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Timing the race of vaccination, new variants, and relaxing restrictions during COVID-19 pandemic

Carolina Ribeiro Xavier\textsuperscript{a}, Rafael Sachetto Oliveira\textsuperscript{a}, Vinícius da Fonseca Vieira\textsuperscript{a}, Bernardo Martins Rocha\textsuperscript{b}, Ruy Freitas Reis\textsuperscript{b}, Bárbara de Melo Quintela\textsuperscript{b}, Marcelo Lobosco\textsuperscript{b}, Rodrigo Weber dos Santos\textsuperscript{b,*}

\textsuperscript{a} Universidade Federal de São João del-Rei, São João del-Rei, MG, Brazil

\textsuperscript{b} Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil

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ABSTRACT

Late in 2019, China identified a new type of coronavirus, SARS-CoV-2, and due to its fast spread, the World Health Organisation (WHO) declared a pandemic named COVID-19. Some variants of this virus were detected, including the Delta, which caused new waves of infections. This work uses an extended version of a SIRD model that includes vaccination effects to measure the impact of the Delta variant in three countries: Germany, Israel and Brazil. The calibrated models were able to reproduce the dynamics of the above countries. In addition, hypothetical scenarios were simulated to quantify the impact of vaccination and mitigation policies during the Delta wave. The results showed that the model could reproduce the complex dynamics observed in the different countries. The estimated increase of transmission rate due to the Delta variant was highest in Israel (7.9), followed by Germany (2.7) and Brazil (1.5). These values may support the hypothesis that people immunised against COVID-19 may lose their defensive antibodies with time since Israel, Germany, and Brazil fully vaccinated half of the population in March, July, and October. The scenario to study the impact of vaccination revealed relative reductions in the total number of deaths between 30% and 250%; an absolute reduction of 300 thousand deaths in Brazil due to vaccination during the Delta wave. The second hypothetical scenario revealed that mitigation policies saved up to 300 thousand Brazilians; relative reductions in the total number of deaths between 24% and 120% in the three analysed countries. Therefore, the results suggest that both vaccination and mitigation policies were crucial in decreasing the spread and the number of deaths during the Delta wave.

1. Introduction

In December 2019, the first Corona Virus Disease (COVID-19) case was identified in Wuhan (China) \cite{1}. Due to the fast spread of the virus, an epidemic started in Wuhan, and by March 2020, the virus reached all five continents (Asia, Europe, Africa, America, and Oceania) \cite{2–4}. On March 11, 2020, the COVID-19 reached more than 118,000 cases in 114 countries, with about 4000 deaths due to complications of this disease \cite{2,5}. The alarming level of the virus spreading led the World Health Organisation (WHO) to declare COVID-19 a pandemic \cite{5}.

Until March 15, 2022, COVID-19 had already infected more than 461.65 million people, 29.44 million in Brazil, 17.73 million in Germany, and 3.73 million in Israel. Fig. 1 illustrates the ratio between the number of infected people and the population size of each country. The global number of deaths has reached more than 6.05 million, of which 655,878 in Brazil, 126,146 in Germany and 10,399 in Israel.\footnote{1}

According to Li et al. \cite{6}, vaccines are fundamental to mitigate the impact of infectious diseases. Their projections indicate that vaccines in general, not only for COVID-19, will have prevented around 69 million deaths from 2000 to 2030. The first safety and efficacy results for vaccines against SARS-CoV-2 have been published between the end of 2020 and the beginning of 2021 \cite{7–9}. This milestone led the world to start a vaccination race as a central goal for controlling the pandemic.

By March 15, 2022, 4.48 billion people were fully vaccinated, 57% of the world population. The number of people fully vaccinated by March 15, 2022, was 157.99 million in Brazil, 6.13 million in Israel and 62.99 million in Germany, corresponding, respectively, to 73.83%, 65.92% and 75.08% of the countries’ populations. Fig. 2 illustrates the ratio between the number of people vaccinated and the population size of each country.

