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Recursive state and parameter estimation of COVID-19 circulating variants dynamics

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ABSTRACT

COVID-19 pandemic response with non-pharmaceutical interventions is an intrinsic control problem. Governments balance social distancing policies to avoid overload on health system without major economic impact. A control strategy requires reliable predictions to be efficient on long-term. SARS-CoV-2 mutability, vaccination coverage and time-varying restrictive measures change virus evolution dynamics frequently. State and parameter estimations are an option to deal with these uncertainties. In this paper, a SIR-based model is proposed considering data available and feedback corrections over time. State and parameter estimations were done on state estimators with augmented states. Three observers were implemented: Constrained Extended Kalman Filter (CEKF), CEKF and Smoother (CEKF&S) and Moving Horizon Estimator (MHE). The parameters estimated therein are based on vaccine efficacy studies regarding transmissibility, severeness of disease and lethality. Social distancing is a measured disturbance calculated with Google mobility data. Six federative units from Brazil are used to evaluate proposed strategy: Amazonas, Mato Grosso do Sul, Rio Grande do Norte, Rio Grande do Sul, Rio de Janeiro and São Paulo. State and parameter estimations were realized from October 1st 2020 to July 1st 2021 during which Zeta and Gamma variants emerged. Results showed an efficient detection of circulating variants from proposed parameter estimation. In addition, it asserted dynamics related to virus mutations. Zeta mutations increase lethality between 19 and 45%, and increased transmissibility between 20 and 38%. Gamma mutations, on the other hand, increased lethality between 62 and 110% while increasing transmissibility between 52 and 107%. Furthermore, parameter estimation indicated existence and temporal change of subnotification on hospitalized and deceased individuals. Overall, dynamics estimated were within expectations and are applicable to control theory.

Introduction

First official cases of COVID-19 are dated from December 2019 in Wuhan, China. Its spread worldwide later months resulted in a pandemic classification from the World Health Organization (WHO) at 11 March 2020¹. The first official case in Brazil was reported two weeks earlier on February 26th 2020 from a man returning to São Paulo from Italy. Social distancing presented effective mitigation over virus spread², however, it generates negative impacts on economy and mental health of overall population³. Vaccination is a control action that progressively reduces virus transmissibility aiming for a disease elimination defined by zero community infections⁴. Nonetheless, vaccination coverage is bounded to vaccine acceptance rate which makes its goal unfeasible even if vaccination provided 100 % efficacy against transmission.

The SARS-CoV-2 virus is highly mutable with thousands of variants documented since its origin on December 2019⁵. Mutations might change dynamics of the system, thus a model parameter updating is required for reliable predictions. Genomic surveillance of SARS-CoV-2 in Brazil indicates four predominant variants from February 2020 to July 2021: B.1.1.33 and B.1.1.28 whose circulation were predominant from pandemic beginning to September 2020; Zeta variant (P.2), which originated in Rio de Janeiro, whose circulation countrywide was predominant from October 2020 to February 2021; Gamma variant (P.1), which originated in Amazonas, whose circulation countrywide was predominant from mid-February 2021 to July 2021⁶. The dynamics from each variant corresponds to a set of parameters that must be estimated to ensure accurate model on an extended period of analysis.

Mathematical modeling of epidemiological evolution by a compartmental model corresponds to a common practice in the control theory⁷⁻¹¹ since its simplicity suits real-time applicability. Transmissibility, disease severeness and lethality properties from the model are deducible from its formulation. The definition of the contagion rate in function of an input variable related to social distancing is common therein. Olivier et al.⁷ defined several compartmental model parameters as time-varying functions. Kohler et al.⁸ formulated hospitalized parameters as function of the state variables. Morato et al.⁹ used a three-step parameter estimation on contagion, recovery and mortality rates. Control theory was mostly focused on mitigating the disease spread in a time window before vaccination availability. In addition, there were discrete and continuous definitions for the input variables.

The first followed government restrictive measures previously implemented^{7,9,10} while the latter was based on Google mobility data¹¹ or arbitrary⁸.

Virus mutations and vaccination coverage affect model dynamics, adding uncertainties towards the system. There are examples of recursive state and parameter estimation application on COVID-19 pandemic scenario. Sun et al.¹² estimated parameters at each discrete time with a grid search, while Menda et al.¹³ estimated them with a neural network. Liao et al.¹⁴, and Morato et al.⁹ estimated parameters with a moving horizon estimation based on a least-square method followed by a regressive method, however, the latter⁹ proposed an additional moving average on the estimation structure. Tsay et al.¹⁵ estimated unmeasured states with an Unscented Kalman Filter. Zhu et al.¹⁶ estimated states and parameters into an augmented state with an Extended Kalman Filter (EKF). Song et al.¹⁷ estimated states with an EKF and parameters with a proposed strategy based on maximum likelihood. Nonetheless, state and parameter estimations in the literature are based on simple models and the authors did not evaluate virus mutations and vaccination dynamics with the estimator results.

In this work, a comprehensive compartmental model is proposed for detecting epidemiological dynamics in terms of transmission, severeness of disease and lethality. The model was formulated considering a recursive estimation approach in which simplifying assumptions were focused on detecting aforementioned dynamics with parameter estimation. The novel contributions comes from identifying a compartmental model for pandemic first wave using temporal prevalence distributions from seroprevalence survey EPICOV19-BR which improved model reliability. In addition, we proposed a recursive state and parameter estimation able to identify COVID-19 variant emergence and characterize its dynamics on epidemiological evolution. Those additional information were obtained from defining estimated parameters from vaccine efficacy studies.

In Section 2, we describe the proposed compartmental model regarding the simplifying assumptions and its identification problem on pandemic first wave. In Section 3, we describe the state and parameter estimation strategies on a augmented state and describe implemented state estimators. In Section 4, we show numerical results from simulations on several Brazilian federative units in comparison to measured data and parameters estimated therein. Finally, Section 5 concludes the paper and set possible future works.

Mathematical Model

Predicting the dynamics of an epidemiological evolution is of utmost importance to control its spread in a population. The modeling by a SIR-based model is conventional in control theory because of its simplicity and real-time applicability. However, SARS-CoV-2 virus presents high mutability which affects model parameters over time. In addition, a relevant percentage of the population have been vaccinated in 2021 which also affects those parameters. Both uncertainty causes were irrelevant on early stages of the COVID-19 pandemic but their systematically increase makes long-term forecasts unreliable. Hence, a feedback is required to accurately forecast the system on an extended period of analysis. In this work, these uncertainties are addressed with a parameter estimation therein an extended state on a state estimator.

