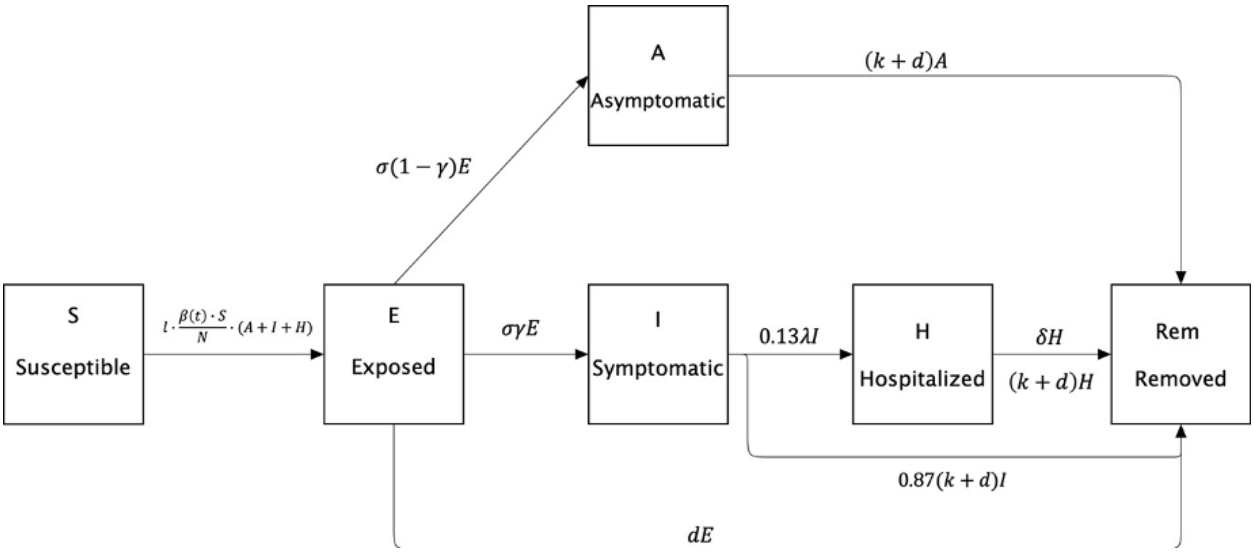

Figure 1: Flow chart of the SEIR model used in this work.

2 Methodology.

A time-dependent SEIR model inspired by a model developed by Xia et al [12, 13] was used, which can be understood by the flow diagram shown in figure 1. This is an update from a previously used preliminary version [13], in which all infected cases ended up hospitalized. Given how unrealistic that sounds, the model now considers that 13% of infected cases are hospitalized, and 87% are recovered through the normal recovery rate (these proportions were taken from Portuguese data [16]. Furthermore, the model considers only one transmission coefficient, one government measure coefficient, and one self-protective measure coefficient.

In this model, S corresponds to the number of susceptible individuals; E, the number of exposed individuals; A, the number of asymptomatic cases; I, the number of mild-to-severe infected cases; H, the number of hospitalized cases; R, the number of removed cases, and finally N, the total population of Portugal.

The model is time-dependent, because $\beta(t)$, the transmission coefficient of the asymptomatic, symptomatic, and hospitalized cases to the susceptible, can vary with time. Although this variation is not continuous. This will be explained later.

σ^{-1} is the mean incubation period, λ^{-1} is the mean time between symptom onset to hospitalization, k^{-1} is the mean infectious/recovery period, δ_{-1} is the mean time from hospitalization to death, γ is the clinical outbreak rate, l represents the self-protective measures taken by individuals, and d the mitigation measurements taken by the government. Of the symptomatic (I) cases 13% need hospitalization, whereas 87% heal without the need to be hospitalized. The time unit is 1 day. The set of differential equations can then be written as:

$$\begin{cases} \frac{\mathrm{d}S(t)}{\mathrm{d}t} = -l \cdot \beta(t) \cdot (\frac{S(t) \cdot A(t)}{N} + \frac{S(t) \cdot I(t)}{N} + \frac{S(t) \cdot H(t)}{N}) \\ \frac{\mathrm{d}E(t)}{\mathrm{d}t} = l \cdot \beta(t) \cdot (\frac{S(t) \cdot A(t)}{N} + \frac{S(t) \cdot I(t)}{N} + \frac{S(t) \cdot H(t)}{N}) - (\sigma + d) \cdot E(t) \\ \frac{\mathrm{d}A(t)}{\mathrm{d}t} = (1-\gamma) \cdot \sigma \cdot E(t) - (k+d) \cdot A(t) \\ \frac{\mathrm{d}I(t)}{\mathrm{d}t} = \gamma \cdot \sigma \cdot E(t) - 0.13\lambda \cdot I(t) - 0.87(k+d) \cdot I(t) \\ \frac{\mathrm{d}H(t)}{\mathrm{d}t} = 0.13\lambda \cdot I(t) - k \cdot H(t) - (\delta + d) \cdot H(t) \\ \frac{\mathrm{d}R(t)}{\mathrm{d}t} = k \cdot [A(t) + H(t) + 0.87I(t)] + d[A(t) + I(t) + H(t) + E(t)] + \delta \cdot H(t) \end{cases} \tag{1}$$