\textsuperscript{*} Corresponding author.

E-mail address: rodrigo.weber@ufjf.edu.br (R.W.d. Santos).

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Fig. 1. Choropleth map for incidence of COVID-19 around the globe. Panel A presents the number of COVID-19 cases relative to the total population while Panel B presents the number of deaths as complications of COVID-19 relative to the total population. Crosshatched area means that the location has no data available.

Fig. 2. Choropleth map for vaccination around the globe. Panel A presents the share of the partially vaccinated population, while Panel B presents the share of the fully vaccinated population, i.e., people who received all doses prescribed by the immunisation protocol. Crosshatched area means that the location has no data availability.

Like any virus, SARS-CoV-2 also mutates. Some of the variants resulting from these mutations may result in a variant of concern, i.e., a new strain that is more infectious, that is more likely to cause breakthrough or re-infections in those who are vaccinated or previously infected [10–13]. Five variants of concern, called Alpha, Beta, Gamma, Delta and Omicron, were identified until the time this paper was written. Fig. 3 illustrates the incidence of these variants in Germany, Israel and Brazil.

First detected in India in October 2020 [15,16], the coronavirus variant known as the Delta has already been registered in more than 130 countries, as published by the World Health Organisation (WHO) on July 30, 2021 [17]. Countries like Israel, England, the United States, and Germany experienced a new wave with the evolution of this variant in 2021, which represented almost 100% of the cases in these countries. This variant has also affected other countries such as Brazil. In addition to the higher level of transmissibility of the Delta variant, different
Fig. 3. Evolution of SARS-CoV-2 variants over time in Germany, Israel, and Brazil. This share may not reflect the actual scenario once only a fraction of all cases are sequenced. Source: Adapted from [14].

Factors contributed to the wave of infections associated with it, such as relaxation of biosafety protocols, time since last vaccine dose, the vaccine effectiveness for this SARS-CoV-2 variant, among others. The Delta variant led some countries to start the application of boosting doses of vaccines.

Many computational modelling studies have investigated how vaccination and non-pharmacological strategies can impact the course of epidemics [18–20]. Borse et al. [21] investigate the 2009–2010 A(H1N1)pdm09 virus propagation and state that the timing of the vaccination program significantly influences the efficacy of immunisation. The authors estimate that many clinical cases, hospitalisations, and deaths were prevented by the vaccination against the virus in the United States, emphasising the importance of public confidence in vaccine programs, and suggest that robust immunisation programs should be addressed in epidemics, especially in the early stages, enhancing its effects. Nguyen and Carlson [22] consider a stochastic SIR model to analyse the impact of time delays of vaccination in the epidemics allowing the authors to define optimal resource allocation strategies. The paper shows that the epidemic is more effectively eradicated, requiring fewer vaccines, when adopting early mass vaccination.

Reis et al. [23] propose a modification of the classic SIRD model [24–27] to investigate the impact of mitigation policies, under-reporting, and uncertainties of the COVID-19 pandemic in South Korea, Italy, and Brazil. This study was extended to analyse the challenges of forecasting COVID-19 peaks, highlighting the importance of using mathematical models for the characterisation of essential features of the dynamics of COVID-19 and for projections of different scenarios that can aid in decision making [28]. In a more recent work from the same authors [29], their original model [23] was extended with the addition of a new time-dependent variable that represents the immunisation rate. This variable uses the vaccine effectiveness and vaccination rate (persons/day) as parameters for simulating different vaccination strategies.

In this work, we evaluate the impact of vaccination, mitigation policies, and the Delta variant on the dynamics of COVID-19 in three different countries: Israel, Germany, and Brazil. A detailed characterisation of the dynamics was performed in these three countries where the Delta variant was dominant during some period, and several parameters of the SIRD model were adjusted to assess the impact of each potential cause of its progression separately.

To conduct this study, we used publicly available epidemic data for these three countries to calibrate the SIRD model between December 2020 and November 19, 2021. In addition, different scenarios were
considered to assess the impact of vaccination and the social restrictions during the Delta wave in the three considered countries.