In this section, a compartmental model is adapted to improve estimation performance and to comprise data availability in Brazil. The model in Equation (1) was adapted from the SIDARTHE model proposed in Giordano et al.¹⁸. The estimated parameters α_0 , x_c and x_m regarding transmissibility, severeness of disease and lethality, respectively, are described later on the section. These parameters are correlated with the dynamics analyzed on COVID-19 vaccine effectiveness studies. We selected a federative unit per Brazilian region to evaluate epidemic progression countrywide, but Southeastern Region is an exception with two. Amazonas (AM) was chosen for the North Region; Mato Grosso do Sul (MS) for the Central-West Region; Rio Grande do Norte (RN) for Northeast Region; Rio Grande do Sul (RS) for South Region; Rio de Janeiro (RJ) and São Paulo (SP) for Southeast Region. The total population N_i from each federative unit i is divided into the following compartments:

- Susceptible (S): individuals prone to infection;
- Latent (L): individuals infected in the incubation period, while they are not infectious;
- Infected (I): undetected asymptomatic individuals;
- Diagnosed (D): detected asymptomatic individuals, whose infection rate is neglected because of the detection of the disease;
- Ailed (A): undetected symptomatic individuals;
- Recognized (R): detected symptomatic individuals, whose infection rate is neglected because of the detection of the disease;
- Threatened (T): individuals hospitalized in nursery or Intensive Care Units (ICU);
- Healed Detected (H_d): individuals cured that were detected while on disease progression;

- Extinct (E): individuals deceased due to the disease;
- Healed with treatment (H_t): individuals cured after a period hospitalized;
- Healed Undetected (H_u): individuals cured of the disease without being detected.

$$\frac{dS}{dt} = -vS \quad (1a)$$

$$\frac{dL}{dt} = vS - \rho L \quad (1b)$$

$$\frac{dI}{dt} = p\rho L - (\lambda + \varepsilon)I \quad (1c)$$

$$\frac{dD}{dt} = \varepsilon I - \lambda_d D \quad (1d)$$

$$\frac{dA}{dt} = (1-p)\rho L - (\theta + \mu + \kappa)A \quad (1e)$$

$$\frac{dR}{dt} = \theta A - (\mu_d + \kappa_d)R \quad (1f)$$

$$\frac{dT}{dt} = \mu A + \mu_d R - (\sigma + \tau)T \quad (1g)$$

$$\frac{dH_d}{dt} = \lambda_d D + \kappa_d R + \sigma T \quad (1h)$$

$$\frac{dE}{dt} = \tau T \quad (1i)$$

$$\frac{dH_t}{dt} = \sigma T \quad (1j)$$

$$\frac{dH_u}{dt} = \lambda I + \kappa A \quad (1k)$$

where all states refers to fractions calculated for a total population N_i informed by Ministry of Health of Brazil¹⁹. v is the infection rate, ρ is the incubation rate and p is the fraction of infected individuals who remain asymptomatic. ε , and θ are the detection rate of I and A , respectively. λ , λ_d , κ , κ_d and σ are the recovery rates of I , D , A , R and T , respectively. τ is the mortality rate whereas μ and μ_d are severe illness rate of A and R , respectively. A scheme of state transitions is shown in Fig. 1.

Figure 1. Schematic diagram of the proposed compartmental model.

The healed compartment from Giordano et al. model¹⁸ is subdivided in three compartments: H_d , H_u and H_t . $H_t \subset H_d$ is a measurable state by Brazilian Severe Acute Respiratory Syndrome (SARS) database^{20,21}. H_d is an unmeasured state corresponding to majority of the cumulative cases on any analysis post first wave. H_u is an unmeasured state containing the majority of post-infection individuals for all federative units studied. The closed system assumption from compartment models implies on the redundancy $S + L + I + D + A + R + T + H_d + E + H_u = 1$, thus we substituted Equation (1k) by Equation (2).

$$H_u = 1 - S - L - I - D - A - R - T - H_d - E \quad (2)$$

The additional state L corresponds to a natural dead time of the system which is usual in control oriented models^{7,10} and in forecast to a lesser extent^{22–24}. Presymptomatics infected are within it as $(1-p)L$, but their infection rate is assumed insignificant to simplify parameter estimation.

We assumed that reinfection dynamics are mitigated by state estimation, thus S in the model Equation (1) is unconnected with healed compartments H_u and H_d , despite reinfections by Gamma²⁵ and Delta²⁶ variants and natural immunity decrease.

The infection rate is simplified into a single parameter to guarantee observability. Infections caused by presymptomatic and detected infected are assumed insignificant in relation to infections caused by undetected infected. In addition, the same infection rate is applied to symptomatic and asymptomatic, although the first are acknowledged as more infectious²⁷.

$$\nu = \alpha(I + A) \quad (3)$$

where α is the contagion rate which consists of the probability a susceptible individual contract the disease from a possible contact with an infectious person. It is a function of non-pharmaceutical interventions (NPI), vaccination coverage and circulating variants. NPI and vaccination mitigate virus spread in the short-term, while virus mutations might affect its transmissibility as it happened for Gamma²⁵ variant.

NPI dynamics are inserted into a compartmental model by time-varying functions²³, independent variables^{8,10,11} or time-varying parameters estimated over time^{14,15}. We focused on these last two as they are better suited to a control-oriented model. First of all, we separated social distancing from other NPI by defining α according to Equation (4).

$$\alpha = \alpha_0(1 - u) \quad (4)$$

where $u \in [0, 1]$ is the manipulated variable related to social distancing and α_0 is the contagion rate estimated. The linearity applied over α and u in Equation (2) gets the correct direction between contagion rate and social distancing. NPI unrelated to social such as mass gathering restrictions and mask requirements are comprised in α_0 .

Social distancing is measurable by Google mobility data as percentage changes in relation to a baseline defined from data-sets before COVID-19 outbreak²⁸. Google mobility data is given in six categories: Recreation, Essentials, Parks, Transit, Workplace and Resident, which are correlated to government action. We defined u as a linear combination among the two most independent categories for simplicity. A cross-correlation matrix with zero lag was calculated to identify them considering data from all federative units studied from February 15th 2020 to July 1st 2021. The cross-correlation normalized was calculated by `xcorr` function from MATLAB and its results can be found in Supplementary Table S1. The similarity among two signals therein is characterized by the absolute difference from 0 where independence is defined. The Essentials signal had a cross-correlation closer to 0 for all categories except itself, however, it is a monthly periodic signal while the others are weekly. Hence, the cross-correlation closest to 0, disregarding Essentials, is related to Parks and Workplace, thus they were selected to define u . Finally, u is defined in the range $[0, 1]$ with addition of contagion weights correlated to heuristic probability of infection for each activity as given by Equation (5). The contagion weight of Parks was doubled because we considered infection on outdoor leisure activities is more likely due to a greater probability of agglomerations and lesser probability of NPI adherence therein.

$$u(t) = \frac{-2 \langle Parks(t) \rangle - \langle Workplace(t) \rangle + 300}{600} \quad (5)$$

where $\langle Parks(t) \rangle$ and $\langle Workplace(t) \rangle$ are weekly moving averages of Parks and Workplace, respectively.

Regarding the equations for undetected asymptomatic and symptomatic individuals, Equations (1c) and (1e), respectively, the fraction of individuals who progress in the disease asymptomatic $p \in [0.15, 0.7]$ according to U.S. Centers for Disease Control and Prevention (CDC)²⁹. Virus mutations, testing policies, and different age distribution explain the broad range. The parameter p is not estimated over time, because available data does not provide observability for it as data is not categorized in symptomatic and asymptomatic. Hence, we defined $p = 0.5$ as an intermediate value whose error is mitigated by the state estimator with estimations of I and A . The vaccine efficacy against infection is correlated to both α_0 and p , since its measurement according to U.S. Food and Drug Administration (FDA) accounts only for symptomatic cases.