The only parameter considered to be known was the mean incubation time, which was taken as $\sigma^{-1} = 5.1$ days from the literature (here using the median as equal to the mean) [**?**]. From the previous work, determined from the Italian recovery data [18], a mean infectious/recovery period of about $k^{-1} \approx 11$ days was used, and taken to be the same in all cases. The clinical outbreak rate which was taken to be $\gamma \approx 7\%$, a mean value from values reported for attack rates [19], in a first approximation, and again, this is an approximate value. The epidemic starts at the 15th of February (the day of the first reported case in Europe) with only one person infected ($I_0 = 1$), being the rest of the values 0, except for S_0

Table 1: The different parameters of the model described by Eq. 1

parameter	Previous work [13]	This work
σ^{-1}	5.1 (days)	5.1 (days)
λ^{-1}	$\sim$4 (days)	To be fitted
δ^{-1}	$\sim$59 (days)	To be fitted
k_1^{-1}	1/14	0.088 (now k)
k_2^{-1}	0.088 (days^{-1})	0.088 (now k)
β	1.16$\pm$0.033) (days^{-1})	To be fitted (time-dependent)
γ	0.0158$\pm$0.034) (days^{-1})	0.07
l	Time-dependent	To be fitted (time-dependent)
d	Time-dependent	To be fitted (time-dependent)
N	10,290,000	10,290,000
S_0	10,289,999	10,289,999
E_0	0	0
A_0	0	0
I_0	1	1
H_0	0	0
R_0	0	0

Table 2: Table of fitted parameters λ and δ as obtained using "NonLinearCurveFit" in Mathematica

parameter	estimate	standard error	t-statistic	p-value
δ	0.0681	0.00219	28	2.75×10^{-9}

which is simply N-1. See table 1 for a breakdown of the different parameters of this model. To solve this system of differential equations the Mathematica code [20] was used, using the function "NonLinearModelFit" [21].

In order to determine the parameters λ, and δ, the number of hospitalized cases and deaths, respectively, as reported by the Portuguese Directorate-General of Health (DGS in Portuguese) and available online, were used [16]. Fits were made on the 27th of March. After determining the values for these parameters, they were used to fit the curve of infected cases in Portugal, where the values of $\beta(t)$, d and l were fitted in five different periods:

- Period 0, from the 15th of February to the 18th of March (day in which the government decreed a State of Emergency),
- Period 1, from the 19th to the 24th of March,
- Period 2, from the 25th to the 30th of March,
- Period 3, from the 31st of March to the 4th of April,
- Period 4, from the 5th to the 10th of April (prediction).

The three parameters β, l, and d were fitted for each of these five periods. All other parameters were fixed.

3 Results.

3.1 Adjusting parameter λ.

The number of deaths in Portugal was taken from [16], and the set of differential equations described in eq. 1 fitted to obtain the best possible fit for δ. An R^2 value of $\sim$0.99 was obtained with the fit. The rest of the parameters are presented in table 2 . Results are shown in figure 2.

3.2 Adjusting parameter λ.

Now, using the value for δ found in 3.1, parameter λ was obtained with a new fit of Eq. 1 to the number of hospitalized cases in Portugal, which again was taken from [16]. The best possible fit gave an R^2 value of $\sim$0.98. The rest of the parameters are presented in table 3, and shown in figure 3.