The remainder of the work is organised as follows: in Section 2, the proposed model is presented in detailed; in Section 3 the results of the simulations are presented; in Section 4 the results are discussed; in Section 5 the limitations of the work are described, and finally, the conclusions of the work are presented in Section 6.

2. Materials and methods

2.1. Mathematical model

For this work, we consider a modification of the model presented in Oliveira et al. [29]. This model is based on the well-known SIRD model [30–34], with the premise of simplicity intending to reduce the parameters to be estimated. The method adopted in this work is divided into two steps: the first one aims to adjust the parameters of the SIRD-based model using real-world data observed in the past; then, the adjusted model is used to forecast the epidemic’s evolution considering different possible scenarios. Unlike the model of Oliveira et al. [29] that only considers a vaccination scheme during the prediction step, this study includes a vaccination scheme both during parameter calibration step, which is based on past data, and the forecasting step, which is done for different scenarios. The following set of equations describe the SIRD-based model proposed in this work:

\[
\begin{align*}
\frac{dS}{dt} &= -\frac{\alpha(t)}{N} (S - \xi(t)S)I, \\
\frac{dI}{dt} &= \frac{\alpha(t)}{N} (S - \xi(t)S)I - \beta(t)I - \gamma(t)I, \\
\frac{dR}{dt} &= \gamma(t)I, \\
\frac{dD}{dt} &= \beta(t)I, \\
C &= I_r + R_r + D.
\end{align*}
\]

where \(S, I, R, D,\) and \(C\) are the variables that represent the number of individuals within a population of size \(N\) that are susceptible, infected, recovered, dead and total confirmed cases, respectively. In addition, \(I_r\) and \(R_r\) represent the individuals reported as infected and recovered,
respectively. The $a(t)$ term is given by

$$a(t) = a(t,r_1,t_i_1,t_f_1)a(t,r_2,t_i_2,t_f_2) \beta,$$

where $\beta$ is the basic infection rate, the terms $a(t,r_1,t_i_1,t_f_1)$ and $a(t,r_2,t_i_2,t_f_2)$ represent different stages of the infection rate. Two different transmission rates $r_1$ and $r_2$ are adopted in the functions to consider different policies for restricting social contact, $r_1$, and a change on the transmissibility of virus variant, $r_2$. The function $a(t,r,t_i,t_f)$ is given by:

$$a(t,r,t_i,t_f) = \begin{cases} 1 & \text{if } t < t_i, \\ \frac{t - t_i}{t_f - t_i} + 1 & \text{if } t_i \leq t \leq t_f, \\ r & \text{otherwise.} \end{cases}$$

This simple approach used for $a(t)$ assumes that when restriction policies start to be adopted at $t_i$, the probability of contact is multiplied by $r_1 < 1.0$ at the end time $t_f$. As the measures are relaxed or a new more transmissible variant appears at the time instant $t_i$, in the final time ($t_f$) the probability of contact or transmission is multiplied by $r_2 > 1.0$. Fig. 4 presents a schematic representation of the $a(t)$ function.

The time dependent input parameter, $v(t)$ represents the fraction of the population that is fully vaccinated, shifted by 15 days, which we assume is the delay between the vaccination date and the date of acquired immunisation.

A recent study [35] showed that AstraZeneca and Pfizer vaccines, widely applied in Brazil, Germany and Israel, managed to reduce the transmission of the virus between 40% and 50%. Thus, we assume in this work that virus transmission is reduced by about 50% among those vaccinated. Therefore, assuming a mean vaccine efficacy $\mu_m = 80\%$ we have $\xi = 0.5 \times 80\% = 0.4$ in Eq. (1).