Following the vaccine efficacy against severe and mild diseases, a parameter x_c is defined as the fraction of symptomatic individuals who develop severe or mild symptoms. Assuming severe and mild illnesses imply hospitalization then x_c is the fraction of individuals moving from A and R to T . Summing up Equations (1e) and (1f):

$$\frac{d(A + R)}{dt} = (1 - p)\rho L - (\mu + \kappa)A - (\mu_d + \kappa_d)R$$

which is simplified by assuming $\mu \approx \mu_d$ and $\kappa \approx \kappa_d$ to:

$$\frac{d(A + R)}{dt} = (1 - p)\rho L - (\mu + \kappa)(A + R)$$

Thus:

$$x_c = \frac{\mu}{\mu + \kappa}$$

Let us rewrite μ and κ as probability function of a symptomatic individual to follow its respective way, then:

$$x_c = \frac{(1 - x_k - x_\theta)\tilde{\mu}}{(1 - x_k - x_\theta)\tilde{\mu} + x_k\tilde{\kappa}} \quad (6)$$

where x_k and x_θ are, respectively, the probabilities of an undetected or detected individual in A to recover. The average rates of severe illness $\tilde{\mu}$ and recovery of a symptomatic $\tilde{\kappa}$ correspond to properties studied in the literature. In this work, we defined $\tilde{\mu} = 1/5 \text{ d}^{-1}$, and $\rho = 1/5.2 \text{ d}^{-1}$ from CDC²⁹, and suited $\tilde{\kappa}$ on test sensitivity. Testing rate is a local and time dependent property that affect both probabilities x_k and x_θ . Let us define a correlated parameter x_s as the fraction of recovered undetected individuals. We have from Equation (1e):

$$x_s = \frac{\kappa}{\mu + \theta + \kappa} = \frac{x_k\tilde{\kappa}}{(1 - x_k - x_\theta)\tilde{\mu} + x_\theta\tilde{\theta} + x_k\tilde{\kappa}} \quad (7)$$

Rewriting Equation (7) for x_k :

$$x_k = \frac{x_s x_\theta \tilde{\theta} + (1 - x_\theta)x_s \tilde{\mu}}{(1 - x_s)\tilde{\kappa} + x_s \tilde{\mu}}$$

and substituting it in Equation (6) rewritten for x_θ :

$$x_\theta = \frac{(1 - x_c - x_s)\tilde{\kappa}\tilde{\mu}}{(1 - x_c - x_s)\tilde{\kappa}\tilde{\mu} + (1 - x_c)x_s\tilde{\theta}\tilde{\mu} + x_c x_s \tilde{\theta}\tilde{\kappa}} \quad (8)$$

Considering x_c and x_s represent fractions of symptomatic infected then $x_s + x_c \in [0, 1]$. Locations with steadier testing policy could estimate x_s as a constant. However, rapid tests and RT-PCR were not available in public health service in early stages of the COVID-19 pandemic in Brazil. Defining x_s as a logistic equation in function of time according to:

$$x_s = a_{x_s} \left(1 - \frac{a_\zeta}{1 + \exp(-b_\zeta(t - c_\zeta))} \right) \quad (9)$$

where a_{x_s} , a_ζ , b_ζ , c_ζ are model parameters identified. The formulation of Equation (9) is based on the empirical knowledge that x_s is initially high and progressively decreases to a steady state once tests are available to overall population. In addition, the set of parameters therein comprises uncertainties regarding test policy.

Analogously to x_s , we define the fraction of recovered undetected asymptomatic individuals x_a from Equation (1c) as:

$$x_a = \frac{\lambda}{\lambda + \varepsilon} = \frac{x_{id}\tilde{\lambda}}{x_{id}\tilde{\lambda} + (1 - x_{id})\tilde{\varepsilon}} \leftrightarrow x_{id} = \frac{x_a\tilde{\varepsilon}}{\tilde{\lambda} + x_a(\tilde{\varepsilon} - \tilde{\lambda})}$$

where x_{id} is the probability of detecting the disease in an asymptomatic individual. Defining x_a similarly to x_s , we have:

$$x_a = a_{x_a} \left(1 - \frac{a_\zeta}{1 + \exp(-b_\zeta(t - c_\zeta))} \right) \quad (10)$$

where a_{x_a} is an additional model parameter identified. Equations (9) and (10) define linear dependence between x_s and x_a to avoid overfit of an excessive amount of model parameters. Nonetheless, test sensibility and probability according to symptom appearance are comprehended therein, and related uncertainties are mitigated in the state estimation.

Finally, we define a parameter x_m analogous to vaccine efficacy against lethality as the fraction of threatened individuals who deace. We define it from Equation (1g) as:

$$x_m = \frac{\tau}{\sigma + \tau} \quad (11)$$

Rewriting Equation (11) as function of a death probability x_e :

$$x_m = \frac{x_e\tilde{\tau}}{(1 - x_e)\tilde{\sigma} + x_e\tilde{\tau}}$$

and isolating x_e give us:

$$x_e = \frac{x_m\tilde{\sigma}}{(1 - x_m)\tilde{\tau} + x_m\tilde{\sigma}} \quad (12)$$

where $\tilde{\sigma}$ is the average recovery rate from hospitalization and $\tilde{\tau}$ is the average mortality rate. These parameters depend on healthcare demand, medical resources, notification delay, virus mutations, vaccine coverage, and testing policy. We assumed correlated uncertainties are mitigated by the state estimator, thus we defined $\tilde{\sigma}$ and $\tilde{\tau}$ as constants to allow estimation further in time. The Brazilian SARS database^{20,21} was used to estimate their value for each federative unit.

The Ministry of Health of Brazil¹⁹ provides data over cumulative confirmed cases, death, and their respective incidences for each federative unit and each county. The Brazilian SARS database^{20,21}, on the other hand, provides clinical data from patients with severe acute respiratory syndrome which comprehend confirmed and suspected cases of COVID-19 and other diseases. It notifies period of hospitalization, evolution date, confirmation status of COVID-19, etc. Summing up all confirmed COVID-19 patients per each federative unit i gives observability on T_i and $H_{t,i}$. In addition, overall means of hospitalized evolution between April 19th 2021 and July 1st 2021 were used to define $\tilde{\sigma}$ and $\tilde{\tau}$. Both databases are daily measured, therefore sampling time $T_s = 1$ d. Average testing rates $\tilde{\epsilon}$ and $\tilde{\theta}$ are location dependent, however, we assumed that correlated uncertainties are comprehended in $a_{\zeta,i}$, $b_{\zeta,i}$ and $c_{\zeta,i}$. Hence, we defined $\tilde{\epsilon} = \tilde{\theta} = 1 \text{ d}^{-1}$ to suit sampling time. In summary, the monitored variable $\mathbf{y}_i$ is defined as:

$$\mathbf{y}_i(k) = \mathbf{h}(\mathbf{x}_i) = \begin{bmatrix} D_i(k) + R_i(k) + T_i(k) + H_{d,i}(k) + E_i(k) \\ E_i(k) \\ T_i(k) \\ H_{t,i}(k) \end{bmatrix} \quad (13)$$

where $\mathbf{x}_i = [S_i \ L_i \ I_i \ D_i \ A_i \ R_i \ T_i \ H_{d,i} \ E_i \ H_{t,i}]^T$.