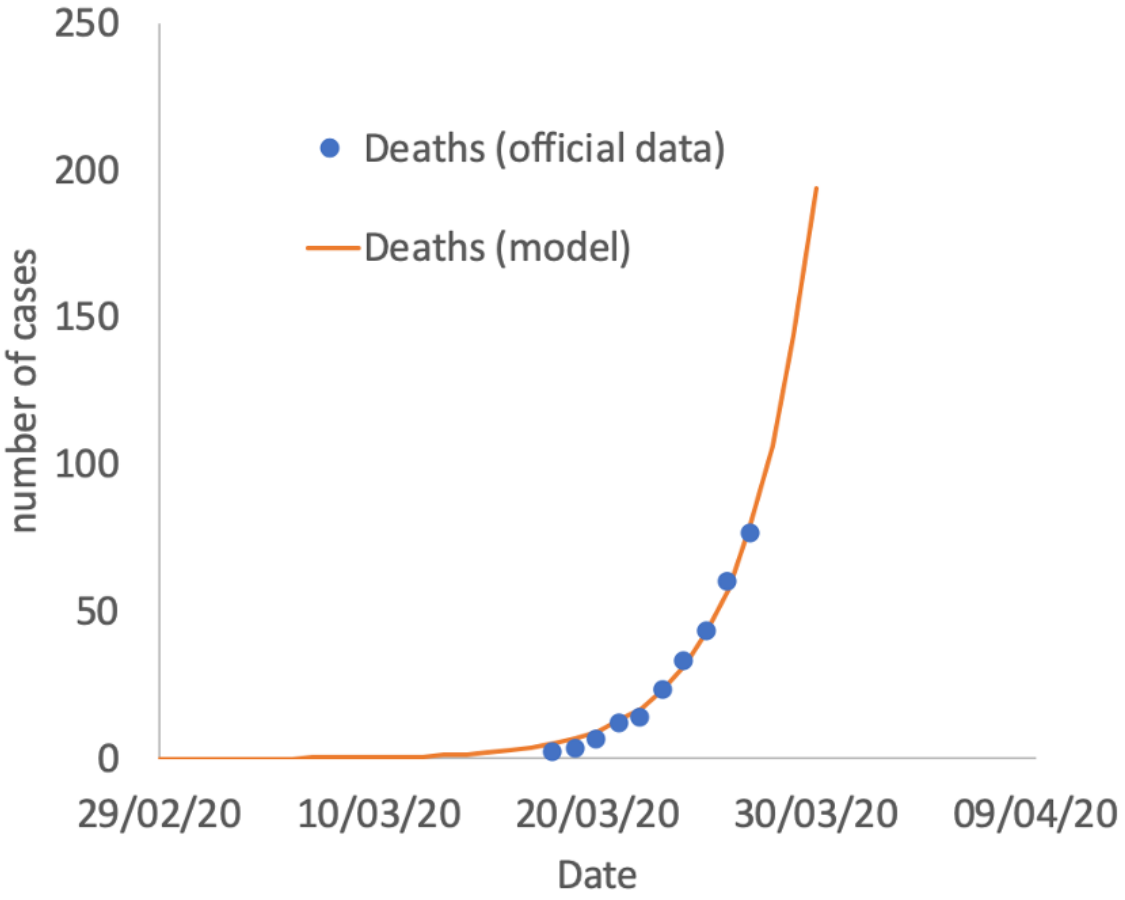

Figure 2: Graphical representation of the adjusted model to the Portuguese official death toll.

Table 3: Table of fitted parameter λ as obtained using "NonLinearCurveFit" in Mathematica

parameter	estimate	standard error	t-statistic	p-value
λ	0.285	0.0141	20.07	2.98×10^{-12}

3.3 Fitting of parameter β in period 0

The parameters needed to fit Eq. 1 to the number of Portuguese active cases until the 18th of March, in order to determine the value of β, were obtained in 3.1, and 3.2. The number of Portuguese active cases was taken from [16]. The fit was obtained with an R^2 of 0.99. The other parameters for β are given in table 4. In this period, no measures were being taken so, $l = 1$; and $d = 0$.

A graphical depiction of the fitted model is given in figure 4.

Table 4: Table of fitted parameters λ and δ as obtained using "NonLinearCurveFit" in Mathematica

parameter	estimate	standard error	t-statistic	p-value
β	1.023	0.00263	388.7	5.19×10^{-35}