In this work, we also modified the mortality rate, $m(t)$ according to the vaccination rate, where $\beta(t) = m(t)/\tau_0$. The number of days from infection until death is represented by $\tau_0 = \tau_1 + \tau_2$, where $\tau_1$ is the incubation time of the virus and $\tau_2$ is the time between the first symptoms until death. The rate at which infected individuals recover from the virus is given by $\gamma(t) = (1 - m(t))(1/\tau_r)$, where $\tau_r$ is the number of days from infection until recovery with $\tau_r = \tau_1 + \tau_3$. $\tau_3$ is the time between the first symptoms until recovery. The percentage of confirmed infected individuals that are notified or reported is represented by $\theta$.

As mentioned before, $m(t)$ changes according to the vaccination rate. The time-dependent parameter $m(t)$ represents a weighted average between the mortality rate among the vaccinated $v(t)$ and unvaccinated
Fig. 7. Active cases, recovery cases, confirmed cases and the number of deaths for Brazil.

\[ m(t) = (m(1 - \nu(t))) + (m(1 - \mu_m)\nu(t)), \]  
(4)

where \( m \) is the death rate of the original model, and \( \mu_m \) is the rate of mortality reduction among the vaccinated population.

In summary, the following assumptions are considered:

1. The effectiveness of vaccines was taken as the average between values reported by manufacturers (\( \mu_m = 0.80 \)) [36,37].
2. The immunity of an individual only exists after he/she is fully vaccinated,
3. Once immunised, the individual still has a 50% chance of transmitting the disease and infecting another individual.

2.2. Numerical simulations

The differential evolution (DE) optimisation method [38] was used to estimate each parameter of the mathematical model to publicly available data for Brazil, Israel, and Germany with the same approach as described before in our previous works [23,28,29]. For this purpose, an in-house implementation was developed using the C programming language.

The objective function consists of the sum of the errors between the active, deaths, and confirmed cases generated by the simulations and the corresponding publicly available data. Here, we consider \( \hat{I}(t) \) as the reported numbers of active cases, \( \hat{D}(t) \) the number of deaths, and \( \hat{C}(t) \) the total confirmed cases. The objective function described by Eq. (6), was used to minimise the relative error \( R_E(\lambda, \hat{\lambda}) \) between the data and the model described by Eq. (5):

\[ R_E(\lambda, \hat{\lambda}) = \frac{\| \hat{\lambda}(t, p) - \hat{\lambda}(\lambda) \|_1}{\| \hat{\lambda}(\lambda) \|_1}, \]  
(5)

\[ \min_{p} O(p) = R_E(I, \hat{I}) + R_E(D, \hat{D}) + R_E(C, \hat{C}), \]  
(6)

where \( p \) is the set of parameters to be estimated.

Instead of taking only the best fit, we consider the existence of a model discrepancy [39] of 5%. Therefore, any parameters \( p \) that satisfy \( O(p) < 5\% \) is taken as a viable solution.

For the rate of daily vaccination, we have used data available in the Our World in Data [2] repository. For three countries study cases, the
Delta variant and relaxed policies were considered, which means that in Eq. (2), $a_1$ and $a_2$ were included.

After the characterisation phase, performed by the parameter’s estimation, the model was used to assess the impact of the vaccination and the restriction policies during the Delta wave. For this, we have simulated, using the adjusted model, two hypothetical situations: (1) a scenario without the vaccine, making $\nu(t) = 0$; (2) a scenario where isolation restrictions are relaxed by 50%, by multiplying $r_2$ by 1.5, at the same time the Delta variant was observed in each country.

3. Results

As proposed in Section 2 the experiments are separated in two: the first one focuses on parameter estimation, and the second one simulates two different hypothetical scenarios to assess the impact of vaccination and isolation policies. Section 3.1 presents estimated parameter values, data, and fitted models for the three analysed countries. In addition, some critical parameters of the model are further investigated. Section 3.2 presents the results of the two proposed scenarios.

3.1. Parameter estimation

The first set of experiments adjusts the model parameters. Table 1 presents all the estimated parameters for each of the three analysed countries.

