

Modeling and Simulation in System Biology Term Project

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Mathematical modeling of COVID-19 in 14.8 million individuals in Bahia, Brazil

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➤ Introduction

COVID-19 is currently rapidly spreading across Asia, Europe, and other continents, a prominent feature is the high rate of human-to-human transmission of the virus, other worrying aspects are the severity of clinical complications and the lack of vaccines or effective drugs to prevent the disease and Accelerate patient recovery. Therefore, the only effective mechanisms currently available to inhibit viral transmission are non-pharmacological interventions (NPIs) and compliance in the population. The sudden increase in the demand for hospitalizations during the pandemic has led to the collapse of health systems due to insufficient medical infrastructure and medical resources, especially affecting countries with limited medical infrastructure, such as the example in this article, Bahia, Brazil. By using compartmentalized models, such as the 3-compartment SIR (susceptibility-infection-recovery), insight into the dynamics of disease transmission can be obtained, based on this model and expanding the number of compartments to study other key aspects of COVID-19. This paper constructs an 8-compartment model based on this principle with time-varying disease transmission capacity, accounting for often undetected transmission of asymptomatic/mild cases, hospitalization of severe cases (requiring clinical/ICU beds) and mortality. Finally, this paper provides a post-assessment of the COVID-19 epidemic in Bahia using data obtained after the initial analysis, focusing on actual clinical/ICU bed usage, COVID-19 cases, and deaths during the period, and the Utility of the proposed model in describing epidemics in real-time.

➤ Methods

✓ Data Sources and Case Definition

The data source used for this study is the daily series of cumulative confirmed COVID-19 cases in Bahia, its capital El Salvador and the remaining cities

and the daily mortality series from public data provided by the Minister of Health of the State of Bahia, which also provided state-level daily bed occupancy rates for clinical and ICU beds. In addition, the management data of the Instituto Couto Maia in El Salvador was accessed.

✓ **SEIIHURD Model**

The SEIIHURD model (as shown in Fig. 1) subdivides the population into 8 segments as follows: susceptible population (S), those who have not been exposed to the disease; exposed (E), individuals who have been exposed to the virus and are in the incubation period, non-infectious period; (I) contagious, i.e. people who are currently infected and able to transmit the disease to contacts; recovered (R), those who were previously infected and recovered from the disease; death (D) death due to COVID-19, after A period of hospitalization or ICU. Infected individuals (I) are further divided into asymptomatic/undetected infections, denoted I_{asym} , and symptomatic infections which are denoted I_{sym} . Notably, the spread of COVID-19 through undocumented infections, including truly asymptomatic (individuals who never develop symptoms) as well as infections with very mild symptoms, has been shown to contribute to the spread of SARS-CoV-210. Therefore, individuals in the I_{asym} compartment represent a group of people who usually do not require hospitalization, are not considered in official data, and define a subset of undetected infections. Finally, a subset of infected people (clinical beds) (H) who will develop severe symptoms requiring hospitalization, and those in critical condition who will eventually require ICU admission (U).

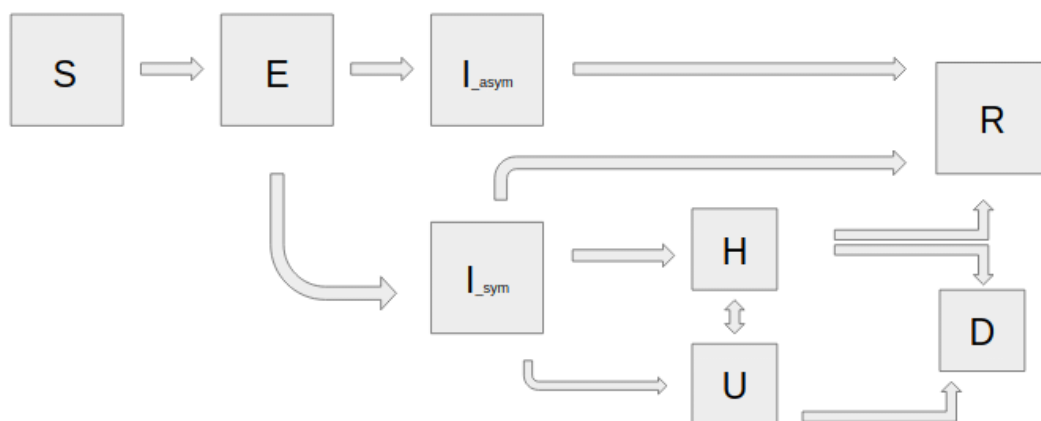


Fig. 1 Flow diagram for modeling the dynamics of COVID-19 transmission in the 8-compartment SEIIHURD model