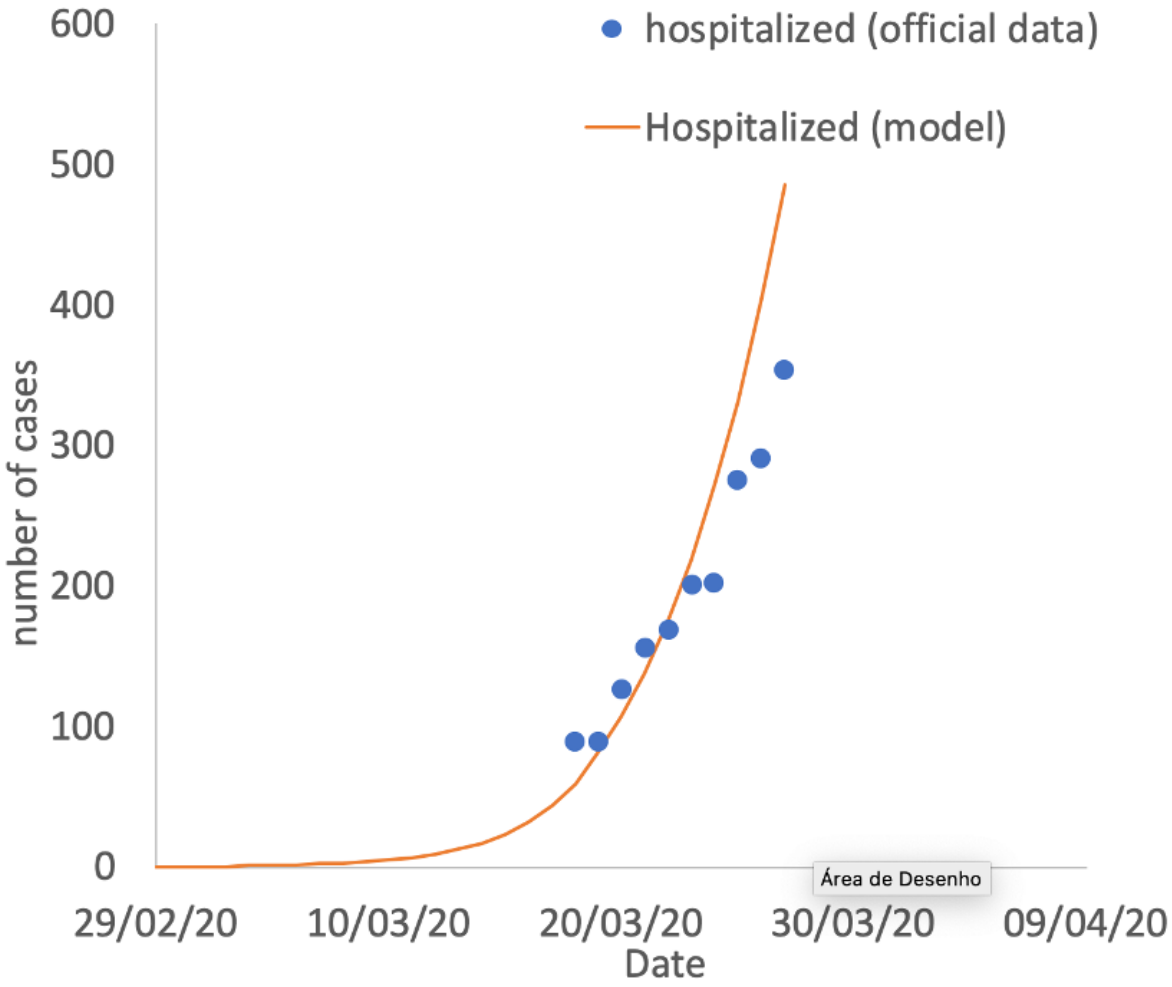

Figure 3: Graphical representation of the adjusted model to the hospitalized cases in Portugal.

Table 5: The obtained parameters of the model described in the previous sections

parameter	this work ($days^{-1}$)
λ	0.285±0.00141
δ	0.0681±0.0002
β	1.023±0.00263

3.4 Discussion of the obtained values for λ, δ, and β for period 0

According to the obtained values of λ, δ, and β, the mean time between onset of symptoms and hospitalization (for the 13% of cases that need to be hospitalized) is of $\lambda^{-1} = 3.51 \pm 0.17$ days, and the mean time of those hospitalized until death is of $\delta^{-1} = 14.6 \pm 0.45$days. Unfortunately, I did not find any official data about these numbers in order to establish a comparison to ascertain their adequacy.

Also, the model assumes that all symptomatic and no asymptomatic cases are being tested, which may not reflect a realistic situation. This is probably very conditional to the number of tests being performed by the country and may also vary with time.