Figs. 5, 6 and 7 show how the adjusted models compare to real data for active cases, number of deaths, recovered and confirmed cases for Germany, Israel, and Brazil, respectively. As one can see, the model reproduces the pandemics behaviour on three different scenarios, even when two different peaks are present.

Fig. 8 shows five violin plots, each one with the distribution of the estimated parameters (fraction of notified cases, mortality rate, contact reduction rates, transmission rates and duration of intervention)
for each country. We use the top 5% of results from the parameter estimation step by DE to characterise the behaviour in different countries.

3.2. Hypothetical scenarios of the pandemics

The second set of experiments uses the estimated parameters shown in Table 1 to produce two hypothetical scenarios. To represent these hypothetical scenarios, the only parameters that have been changed were $v(t)$ and $r_2$, as described below.

3.2.1. Scenario 1

The first hypothetical scenario simulates the pandemic in the absence of vaccines, i.e., we assume $v(t) = 0$, ∀t. Figs. 9, 10, and 11 show the evolution of the pandemic if the vaccination campaigns had not started in the three countries.

3.2.2. Scenario 2

Scenario 2 considers that the restrictions were relaxed in the period between $t_1$ and $t_1 + \Delta_1$, i.e., during the Delta wave. Figs. 12, 13 and 14 show the evolution of the pandemic if social distancing was reduced by 50% during the period of the Delta wave.

4. Discussion

4.1. Characterisation of the Delta wave in different countries

From the results presented in Section 3.1 we can see that the model was able to reproduce the observed data collected for Germany (Fig. 5), Israel (Fig. 6) and Brazil (Fig. 7). Table 1 and Fig. 8 compare the different countries, and Table 2 presents quantitative indicators which allow assessing the quality of the fitting. With respect to the mortality rate, the values estimated for $m$ in the violin plots are highest in Germany, followed by Brazil and Israel. The observed mortality rates
follow a negative correlation with the median age of the populations of these countries: 30 years old for Israel, 33 for Brazil and 45 for Germany [40].

On the other hand, the parameters found for $\theta$ suggest that under-reporting of cases in Brazil is more significant than in Germany and Israel.

The contact reduction rates associated with non-pharmacological mitigation policies ($r_1$) are very distinct in the three studied countries: about 0.85 in Brazil (poor), 0.6 in Israel (moderate), and 0.2 in Germany (strong). Since higher values of $r_1$ indicate scenarios with the adoption of social distancing policies, Germany showed the highest isolation, with a high concentration of values in the bottom region the violin plots, as Fig. 8 shows.

The parameter $\Delta_2$ estimates the duration the Delta variant took to generate an impact in the transmission rate of each country. The values found were between 5 and 25 days.

Finally, the increase of the transmission rate during the Delta wave was highest in Israel ($r_2 = 7.9$), followed by Germany (2.7) and Brazil (1.5). These very different values could be related to the fact that immunised persons against COVID-19 may lose approximately half of their defensive antibodies every three months [41]. Indeed, Israel, Germany, and Brazil fully vaccinated half of the population in March, July, and October, respectively. Another essential piece of information to interpret these results is that previous to the Delta wave, the predominant variant in Israel and Germany was the Alpha, while in Brazil, it was the Gamma variant, which was reported to be more transmissible than the Alpha one [42]. This may help explain why Brazil was less affected by the Delta wave (lowest estimated value of $r_2$) than Germany and Israel.

4.2. Quantifying the impact of vaccination during the Delta wave

The simulations of the hypothetical scenario 1 that considers the absence of vaccines are presented in Figs. 9, 10, and 11. In terms of
active infected persons, we would have 5 to 8 times more active cases in Israel and Germany without vaccines. In the case of Brazil, the increase would be 7%, corresponding to an increase of 100 thousand active cases. These data follow a positive correlation with the vaccination coverage of the population of each of these countries during the Delta wave: highest in Israel, followed by Germany and Brazil.