This model assumes that hospital containment procedures reduce the chance of contact with susceptible individuals, so transmission of individuals in H and U compartments is ignored. Patient mobility between H and U compartments was also considered, as individuals initially admitted to the clinical ward may worsen their condition and require ICU beds. In addition, all patients in U were transferred to H prior to discharge and recovery. The authors observed that all patients requiring ICU beds had one of two outcomes: they were transferred to an inpatient unit (H) prior to recovery and discharge, or they died of disease.

✓ **Model Construction**

Taking local interventions in movement restrictions into account (such as government quarantine orders), the authors treat transmission rates as a function of time and vary by local measures. To define β , let $\{t_1, t_2, \dots, t_n\}$ be a set of time points defining the change in transmission rate. Then, we can write β as a function of time t as equation (1)

$$\beta(t) = \beta_0 \mathcal{H}(t_1 - t) + \sum_{i=1}^{n-1} \beta_i \mathcal{H}(t_{i+1} - t) \mathcal{H}(t - t_i) + \beta_n \mathcal{H}(t - t_n), \quad (1)$$

where $\mathcal{H}(t) = \lim_{k \rightarrow \infty} \frac{1}{1 + \exp(-2kt)}$ is a Heaviside step function, β_i are transmission rates that can be obtained by the fitting of the data to the time interval defined by the t_i 's. The system of differential equations then reads:

$$\frac{dS}{dt} = \frac{-\beta(t)S(I_s + \delta I_a)}{N}, \quad (2)$$

$$\frac{dE}{dt} = \frac{\beta(t)S(I_s + \delta I_a)}{N} - \kappa E, \quad (3)$$

$$\frac{dI_a}{dt} = (1 - p)\kappa E - \gamma_a I_a, \quad (4)$$

$$\frac{dI_s}{dt} = p\kappa E - \gamma_s I_s, \quad (5)$$

$$\frac{dH}{dt} = h\xi\gamma_s I_s + (1 - \mu_U + \omega_U \mu_U)\gamma_U U - \gamma_H H, \quad (6)$$

$$\frac{dR}{dt} = \gamma_a I_a + (1 - h)\gamma_s I_s + (1 - \mu_H)(1 - \omega_H)\gamma_H H, \quad (7)$$

$$\frac{dR}{dt} = \gamma_a I_a + (1 - h) \gamma_s I_s + (1 - \mu_H)(1 - \omega_H) \gamma_H H, \quad (8)$$

$$\frac{dD}{dt} = (1 - \omega_H) \mu_H \gamma_H H + (1 - \omega_U) \mu_U \gamma_U U, \quad (9)$$

✓ Parameters

Key epidemiological parameters used in the SEIIHURD model:

Parameters	Description
N	Size of initial population.
β	Transmission rate that varies over time.
β_0	Pre-intervention transmission rate
β_1	Post-intervention transmission rate
δ	Asymptomatic/non-detected infectivity factor
κ	Mean exposed period, or incubation time (days^{-1}).
p	Proportion of latent (E) that proceed to symptomatic infective.
γ_a	Mean asymptomatic period (days^{-1}).
γ_s	Mean symptomatic period (days^{-1}).
h	Proportion of symptomatic needing hospitalization or ICU (severe or critical cases).
$1-\xi$	Proportion of hospitalized symptomatic that proceed to ICU (critical cases).
γ_H	Mean hospitalization (clinical beds) period (days^{-1})
γ_U	Mean period in ICU (days^{-1}).
μ_H	Death rate of individuals in general ward.
μ_U	Death rate of individuals in ICU.
ω_H	Proportion of hospitalized that goes to ICU
ω_U	Proportion of ICU that goes to hospitalization

➤ Results of the original paper

✓ The impact of social distancing and government intervention on disease transmission

Authors begin their analysis by assessing the impact of local non-pharmaceutical interventions (NPIs) on disease transmission in the state of Bahia, its capital, El Salvador, and the rest of the city. For this, the model was fitted using the number of confirmed cases as declared by local authorities

(Fig. 2) and the authors estimated parameters related to the transmission rate (β_0, β_1), the time point when it changes, and the factor that reduce the infectivity of the asymptomatic/non-detected, δ . The results showed that with an initial transmission rate of $\beta_0 = 1.28$ ([1.26–1.30] 95% CI), the transmission rate decreased by 36% 27 days after the state's first confirmed case, yielding $\beta_1 = 0.92$ ([0.91, 0.93] 95% CI). In El Salvador (population 2.6 million), the drop was even 54.7%, while the remaining cities saw a drop of about 40.6%.