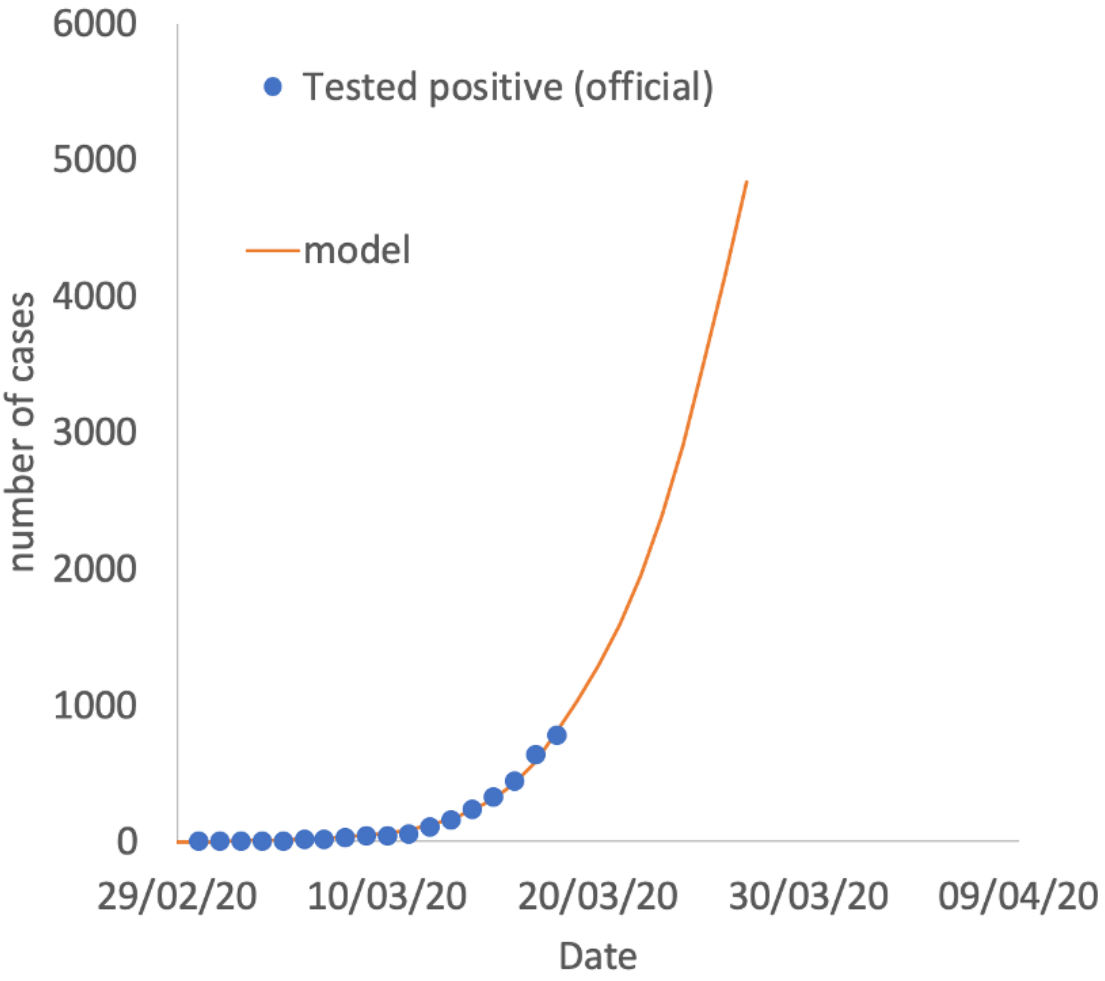

Figure 4: Graphical representation of the adjusted model to the Portuguese government official active cases.

4 Time evolution of SARS-CoV-2 in Portugal, considering time adjustable parameters.

In an epidemic outbreak such as the current one, governments and the population take protective measures to attempt to contain the spread of the virus. In this paper, parameters l and d, inspired by the paper from Xia *et al* [12, 13] , are introduced as explained in section 3. These parameters are meant to take into account two things:

- Isolation and monitoring measures taken by the government (parameter d);
- Self-protection measures taken by the population (parameter l).

In a previous study, four different scenarios in addition to an "out-of-control" scenario, were devised. To note that we are currently working with $d_1 = d_2 = d_3 = d_4 = d$ and $l_1 = l_2 = l_3 = l$.

The day considered for the initiation of these measures is day 33 corresponding to the 19th of March 2020 which is 5 days after the government implemented the measures, giving the virus another cycle of infection before the measures take effect.

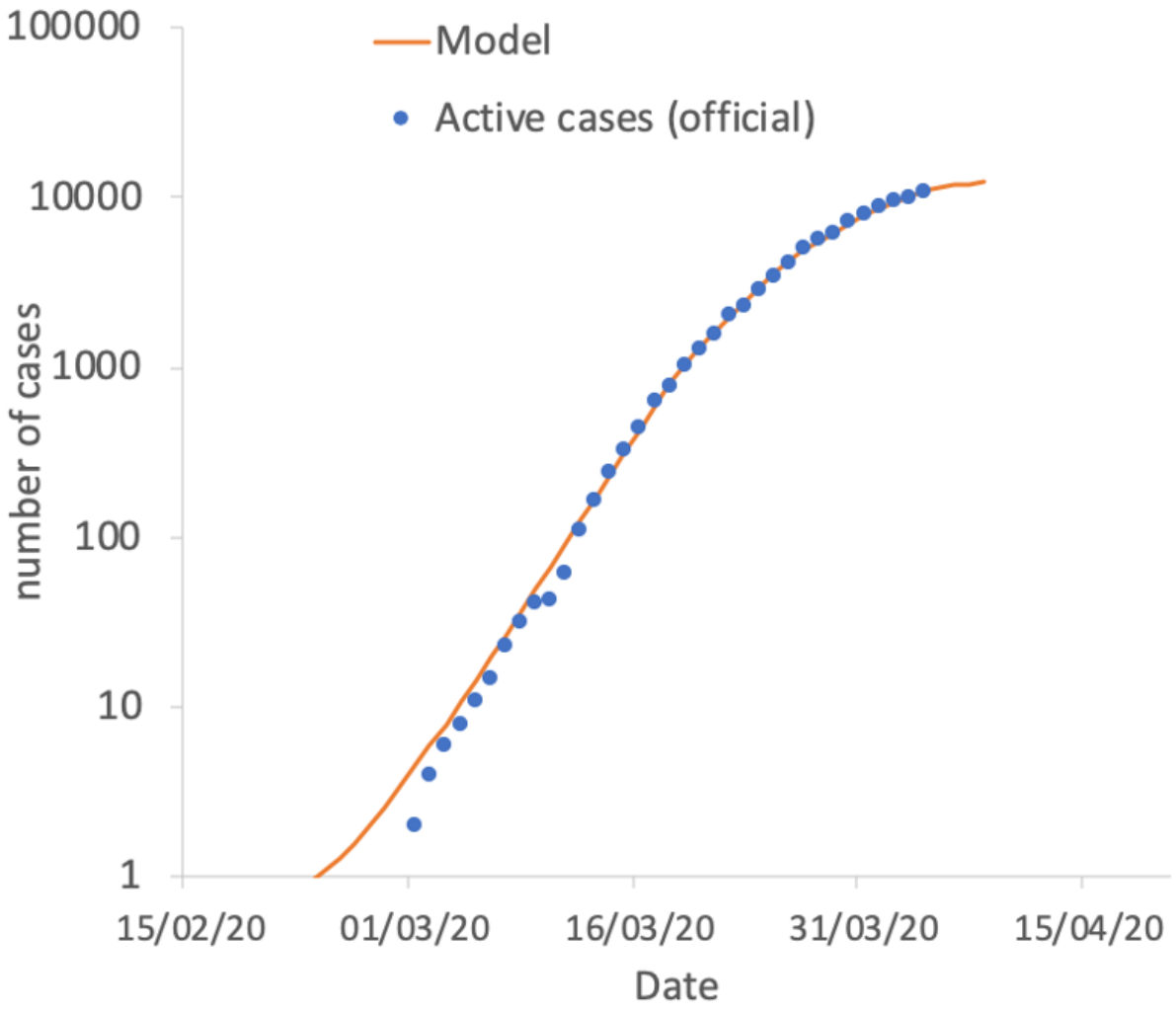

Figure 5: Graphical representation of official active cases in Portugal and the model. Blue dots represent official data, the orange line the model.