In terms of deaths, the highest impact due to the absence of vaccination was observed in Israel, with three times more deaths than with vaccines. This also agrees with the fact that during the Delta wave, Israel, among these countries, had the highest percentage of the population fully vaccinated. The results suggest that vaccination saved 30 thousand (a reduction of 30% in the total of deaths) and 300 thousand (a reduction of 50%) Germans and Brazilians, respectively, during this period.

4.3. Quantifying the importance of restriction and mitigation policies during the Delta wave

The simulations of the hypothetical scenario 2 that relax restrictions or isolation policies by increasing the contact rate by 50% is presented in Figs. 12, 13 and 14. In terms of active infected persons, we would have 10, 6 and 2 times more active cases in Germany, Israel and Brazil, respectively. This agrees with the values of contact reduction, $r_1$, estimated for this countries: 0.85 in Brazil (poor), 0.6 in Israel (moderate), and 0.2 in Germany (strong).

In terms of deaths, the results suggest that mitigation policies saved nine thousand (120% reduction in total deaths), 22 thousand (24% reduction), and 300 thousand (50% reduction) of Israeli, Germans and Brazilians, respectively, during this period.
5. Limitations

The main model limitation is related to the uncomprehended behaviour of the disease and its interaction with vaccination, which are currently under investigation. For instance, there is no consensus on how often COVID-19 reinfections occur and how they can affect the transmission dynamics.

Other limitations come from the hypotheses taken in the model formulation. As previously stated in Section 2, we focused on a simplified model with few parameters that could be adjusted to study different scenarios. Nevertheless, our results suggest that the simplified model did not compromise the studies carried out in this work to understand better the effect of changes in restrictive measures and the dynamics of the disease, adopting parameters adjusted for different countries.

6. Conclusions

In this work, we considered an extension of the SIRD model described in Oliveira et al. [29] and Reis et al. [23], adding the effects of the Delta variant. In this context, two types of experiments were performed, characterising essential features of the pandemic dynamics via parameter estimation and simulations of hypothetical scenarios to quantify the impact of vaccination and mitigation policies during the Delta wave. The first one adjusts the models to data observed in each of the three countries considered in this paper. It was possible to observe that the adjusted models could reproduce the different pandemic dynamics observed in Israel, Germany, and Brazil.

Among the analysed countries, Israel and Germany clearly experienced new waves due to the emergence of the Delta variant. In the case of Brazil one can observe a small increase in the number of cases. In
all cases, the adjusted parameters have distinguished two moments of the pandemic: before the Delta variant and after the Delta variant.

The model estimated that Brazil presented a lower mortality rate than Germany and Israel, but a higher under-reporting number of cases than these countries. The estimates for the contact reduction rates associated with non-pharmacological mitigation policies were very distinct in the three studied countries: poor mitigation policies in Brazil, moderate in Israel, and strong in Germany.

The Delta factor, which models the increase of virus transmission rate due to the Delta variant, was found to be highest in Israel (7.9), followed by Germany (2.7), and Brazil (1.5). The observed values may reflect the fact that immunised persons against COVID-19 lose approximately half of their defensive antibodies every three months [41]. Indeed, Israel, Germany, and Brazil fully vaccinated half of the population in March, July, and October, respectively. In addition, previous to the Delta wave, the predominant variant in Israel and Germany was the Alpha, while in Brazil, it was the Gamma variant, which was reported to be more transmissible than the Alpha [42]. This may help explain why Brazil was less affected by the Delta wave than Germany and Israel.

Finally, hypothetical scenarios were evaluated, considering the absence of vaccines and the relaxation of restriction policies.

The results suggest that vaccination saved 30 thousand (a reduction of 30% in the total of deaths) and 300 thousand (a reduction of 50%) Germans and Brazilians, respectively, during this period. In the case of Israel, the country with the best vaccination coverage during this period, vaccination saved up to 18 thousand persons (a reduction of 250%).

The results quantified that mitigation policies saved nine thousand (120% reduction in total deaths), 22 thousand (24% reduction), and 300 thousand (50% reduction) of Israeli, Germans and Brazilians, respectively, during this period.