EPICOV19-BR provides additional data over temporal distributions on Brazil, in addition to measured data in Equation (13). It surveyed COVID-19 prevalence in cities from all regions on different timelines^{30,31}. Let us consider the prevalence estimations from federative units given by Marra and Quartin³² based on three phases of EPICOV19-BR. Furthermore, if we assume $\tilde{\lambda} = \tilde{\kappa} = 1/15 \text{ d}^{-1}$ then we correlate states $H_{d,i}$ and $H_{u,i}$ with test sensitivity. EPICOV19-BR did not test hospitalized patients³⁰, and used a IgM and IgG antibody test more sensitive 15 days after appearance of symptoms³³. Hence, the state transition model $\mathbf{f}(\mathbf{x}_i, u_i)$ for each federative unit i is defined in Equation (14).

$$\begin{aligned} \frac{dS_i}{dt} &= -v_i S_i \\ \frac{dL_i}{dt} &= v_i S_i - \rho L_i \\ \frac{dI_i}{dt} &= \rho \rho L_i - (\lambda_i + \epsilon_i) I_i \\ \frac{dD_i}{dt} &= \epsilon_i I_i - \lambda_i D_i \\ \frac{dA_i}{dt} &= (1 - \rho) \rho L_i - (\theta_i + \mu_i + \kappa_i) A_i \\ \frac{dR_i}{dt} &= \theta_i A_i - (\mu_i + \kappa_i) R_i \\ \frac{dT_i}{dt} &= \mu_i (A_i + R_i) - (\sigma_i + \tau_i) T_i \\ \frac{dH_{d,i}}{dt} &= \lambda_i D_i + \kappa_i R_i + \sigma_i T_i \\ \frac{dE_i}{dt} &= \tau_i T_i \\ \frac{dH_{t,i}}{dt} &= \sigma_i T_i \\ H_{u,i} &= 1 - S_i - L_i - I_i - D_i - A_i - R_i - T_i - H_{d,i} - E_i \\ v_i &= \alpha_{0,i} (1 - u_i) (I_i + A_i) \\ x_{a,i} &= a_{x_{a,i}} \left(1 - \frac{a_{\zeta,i}}{1 + \exp(-b_{\zeta,i}(t - c_{\zeta,i}))} \right), \quad x_{s,i} = a_{x_{s,i}} \left(1 - \frac{a_{\zeta,i}}{1 + \exp(-b_{\zeta,i}(t - c_{\zeta,i}))} \right), \quad x_{id,i} = \frac{x_{a,i} \tilde{\epsilon}}{\tilde{\lambda} + x_{a,i}(\tilde{\epsilon} - \tilde{\lambda})} \\ x_{k,i} &= \frac{x_{s,i} x_{\theta,i} \tilde{\theta} + (1 - x_{\theta,i}) x_{s,i} \tilde{\mu}}{(1 - x_{s,i}) \tilde{\kappa} + x_{s,i} \tilde{\mu}}, \quad x_{\theta,i} = \frac{(1 - x_{c,i} - x_{s,i}) \tilde{\kappa} \tilde{\mu}}{(1 - x_{c,i} - x_{s,i}) \tilde{\kappa} \tilde{\mu} + (1 - x_{c,i}) x_{s,i} \tilde{\theta} \tilde{\mu} + x_{c,i} x_{s,i} \tilde{\theta} \tilde{\kappa}}, \quad x_{e,i} = \frac{x_{m,i} \tilde{\sigma}_i}{(1 - x_{m,i}) \tilde{\tau}_i + x_{m,i} \tilde{\sigma}_i} \\ \lambda_i &= (1 - x_{id,i}) \tilde{\lambda}, \quad \epsilon_i = x_{id,i} \tilde{\epsilon}, \quad \theta_i = x_{\theta,i} \tilde{\theta}, \quad \kappa_i = x_{k,i} \tilde{\kappa}, \quad \mu_i = (1 - x_{k,i} - x_{\theta,i}) \tilde{\mu}, \quad \sigma_i = (1 - x_{e,i}) \tilde{\sigma}_i, \quad \tau_i = x_{e,i} \tilde{\tau}_i \end{aligned} \quad (14)$$

Now let us suppose test sensitivity is 100 % during T_p days and it decays suddenly to zero. Therefore, the prevalence distributions from EPICOV19-BR for each studied federative unit i during each phase $j \in \{1, 2, 3\}$ are given by Equation (15), where prevalence bounds $Pre_{i,j,min}$ and $Pre_{i,j,max}$ can be found in Supplementary Table S2³². In addition, the decision variable $T_p \in \mathbb{N}$ was arbitrated as $T_p = 50$.

$$Pre_{i,j,min} \leq \frac{1}{N_{total,j}} \sum_{k=0}^{N_{total,j}-1} (H_{d,i}(N_{ep,j}+k) + H_{u,i}(N_{ep,j}+k) - H_{d,i}(N_{ep,j}+k-T_p) + H_{u,i}(N_{ep,j}+k-T_p)) \leq Pre_{i,j,max} \quad (15)$$

where $t(N_{ep,1}) = 14/\text{May}/2020$, $t(N_{ep,2}) = 4/\text{June}/2020$, $t(N_{ep,3}) = 21/\text{June}/2020$ are initial dates from first, second and third phases of EPICOV19-BR, respectively, while $N_{total,1} = 8$, and $N_{total,2} = N_{total,3} = 4$ correspond to their respective duration in days. On early stages of pandemic outbreak recovered individuals are approximately null, thus we defined $H_{d,i}(N_{ep,j}+k-T_p) = H_{u,i}(N_{ep,j}+k-T_p) = 0 \forall \{N_{ep,j}+k < T_p | j \in \{1, 2, 3\}\}$.

Gene sequences reported in GISAID⁶ indicate Zeta variant appearance in mid-October. Hence, identification step is bounded at $t(N_f) = 1/\text{October}/2020$ to guarantee steady circulation of variants B.1.1.28 and B.1.1.33. The lower bound aims at an imported infection neglectful in the system, when $[I_i(t_{0,i}) D_i(t_{0,i}) A_i(t_{0,i}) R_i(t_{0,i}) T_i(t_{0,i}) H_{d,i}(t_{0,i}) E_i(t_{0,i}) H_{t,i}(t_{0,i}) H_{u,i}(t_{0,i})]^T \approx \mathbf{0}$. Therefore, only $S_i(t_{0,i})$ and $L_i(t_{0,i})$ were considered as optimization variables for the model identification. Hospitalized individuals T_i were used to define $\{N_{0,i} | t_{0,i} = t(N_{0,i})\}$ from the solution of a system composed by $T_i(N_{0,i}) > 0.00003$, $T_p - N_{ep,3} - N_{0,i} \geq 0$, $N_{0,i} \in \mathbb{N}$, for each federative unit i . The model identification considered an Integral Time-Squared Error performance criteria for reducing the error weight of imported infections.