4.1 Implementing a dynamic model to follow the trajectory of the curve.

In the current analysis, instead of using set values from educated guesses as done in my previous work, the values of β, d and l are adjustable to the curve. In order to fit the results, four periods of five days each, from the 19th of March, were considered. In the first three periods, the same official data to fit the results was used. Initial conditions were taken from the previous period, and equation 1 was solved for the trajectory of the curve in the remainder of days in the same period. This procedure was performed for each period. This allowed for a dynamic follow-up of the trajectory, adjusting the parameters to the best possible fit to the curve in each period. The obtained results are summarized in table 6. A graphical depiction of the evolution of the obtained curve for infected cases is given in 5. For hospitalized cases, this is provided in figure 6.

As is clear from the figures, the number of active and hospitalized cases is nearing a maximum. According to this dynamic model, this should be reached between the 10th and the 15th of April. The values at which the maxima will be around $\sim$13,000 active cases, and $\sim$2,500 hospitalized cases. Considering that the number of ICU cases has been between 20-30% of the total of hospitalized cases (see data), this would mean a number of about 500 750 cases in ICU.

Table 6: Obtained parameters for each of the periods considered

period	β (days^{-1})	l (no units)	d (days^{-1})	R^2
Period 1 (19th to 24th March 2020)	1.101±0.0167	0.641±0.009	0.0353±.0816	0.999
Period 2 (25th to 30th March 2020)	1.052±0.0315	0.379±0.011	0.0100±0.105	0.999
Period 3 (31th to 4th April 2020)	0.509±0.0009	0.489±0.009	0.0100±0.033	0.999