In summary, the results suggest that both vaccination and mitigation policies were crucial in decreasing both the spread and the number of deaths during the Delta wave.
CRediT authorship contribution statement

Carolina Ribeiro Xavier: Conceptualization, Data curation, Software, Investigation, Validation, Visualization, Roles/Writing – original draft, Writing – review & editing. Rafael Sachetto Oliveira: Conceptualization, Investigation, Methodology, Software, Validation, Visualization, Roles/Writing – original draft, Writing – review & editing. Vinícius da Fonseca Vieira: Data curation, Investigation, Validation, Visualization, Roles/Writing – original draft, Writing – review & editing. Bernardo Martins Rocha: Investigation, Validation, Visualization, Writing – review & editing. Ruy Freitas Reis: Investigation, Validation, Visualization, Writing – review & editing. Bárbara de Melo Quintela: Investigation, Validation, Visualization, Writing – review & editing. Marcelo Lobasco: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Supervision, Validation, Visualization, Roles/Writing – original draft, Writing – review & editing. Rodrigo Weber dos Santos: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Roles/Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1

| Parameters                  | Germany | Brazil |
|-----------------------------|---------|--------|
| b                           | 0.085266 | 0.147085 |
| w                           | 0.018850 | 0.000880 |
| r1                          | 0.214431 | 0.606899 |
| r2                          | 39.049589 | 22.293633 |
| r3                          | 21.594887 | 22.293633 |
| r4                          | 7.918693 | 2.717870 |
| r5                          | 109.069294 | 170.240946 |
| r6                          | 22.999850 | 14.546485 |
| r7                          | 8.484022 | 3.063787 |
| r8                          | 39.894601 | 39.595420 |
| r9                          | 7.088910 | 7.332446 |
| r10                         | 0.406565 | 0.346774 |

Table 2

| O(p) (6)            | Germany | Israel |
|---------------------|---------|--------|
| Best                | 0.0627  | 0.1549 |
| Mean                | 0.0717  | 0.1584 |
| Worst               | 0.3206  | 0.3210 |

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[46] B. de Melo Quintela received the MS degree in computational modelling at the Federal University of Juiz de Fora (UFJF), a master in science’s degree in Computational Modelling from the Federal University of Juiz de Fora (UFJF), a master’s degree in Computational Engineering from the Federal University of Rio de Janeiro (2015). She is currently an associate professor at the Federal University of Juiz de Fora. Her research interests include multiscale modelling for in silico medicine and computational immunology.

[47] Ruy Freitas Reis holds a bachelor’s degree in Exact Science (2012), Computer Science (2013) and Computational Engineer-ing (2014) at the Universidade Federal de Juiz de Fora (UFJF), a master’s degree (2014) and a doctorate (2018) in Computer Modelling at the UFJF as well. He is currently Adjunct Professor in Computer Science Department at the UFJF. He has experience in computational modelling, bio-heat, computational immunology, finite difference method, finite volume method, finite element method, distributed, and high-performance computing.

[48] Marcelo Lobosco holds a bachelor’s degree in Informatics from Fluminense Federal University (1996), a master in Science’s degree in Applied Computing and Automation from Fluminense Federal University (1999), and a Doctor in Science’s degree in Systems Engineering and Computing from Federal University of Rio de Janeiro (2005). He is currently an Associate Professor at the Federal University of Juiz de Fora. Marcelo Lobosco has experience in Computer Science, working mainly on the following topics: computational immunology and high-performance computing.

[49] Rodrigo Weber dos Santos holds a bachelor’s degree in Electrical/Electronic Engineering from Universidade Federal do Rio de Janeiro (1996), a master in science’s degree in Computer and Systems Engineering from Universidade Federal do Rio de Janeiro (1998) and a doctor in science’s degree in Mathematics from Universidade Federal do Rio de Janeiro (2002). He is currently Full Professor at the Federal University of Juiz de Fora. He has experience in Computational Modelling and Biomedical Engineering, with a focus on the Modelling of Biological Systems.