The nonlinear optimization problem in Equation (16) was solved separately for each federative unit i with IPOPT³⁴ via CasADI/MATLAB³⁵.

$$\min_{\text{ident}_i} \sum_{k=N_{0,i}}^{N_f} (k - N_{0,i} + 1) \|\mathbf{y}_i(k) - \mathbf{z}_i(k)\|_{\mathbf{Q}_{id,i}}^2$$

Subject to Equation (15) and:

$$\begin{aligned} \mathbf{x}_i(k+1) &= \mathbf{x}_i(k) + \int_k^{k+1} \mathbf{f}(\mathbf{x}_i(t), u_i(t)) dt \\ \mathbf{y}_i(k) &= \mathbf{h}(\mathbf{x}_i(k)) \\ S_i(t_{0,i}) &\in [0.9, 1], L_i(t_{0,i}) \in [0, 0.1], \alpha_{0,i} \geq 0, a_{x_{a,i}} \in [0, 0.1], a_{x_{s,i}} \in [0, 0.1], x_{c,i} \in [0, 1], x_{m,i} \in [0, 1] \\ a_{\zeta,i} &\in [0, 1], b_{\zeta,i} \in [0, 0.25], c_{\zeta,i} \geq 0, x_{a,i} \in [0, 1], x_{s,i} \in [0, 1], x_{s,i} + x_{c,i} \in [0, 1], x_{a,i} \geq x_{s,i} \end{aligned} \quad (16)$$

where $\text{ident}_i = [S_i(t_{0,i}) L_i(t_{0,i}) \alpha_{0,i} a_{x_{a,i}} a_{x_{s,i}} x_{c,i} x_{m,i} a_{\zeta,i} b_{\zeta,i} c_{\zeta,i}]^T$, $\mathbf{z}_i$ are the measured variables and $\mathbf{Q}_{id,i} \in \mathbb{R}^{4 \times 4}$ is a weight matrix calculated to normalize measurements from early stages of the pandemic to July 1st 2021 according to Equation (17). All integration therein state estimators are solved with cvodes via CasADI/MATLAB. The initial guess was set as $\text{ident}_{0,i} = [0.95 \ 0.05 \ 0.1 \ 0.9 \ 0.9 \ 0.02 \ 0.1 \ 0.1 \ 0.1 \ 20]^T$. Results and location dependent parameters are shown in Table 1.

$$\mathbf{Q}_{id,i,j} = \frac{1}{(y_{j,max} - y_{j,min})^2}, j \in \{1, 2, 3, 4\} \quad (17)$$

State and Parameter Estimation

State estimation is essential for a model with uncertainties and without measurements from all states. It comprehends the estimation of unknown properties based on available measurements while filtering them to reduce the noise effects. The proposed model in Equation (14) has S_i , L_i , I_i , and A_i as unmeasurable, D_i , R_i , and $H_{d,i}$ as unmeasured, and T_i , E_i and $H_{t,i}$ as measured states. Besides, the sum of the states D_i , R_i , T_i , $H_{d,i}$, and E_i , which represents the confirmed cases, is also a measured variable. Furthermore, the epidemiological model parameters have uncertainties related to time-varying NPI, its acceptance from population, circulating virus variants and vaccine coverage. Hence, a state estimator is required to accurately forecast the epidemiological evolution of the COVID-19 on each analyzed federative unit i . In this work, we selected the parameters $\alpha_{0,i}$, $x_{c,i}$ and $x_{m,i}$ to be estimated over time. The parameter estimation was done with an augmented state $\mathbf{X}_i$ within a state estimator. In this case, the state $\mathbf{X}_i$ is defined as:

$$\mathbf{X}_i = \begin{bmatrix} \mathbf{x}_i \\ \boldsymbol{\psi}_i \end{bmatrix}$$

Table 1. Initial states and parameters of the proposed model for each federative unit i .

	AM	MS	RN	RS	RJ	SP
$t_{0,i}$	03/April/2020	19/April/2020	19/April/2020	19/April/2020	15/April/2020	27/March/2020
$S_i(t_{0,i})$	0.9429	0.9996	0.9933	0.9994	0.9764	0.9954
$L_i(t_{0,i})$	0.0571	0.0004	0.0067	0.0006	0.0236	0.0046
$\alpha_{0,i}$	0.2054	0.3465	0.3625	0.3857	0.2652	0.3017
$a_{x_{a,i}}$	1.0000	0.8876	0.9998	0.9794	0.9998	1.0000
$a_{x_{s,i}}$	0.9726	0.8876	0.9425	0.8914	0.9475	0.8859
$x_{c,i}$	0.0274	0.0939	0.0575	0.1086	0.0525	0.1141
$x_{m,i}$	0.3753	0.2565	0.4497	0.2832	0.4375	0.2663
$a_{\zeta,i}$	0.2639	0.5991	0.5597	0.6560	0.1738	0.5316
$b_{\zeta,i}$	0.2499	0.1081	0.1820	0.0440	0.2499	0.0548
$c_{\zeta,i}$	40.8723	69.6388	49.8618	72.0821	28.4936	68.4612
$\tilde{\sigma}_i$	0.0782	0.0859	0.0721	0.0822	0.0491	0.0794
$\tilde{\tau}_i$	0.0672	0.0645	0.0766	0.0614	0.0726	0.0673

where $\psi_i = [\alpha_{0,i} x_{c,i} x_{m,i}]^T$ are the parameters to be estimated.

Time-varying dynamics from ψ_i are unknown, thus we assumed their differential equations equals to zero and they are subject to an artificial noise. Therefore, the state transition model $\mathbf{F}(\mathbf{x}_i, u_i)$ for the augmented state is:

$$\mathbf{F}(\mathbf{X}_i, u_i) = \begin{bmatrix} \mathbf{f}(\mathbf{x}_i, u_i) \\ \mathbf{0} \end{bmatrix}$$

Measurements in process control are usually within seconds or minutes that limits real-time applicability for state estimators. Nonetheless, the sampling time $T_s = 1$ d allows an analysis over different strategies of state estimation. In this work, we evaluated the same scenario for each analyzed federative unit with a Constrained Extended Kalman Filter (CEKF)³⁶, a Constrained Extended Kalman Filter and Smoother (CEKF&S), and a Moving Horizon Estimator (MHE)³⁷. We used constrained observers to satisfy feasible region $\mathcal{X} = \{\mathbf{0} \leq \mathbf{x}_i \leq \mathbf{1}, H_{u,i} \in [0, 1], \alpha_{0,i} \geq 0, x_{c,i} \in [0, 1], x_{m,i} \in [0, 1], x_{s,i} + x_{c,i} \in [0, 1]\}$.

CEKF is the extension of the Kalman filter for nonlinear models. It uses a first-order Taylor expansion of the system model to estimate current value based on the latest measurement and estimated state. The COVID-19 data, however, is given in weekly cycles in which weekends have fewer notifications that are updated on working days. The CEKF&S is an intermediate option between a regular CEKF and a MHE regarding both computational time and performance. It comprehends a forward estimation from a moving horizon with a CEKF followed by a backward estimation with a smoothing equation. The weekly oscillations are attenuated in the resulting state and covariance update. The MHE uses a moving horizon of estimated states and measured variables in a nonlinear problem, which is solved at each sampling time. This optimization problem has N_p times the degrees of freedom of the CEKF, where N_p is the horizon size. Therefore, it has better estimation at the cost of a significant higher computational time.

The error covariance matrix $\mathbf{P}_{0,i}$ and the initial estimated state $\mathbf{X}_{0,i}$ of each federative unit i are defined at $t_f = 1/\text{October}/2020$. $\mathbf{x}_{0,i}$ and $\mathbf{y}_{0,i}$ can be found in Supplementary Table S3, while $\psi_{0,i}$ was already shown in Table 1. The matrix $\mathbf{P}_{0,i}$ was defined as $\mathbf{P}_{0,i} = 10 \text{ diag} \left(\text{diag} \left(\begin{bmatrix} 3\mathbf{x}_{0,i}^T & \psi_{0,i}^T \end{bmatrix} \begin{bmatrix} 3\mathbf{x}_{0,i}^T & \psi_{0,i}^T \end{bmatrix}^T \right) \right)$, the covariance matrix of process noise $\mathbf{Q}_{k,i}$ was defined as $\mathbf{Q}_{k,i} = \mathbf{P}_{0,i}$ and the covariance matrix of observation noise $\mathbf{R}_{k,i}$ was defined as $\mathbf{R}_{k,i} = 1000 \text{ diag} \left(\text{diag} \left(\mathbf{y}_{0,i} \mathbf{y}_{0,i}^T \right) \right)$.