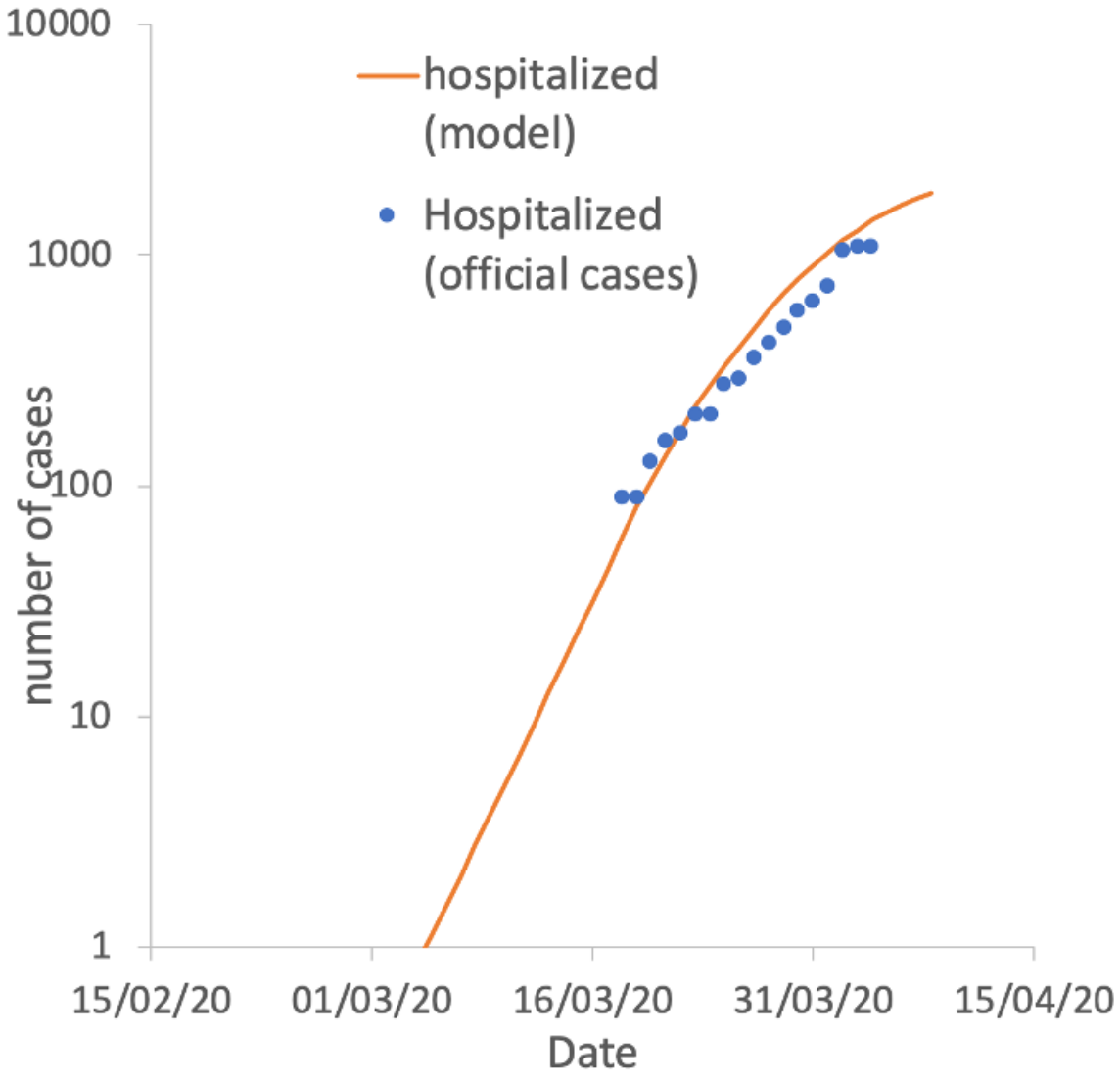

Figure 6: Graphical representation of hospitalized cases in Portugal. Blue dots represent official data, the orange line the model.

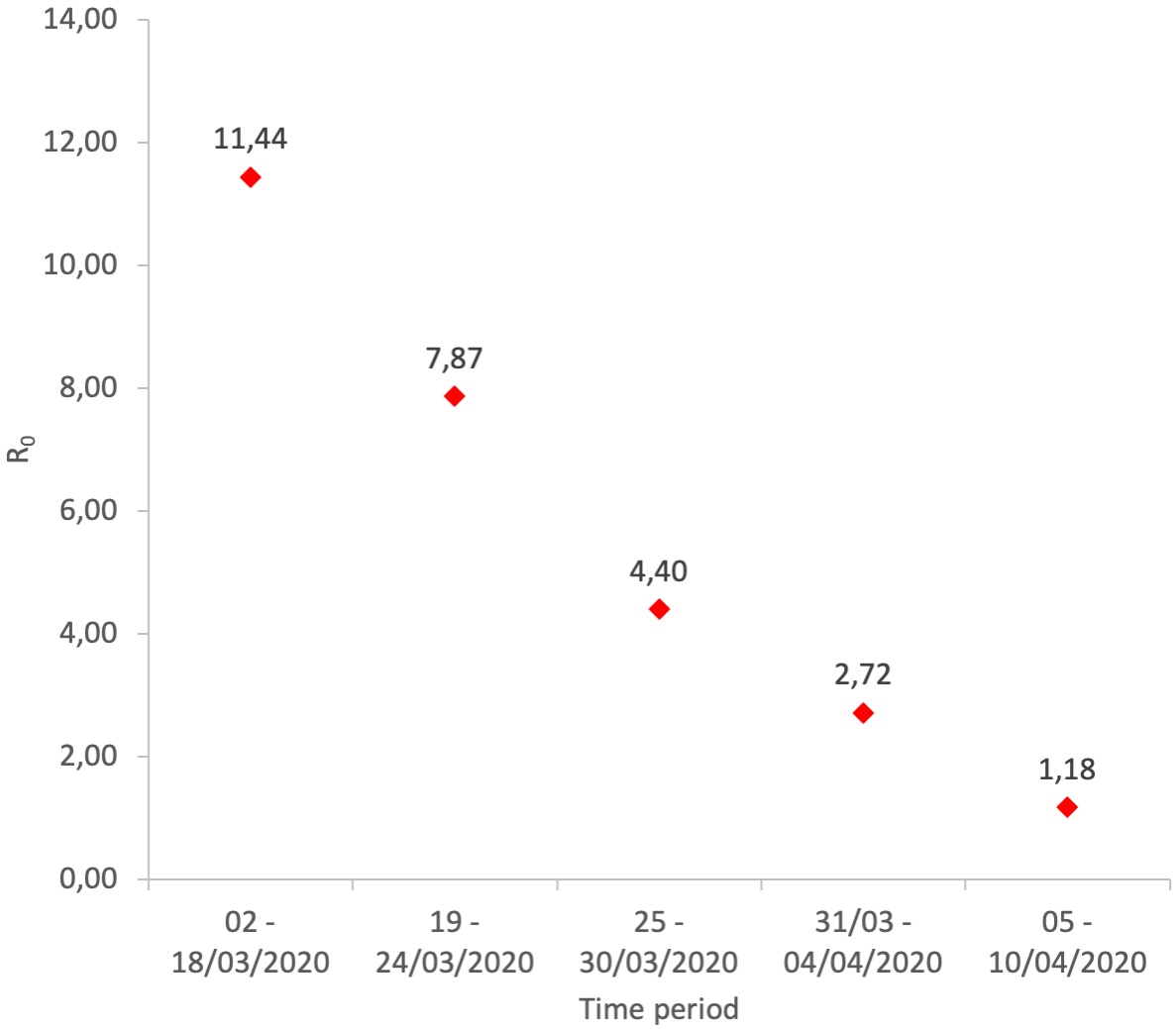

Figure 7: Graphical representation of R_0 for each time period.

Table 7: Obtained parameters for each of the periods considered

period	β (days^{-1})	l (no units)	β_{eff} (days^{-1}
Period 0 (2nd to 19th March 2020)	1.023±0.0026	1	1.023±0.0026
Period 1 (19th to 24th March 2020)	1.101±0.0167	0.641±0.009	0.706±.00146
Period 2 (25th to 30th March 2020)	1.052±0.0315	0.379±0.011	0.399±0.0166
Period 3 (31th to 4th April 2020)	0.509±0.0009	0.489±0.009	0.249±0.0005
*Period 4 (5th to 10th April 2020)	0.361	0.299	0.108

The last period corresponds to a prediction of the values for the five days following period 3 (5th to the 10th of April 2020). Considering that both l and β diminish linearly, we can estimate their value for the considered period, as can be seen in table 7:

In this table, we are already considering the effective value of the transmission rate, $\beta_{eff}(t)$:

$$\beta_{eff}(t) = l \cdot \beta(t) \tag{2}$$

4.2 Estimating R_0 for this model.

The obtained values for β, allow for an estimate of the basic reproduction number for all considered periods.

Following the formalism proposed by Van der Driessche and Watmough [22], and $\alpha = 0.13$ we can define $\mathscr{F}$ and $\mathscr{V}$, that the equilibrium state is given by $(S_0, 0, 0, 0)$:

$$\mathscr{F} = \begin{pmatrix} l\frac{S\beta}{N}(A + I + H) \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad \mathscr{V} = \begin{pmatrix} (\sigma + d)E \\ -(1-\gamma)\sigma E + (k+d)A \\ -\gamma\sigma E + \alpha\lambda I + (1-\alpha)(k+d)I \\ -\alpha\lambda I - kH - (\delta + d)H \end{pmatrix} \tag{3}$$

We can then determine the Jacobian matrices:

$$F = \begin{pmatrix} 0 & l\frac{S\beta}{N} & l\frac{S\beta}{N} & l\frac{S\beta}{N} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} \sigma + d & 0 & 0 & 0 \\ -(1-\gamma)\sigma & k+d & 0 & 0 \\ -\gamma\sigma & 0 & \alpha\lambda+(1-\alpha)(k+d) & 0 \\ 0 & 0 & 0 & -k-(\delta+d) \end{pmatrix} \tag{4}$$

We also need V^{-1}:

$$V^{-1} = \begin{pmatrix} \frac{1}{\sigma+d} & 0 & 0 & 0 \\ \frac{(1-\gamma)\sigma}{(\sigma+d)(k+d)} & \frac{1}{k+d} & 0 & 0 \\ \frac{\gamma\sigma}{(\alpha\lambda+(1-\alpha)(k+d))(\sigma+d)} & 0 & \frac{1}{\alpha\lambda+(1-\alpha)(k+d)} & 0 \\ 0 & 0 & 0 & -\frac{1}{k+(\delta+d)} \end{pmatrix} \tag{5}$$

And R_c will simply be

$$R_c = \rho(FV^{-1}) = l\frac{S\beta}{N}\left(\frac{(1-\gamma)\sigma}{(\sigma+d)(k+d)} + \frac{\gamma\sigma}{(\alpha\lambda+(1-\alpha)(k+d))(\sigma+d)}\right) \tag{6}$$

For R_0, $l = 1$, and $d = 0$, and so:

$$R_0 = \rho(FV^{-1}) = \frac{S_0\beta}{N}\left(\frac{1-\gamma}{k} + \frac{\gamma}{\alpha\lambda+(1-\alpha)k}\right) \tag{7}$$

This gives a value of $R_0 = 11.44$, indicating a very active spread of the virus in this first stage, although this value seems higher than most studies. In this model, given that cases will only resolve after a period of about $k^{-1} \sim 10$ days, during which time they will be able to infect another individual. Also, there is a very high uncertainty for the appropriate incubation time of this virus, which some authors claim can be of up to 27 days [23, 24]. This is still something that needs to be analysed in more detail.

This permits us to estimate the value for the evolution of the basic reproduction number R_c with time, as can be seen in figure 7.

As can be seen the value of R_0 is diminishing with time, with a predicted value already very close to 1 for the period of the 5th to the 10th of April 2020, implying that the situation may be under control in the country.

5 Conclusions.

SEIR models, although sometimes blunt in their deterministic approach, are valuable tools to model epidemic outbreaks. If used carefully and dynamically (i.e. with adjustable parameters on given periods) it is possible to accurately predict the trajectory of an epidemic curve within a five to ten-day period. Protective and isolation measures are currently the only weapon at our disposal to control this epidemic. SEIR models are effective in taking these measures into account by the insertion of one or two extra parameters. Variation of such parameters can be demonstrative of the power of any given measure, be it in terms of self-protection (washing hands frequently, social isolation, etc.) or community measures (closing down schools, parks, etc.).

6 Limitations of this study and scope of application

This study is intended for academic purposes only and should not be used in any other way. It intends to provide tools for scientists to model the trajectory of active and hospitalized cases in the current pandemic. With this model, and still within the predictions made with the previous study, it seems that a maximum of $\sim$13,000 active cases and $\sim$2,500 hospitalized cases will be reached between the 9th-20th of April.

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