Let us define the model with uncertainties:

$$\begin{aligned} \mathbf{X}_i(k|k-1) &= \mathbf{X}_i(k-1|k-1) + \int_{k-1}^k \mathbf{F}(\mathbf{X}_i(t), u_i(t)) dt + \omega_{k-1,i} \\ \mathbf{y}_i(k|k-1) &= \mathbf{h}(\mathbf{X}_i(k|k-1)) + \mathbf{v}_{k,i} \end{aligned} \quad (18)$$

where $\omega_{k,i} \sim \mathcal{N}(\mathbf{0}, \mathbf{Q}_{k,i})$ and $\mathbf{v}_{k,i} \sim \mathcal{N}(\mathbf{0}, \mathbf{R}_{k,i})$ are the process and measurement noise, respectively.

The linearization of Equation (18) into a state-space model yields:

$$\mathbf{X}_i(k|k-1) = \phi_{k-1,i} \mathbf{X}_i(k-1|k-1) \quad (19a)$$

$$\mathbf{y}_i(k|k-1) = \mathbf{H}_{k,i} \mathbf{X}_i(k|k-1) \quad (19b)$$

where output matrix $\mathbf{H}_{k,i}$ and state transition matrix $\phi_{k,i}$ are defined as:

$$\mathbf{H}_{k,i} = \left(\frac{\partial \mathbf{h}(\mathbf{X}_i(k|k-1))}{\partial \mathbf{X}_i} \right)_{\mathbf{X}_i(k|k-1)} \quad (19c)$$

$$\phi_{k,i} = \exp(\mathbf{G}_{k,i} T_s) = \exp(\mathbf{G}_{k,i}) \quad (19d)$$

$$\mathbf{G}_{k,i} = \left(\frac{\partial \mathbf{F}(\mathbf{X}_i(k|k), u_i(k))}{\partial \mathbf{X}_i} \right)_{\mathbf{X}_i(k|k), u_i(k)} \quad (19e)$$

whose analytical expressions for these Jacobian matrices can be found in Supplementary Equation S1. We remark Equation (19b) is equivalent to $\mathbf{h}(\mathbf{X}_i(k|k-1))$ as it is a linear function.

The initial conditions for each federative unit i were defined as $\mathbf{X}_{0,i} = \mathbf{X}_i(N_f|N_f)$, and $\mathbf{P}_{0,i} = \mathbf{P}_{N_f|N_f,i}$ for all state estimators. All simulations with state estimation started at $t_f = 1/\text{October}/2020$ and end at $t_{sim} = t(N_{sim}) = 1/\text{July}/2021$. State estimators performance was evaluated by Mean Absolute Percentage Error (MAPE) calculated for each output $\{y_j|j \in \{1, 2, 3, 4\}\}$ as:

$$MAPE_j = \frac{100}{N_{sim} - N_f} \sum_{k=1}^{N_{sim}-N_f} \left| \frac{z(k) - y(k)}{z(k)} \right|$$

CEKF

For sake of notation simplicity, the subscript i , denoting each federative unit, was suppressed from the estimators description. For the CEKF, the optimization problem in Equation (20) to update $\mathbf{X}(k|k)$ at each discrete time k corresponds to a quadratic programming, which was solved at each iteration with qpOASES³⁸ via CasADI/MATLAB.

$$\min_{\mathbf{X}(k|k)} \|\mathbf{y}(k|k) - \mathbf{z}(k)\|_{\mathbf{R}_k^{-1}}^2 + \|\mathbf{X}(k|k) - \mathbf{X}(k|k-1)\|_{\mathbf{P}_{k-1|k-1}}^2$$

Subject to:

$$\begin{aligned} \mathbf{X}(k|k-1) &= \mathbf{X}(k-1|k-1) + \int_{k-1}^k \mathbf{F}(\mathbf{X}(t), u(t)) dt \\ \mathbf{y}(k|k) &= \mathbf{H}_k \mathbf{X}(k|k) \\ \mathbf{X}(k|k) &\in \mathcal{X} \end{aligned} \quad (20)$$

The state covariance matrix $\mathbf{P}_{k|k}$ is updated via Riccati equation in discrete time as follows:

$$\mathbf{P}_{k|k} = \phi_{k-1} \mathbf{P}_{k-1|k-1} \phi_{k-1}^T - \phi_{k-1} \mathbf{P}_{k-1|k-1} \mathbf{H}_k^T [\mathbf{H}_k \mathbf{P}_{k-1|k-1} \mathbf{H}_k^T + \mathbf{R}_k]^{-1} \mathbf{H}_k \mathbf{P}_{k-1|k-1} \phi_{k-1}^T + \mathbf{Q}_{k-1} \quad (21)$$

Thereafter the discrete time is advanced to $k+1$ and Equations (20) and (21) are solved again to update $\mathbf{X}(k|k)$ and $\mathbf{P}_{k|k}$.

CEKF&S

The CEKF&S was implemented according to formulation from Salau et al.³⁹. The state estimation is initially done N_p times with the CEKF from previous section, resulting the vectors $\tilde{\mathbf{P}}_{k|k} = [\mathbf{P}_{k-N_p|k-N_p}^T \mathbf{P}_{k-N_p+1|k-N_p+1}^T \cdots \mathbf{P}_{k|k}^T]^T$ and $\tilde{\mathbf{X}}(k|k) = [\mathbf{X}(k-N_p|k-N_p)^T \mathbf{X}(k-N_p+1|k-N_p+1)^T \cdots \mathbf{X}(k|k)^T]^T$.

Let us define $\mathbf{X}^S(k) = \mathbf{X}(k|k)$ and $\mathbf{P}_k^S = \mathbf{P}_{k|k}$ for estimating backward with Rauch-Tung-Striebel (RTS) smooth equations⁴⁰. Then, solving Equation (22) for $\{j \in [1, N_p] | j \in \mathbb{N}\}$, yields the solution $\mathbf{X}^S(k-N_p)$ and $\mathbf{P}_{k-N_p}^S$.

$$\begin{aligned} \mathbf{X}(k+1-j|k-j) &= \mathbf{X}(k-j|k-j) + \int_{k-j}^{k+1-j} \mathbf{F}(\mathbf{X}(t), u(t)) dt \\ \mathbf{P}_{k+1-j|k-j} &= \phi_{k-j} \mathbf{P}_{k-j|k-j} \phi_{k-j}^T + \mathbf{Q}_{k-j} \\ \mathbf{C}_{k-j} &= \mathbf{P}_{k-j|k-j} \phi_{k-j}^T [\mathbf{P}_{k+1-j|k-j}]^{-1} \\ \mathbf{X}^S(k-j) &= \mathbf{X}(k-j|k-j) + \mathbf{C}_{k-j} [\mathbf{X}^S(k+1-j) - \mathbf{X}(k+1-j|k-j)] \\ \mathbf{P}_{k-j}^S &= \mathbf{P}_{k-j|k-j} + \mathbf{C}_{k-j} [\mathbf{P}_{k+1-j}^S - \mathbf{P}_{k+1-j|k-j}] \mathbf{C}_{k-j}^T \end{aligned} \quad (22)$$

The smoothed result is set as initial condition $\mathbf{X}(k-N_p|k-N_p) = \mathbf{X}^S(k-N_p)$ and $\mathbf{P}_{k-N_p|k-N_p} = \mathbf{P}_{k-N_p}^S$ for the CEKF to estimate them forward until current step k . State and covariance estimations from each step are used to update their respective

values in the vectors $\tilde{\mathbf{X}}(k|k)$ and $\tilde{\mathbf{P}}_{k|k}$. An additional CEKF iteration is used to build $\tilde{\mathbf{X}}(k|k)$ and $\tilde{\mathbf{P}}_{k|k}$ for the next discrete time. Two horizon sizes $N_{p,1} = 7$ and $N_{p,2} = 28$ were used in the simulations to evaluate the effect of N_p over the estimator performance.

MHE

The MHE was implemented according to formulation from Rawlings et al.⁴¹. The past horizon $N_p = \min(k - N_f, N_{p,0})$ at each discrete time k , where $N_{p,0}$ is the given horizon size for the estimator. In this way, we can set initial condition for the optimization problem in Equation (23) as $\mathbf{P}_{k-N_p-1|k-N_p-1}$ and $\mathbf{X}(k - N_p - 1|k - 1)$. The state is updated at each discrete time k with the solution of this nonlinear programming, which was solved at each iteration with IPOPT via CasADI/MATLAB.

$$\min_{\mathbf{X}_k} \quad \|\hat{\mathbf{X}}(k - N_p|k) - \mathbf{X}(k - N_p|k)\|_{\mathbf{P}_{k-N_p-1|k-N_p-1}^{-1}}^2 + \sum_{j=k-N_p+1}^k \|\hat{\mathbf{X}}(j|k) - \mathbf{X}(j|k)\|_{\mathbf{Q}_{j-1}^{-1}}^2 + \sum_{j=k-N_p}^k \|\mathbf{y}(j|k) - \mathbf{z}(j)\|_{\mathbf{R}_j^{-1}}^2$$

Subject to:

$$\begin{aligned} \mathbf{X}(j|k) &= \hat{\mathbf{X}}(j-1|k) + \int_{j-1}^j \mathbf{F}(\mathbf{X}(t), u(t)) dt \\ \mathbf{y}(j|k) &= \mathbf{H}_j \mathbf{X}(j|k) \\ \hat{\mathbf{X}}(j|k) &\in \mathcal{X} \\ j &\in [k - N_p, k], j \in \mathbb{N} \end{aligned} \tag{23}$$

where $\mathbf{X}_k = [\hat{\mathbf{X}}(k - N_p|k)^T \hat{\mathbf{X}}(k - N_p + 1|k)^T \dots \hat{\mathbf{X}}(k|k)^T]^T$ are the estimated states and $\hat{\mathbf{X}}(k - N_p - 1|k) = \mathbf{X}(k - N_p - 1|k - 1)$. The state covariance matrix $\mathbf{P}_{k|k}$ is updated via the Riccati Equation (21).

The MHE gives estimations over a horizon $\mathbf{X}_k$ based on initial conditions $\mathbf{P}_{k-N_p-1|k-N_p-1}$ and $\mathbf{X}(k - N_p - 1|k - 1)$. Current estimation at a discrete time k are $\hat{\mathbf{X}}(k|k) \in \mathbf{X}_k$ and $\mathbf{P}_{k|k}$. The advance in discrete time is carried out by solving Equations (23) and (21) based on previous estimations from $k - N_p - 1$ and $k - 1$. MHE was implemented with $N_{p,0} = 7$.

Simulation results and discussion

In this section, we present the results from simulations for federative units Amazonas (AM), Mato Grosso do Sul (MS), Rio Grande do Norte (RN), Rio Grande do Sul (RS), Rio de Janeiro (RJ) and São Paulo (SP). States and parameters were estimated from 1/October/2020 to 1/July/2021. Confirmed cases (y_1) and Extinct (y_2) measures were obtained from Ministry of Health of Brazil¹⁹ while Hospitalized (y_3) and Healed with treatment (y_4) were obtained from Brazilian SARS database^{20,21}. Input variable u_i , calculated with Google mobility data, is presented in Fig. 2 for each federative unit.

Figure 2. Time evolution of input variable related to social distancing.

All three state estimators were able to drive estimation towards measures $\mathbf{z}_i$ for each federative unit, since MAPE results were smaller than 5% as can be seen in Table 2. Hence, COVID-19 dynamic evolution on regional populations were captured despite model assumptions. The better overall estimations of y_2 and y_4 , and the larger estimation error on y_1 and y_3 for Amazonas and Rio de Janeiro were caused by the tuning $\mathbf{P}_{0,i}$ and $\mathbf{Q}_{k,i}$ based on $\psi_{0,i}$ values from Table 1. The usage of the same tuning formulation for all analyzed federative units implied into some suboptimal sets of tuning parameters. Table 2 let us identify a worst estimation from CEKF followed by CEKF&S and MHE according to expectations. Moreover, the increase of horizon size N_p from 7 to 28 showed no significant gain in estimation accuracy of CEKF&S. Time evolution of outputs measures from all federative units can be found in Supplementary Figs. S1-S5, except for Amazonas that is shown in Fig. 3.

Table 2. Mean absolute percentage error for simulation with state estimation for each federative unit i .

	State Estimator	AM	MS	RN	RS	RJ	SP
y_1	CEKF	4.17	0.64	1.11	1.40	2.70	0.73
	CEKF&S ($N_p = 7$)	2.30	0.56	0.93	1.10	1.50	0.61
	CEKF&S ($N_p = 28$)	2.16	0.71	1.13	1.32	1.54	0.84
	MHE ($N_p = 7$)	0.39	0.42	1.13	0.97	0.53	0.46
y_2	CEKF	0.43	0.45	0.35	0.45	0.34	0.32
	CEKF&S ($N_p = 7$)	0.38	0.40	0.32	0.33	0.39	0.30
	CEKF&S ($N_p = 28$)	0.42	0.44	0.34	0.35	0.42	0.31
	MHE ($N_p = 7$)	0.38	0.36	0.34	0.32	0.39	0.27
y_3	CEKF	2.96	3.80	3.43	1.72	4.21	2.29
	CEKF&S ($N_p = 7$)	2.67	2.84	2.73	2.90	1.64	1.76
	CEKF&S ($N_p = 28$)	2.62	3.06	2.69	3.04	1.53	1.72
	MHE ($N_p = 7$)	2.39	2.09	2.63	2.52	1.38	1.32
y_4	CEKF	0.38	0.23	0.26	0.39	0.19	0.10
	CEKF&S ($N_p = 7$)	0.28	0.20	0.22	0.19	0.32	0.10
	CEKF&S ($N_p = 28$)	0.32	0.22	0.22	0.21	0.38	0.13
	MHE ($N_p = 7$)	0.19	0.18	0.22	0.22	0.31	0.12

Amazonas had only two coronavirus waves identifiable through y_3 as can be seen in Figs. 3 unlike the other analyzed federative units. Data from GISAID⁶ indicated that variants B.1.1.33, B.1.1.28 and a local B.1.378 kept circulating significantly from 1/October/2020 to 4/December/2020 when first Gamma variant sequence was identified. Hence, predominant circulation of Zeta variant, started at mid-October 2020, was quickly overlapped by Gamma variant and a single wave happened. The estimated parameters shown in Figs. 4-6 represent this profile specifically with MHE estimations, and indicates CEKF&S with $N_p = 7$ had closer parameter estimations with MHE than CEKF&S with $N_p = 28$. It is important to emphasize that MHE was applied with $N_p = 7$, which could explain this proximity.

Figure 3. Time evolution of measures and estimated outputs from Amazonas (AM).

All other federative units also had an overlap of Zeta and Gamma waves, however, there were greater periods with circulation of Zeta. Figs. 4-6 infer in a rougher parameter estimation from CEKF&S with $N_p = 28$, despite having greater horizon size.

The moving horizon with estimated states backward and forward might smooth estimations overall, but each estimation still considers a single past estimation and measure. Further studies towards effects of N_p in CEKF&S are required, but these were not the subject of this work. Since MHE provides better state and parameter estimations overall, any descriptions henceforth is related to these estimates.

Figure 4. Time evolution of estimated contagion rate α_0 from all analyzed federative units.

Age distribution and local healthcare do not explain the discrepancy from $x_{c,i}$ and $x_{m,i}$ among the analyzed federative units observed on Figs. 5 and 6, respectively. It is caused by model assumption that all hospitalized individuals are identified for COVID-19. Some case studies presented higher $x_{c,i}$ altogether with lower $x_{m,i}$ which do not affect the Infection-Fatality-Rate (IFR), but indicate subnotification on COVID-19 cases among hospitalized individuals. Amazonas, Rio Grande do Norte and Rio de Janeiro presented testing policy focused on more severe hospitalizations. IFR calculus defined in Equation (24) highlight this dynamic.

$$IFR_i = (1 - p)x_{c,i}x_{m,i} \quad (24)$$

The results presented in Fig. 7 indicate a guaranteed subnotification of deaths in Amazonas. In addition with Figs. 5 and 6, it indicates that subnotification on hospitalized individuals in Rio de Janeiro and Rio Grande do Norte decreased over time, following $x_{m,i}$ decrease. The Zeta appearance and effects are unidentifiable from parameter estimations in Rio de Janeiro despite it being the source of this variant. It is possible that $\alpha_{0,i}$ was unchanged because the implemented NPI and its acceptance or different testing policy on general population had balanced dynamics from circulating variants. The lethality evaluation of a variant with $x_{m,i}$ is unfeasible because it decreased in Rio Grande do Norte and Rio de Janeiro due to testing policy. In addition, its peaks in Mato Grosso do Sul, Rio Grande do Sul and São Paulo are explained by delayed notifications after overload of health system, which temporarily increases mortality. Hence, we used IFR_i to conclude that Zeta variant increased lethality from 19% in São Paulo to 45% in Rio Grande do Norte based on $IFR_i(t_{0,i})$ calculated with values from Table 1. In addition, $\alpha_{0,i}$ estimation indicates Zeta transmissibility increased from 20% in Mato Grosso do Sul to 38% in Rio Grande do Norte.

Amazonas faced oxygen shortage on Gamma variant wave which implicated in mortality increase beyond virus mutations. Nonetheless, estimates of $\alpha_{0,i}$ had an increase of 66% over its initial value, while $x_{c,i}$ had an increase of 58 %. In addition, its estimations on $x_{c,i}$ are smoother which allowed to identify increase in severeness of disease ranging from 36% in Rio de Janeiro to 73% in Rio Grande do Norte. Rio de Janeiro also presented low estimates on $\alpha_{0,i}$ and IFR_i for Gamma variant, with an increase of only 19% transmissibility, and 20% lethality, thus we disregarded its results. The analysis through IFR_i indicated a lethality increase between 62% in Rio Grande do Norte and 110% in Rio Grande do Sul for Gamma variant. Moreover, transmissibility increased between 52% in Mato Grosso do Sul and 107% in Rio Grande do Sul based on $\alpha_{0,i}$ values from Table 1. Further analysis on IFR_i points out variant spread countrywide, being Amazonas its source. Gamma variant initially spread

Figure 5. Time evolution of estimated fraction of symptomatic individuals who develop mild and severe symptoms x_c from all analyzed federative units.

Figure 6. Time evolution of estimated fraction of threatened individuals who decease x_m from all analyzed federative units.

Figure 7. Time evolution of IFR considering estimated parameters.

to the farthest studied case from Amazonas: Rio Grande do Sul. Afterwards, it spread to the Brazilian economic center, São Paulo, and thereafter to the rest of the federative units with similar rate. The quicker propagation of Gamma to the farthest location from Amazonas is explained by less rigid NPIs, which is pointed out by estimation of $\alpha_{0,i}$. Rio Grande do Sul had the highest estimations of $\alpha_{0,i}$ with similar u_i values on overall parameter estimations. São Paulo had only the forth highest $\alpha_{0,i}$ among the studied cases. However, it was the second to contract Gamma significantly, which enforces theory that it spread countrywide afterwards. Overall, $\alpha_{0,i}$ indicated with more evidence the emergence of circulating variants in the system. Finally, IFR_i decreased in later times for most federative units until 1/July/2021, indicating that vaccination coverage does reduce mortality on infected individuals.

The computational time of the three state estimators were evaluated throughout average simulation time among all analyzed federative units for 273 d, from 1/October/2020 to 1/July/2021. Simulation time was measured by tic and toc function in MATLAB. All simulations were carried out sequentially on a AMD Ryzen 5 5600X 3.70 GHz to mitigate computational noises. The average simulation time was measured as 21.6 s for CEKF, 101 s for CEKF&S with $N_p = 7$, 315 s for CEKF&S with $N_p = 28$, and 13616 s for MHE. Even the average execution time of 50 s per sampling time for the MHE implies in real-time applicability of the state estimators with the selected tuning in the COVID-19 pandemic scenario, since all of them have execution time lower than the sampling time $T_s = 1$ d. CEKF&S performance and computational time were between the CEKF and the MHE which enforce it as an alternative for processes with faster sampling times.

Conclusion

In this work, we presented a model proposition capable of identifying COVID-19 subnotification on hospitalized and deceased individuals by comparison of $x_{c,i}$, $x_{m,i}$ and IFR_i among analyzed federative units. We remark that this model is suitable for control strategies, assuming there are available hospitalized data.

The performance among estimators confirmed MHE as a better and more suitable state estimator for COVID-19 due to daily sampling time. Nonetheless, CEKF&S presented reasonable estimations in comparison, and a significant reduction in computational time, which altogether make it applicable in real-time applications.

Parameter estimations identified a lethality increase ranging from 19 to 45% and transmissibility increase between 20 and 38% for Zeta mutation. In addition, we identified Gamma mutations caused a lethality increase ranging from 62 to 110% and a transmissibility increase between 52 and 107%. The variants emergence and their dynamics were well detected by the estimation strategy, which decreases uncertainties on predictions. Moreover, an initial decrease of lethality due to vaccination was also observed. Hence, the parameter estimation within a recursive state estimation can deal with dynamic uncertainties from COVID-19 pandemic scenario.

Future works accounts for the implementation of an economic model predictive control and studies over inserting vaccination in the proposed model. Delta variant is predominant in Brazil since August 2021. It was disregarded from an initial analysis because its mutation highly increase contagion on vaccinated people which are measured. Therefore, a model comprising vaccinated individuals should generate better estimations for Delta dynamics.

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Author contributions statement

A.R.S designed the research and D.M.S performed the research and wrote the manuscript. All authors reviewed the manuscript.

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Competing interests

The authors declare no competing interests

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