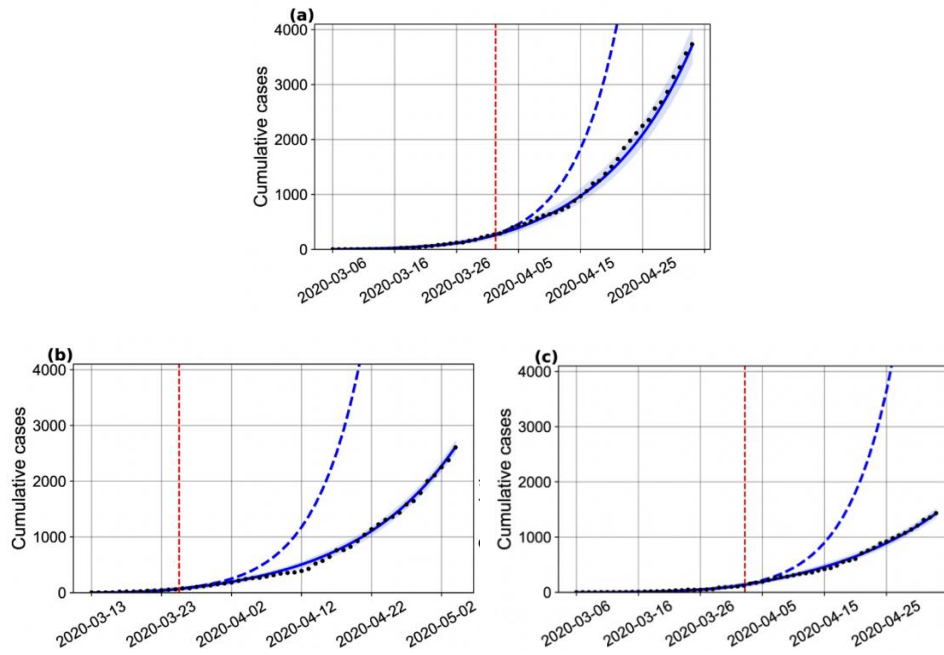


Fig. 2 (a) in Bahia; (b) in Salvador, and (c) in the remaining 416 cities. The parameters $\kappa = 1/4$, $p = 0.2$, $\gamma_a = 1/3.5$, $\gamma_s = 1/4$ were fixed and h was set to zero for the capital and inland cities. The black dots correspond to the actual number of cases. The vertical dashed red lines are the dates of transition from β_0 to β_1 . The blue dashed and full lines represent the evolution of the epidemic with a fixed transmission rate β_0 and with both β_0 and β_1 , respectively. The shaded error bands represent 95% confidence intervals of the mean calculated using the weighted non-parametric bootstrap method.

✓ Real-time modeling

Using the latest epidemiological data, the authors were able to compare the original predictions of the SEIIHURD model with COVID-19 in Bahia until September 13, 2020. For this post-hoc evaluation, they first compared the 30-day forecasts of the original model (calibrated on May 4) with actual data for that period (Fig. 3), inferring that homogeneous models, such as theirs, have limited long-term forecasting power for the entire state, and in the actual case where the model is used to predict the allocation of medical resources, recalibration using more current data will improve the accuracy of the predictions while providing a reasonable time frame for policymakers to manage resources.

The original model's 30-day forecast (calibrated on May 4, 2020) predicted the number of reported cases, deaths, and ICU needs well, with actual values falling within the confidence intervals of the authors' predictions (Fig. 3). Confirming their original predictions, under a scenario where interventions were maintained, the ICU bed availability would be exhausted by May 13, while this capacity was actually reached on May 24, 2020 (11 days later) as indicated by the data, also within the range of the estimated confidence interval. For hospitalization requirements, the results shown are less accurate. The collapse is expected on May 9, and the clinical bed occupancy-related data is only at full capacity on May 29. It may be due to changes in hospitalization parameters, but the authors were unable to obtain the latest data.

Finally, to describe the latest transmission dynamics in Bahia, we re-estimated our model using data available as of September 13, 2020 (Fig. 4).

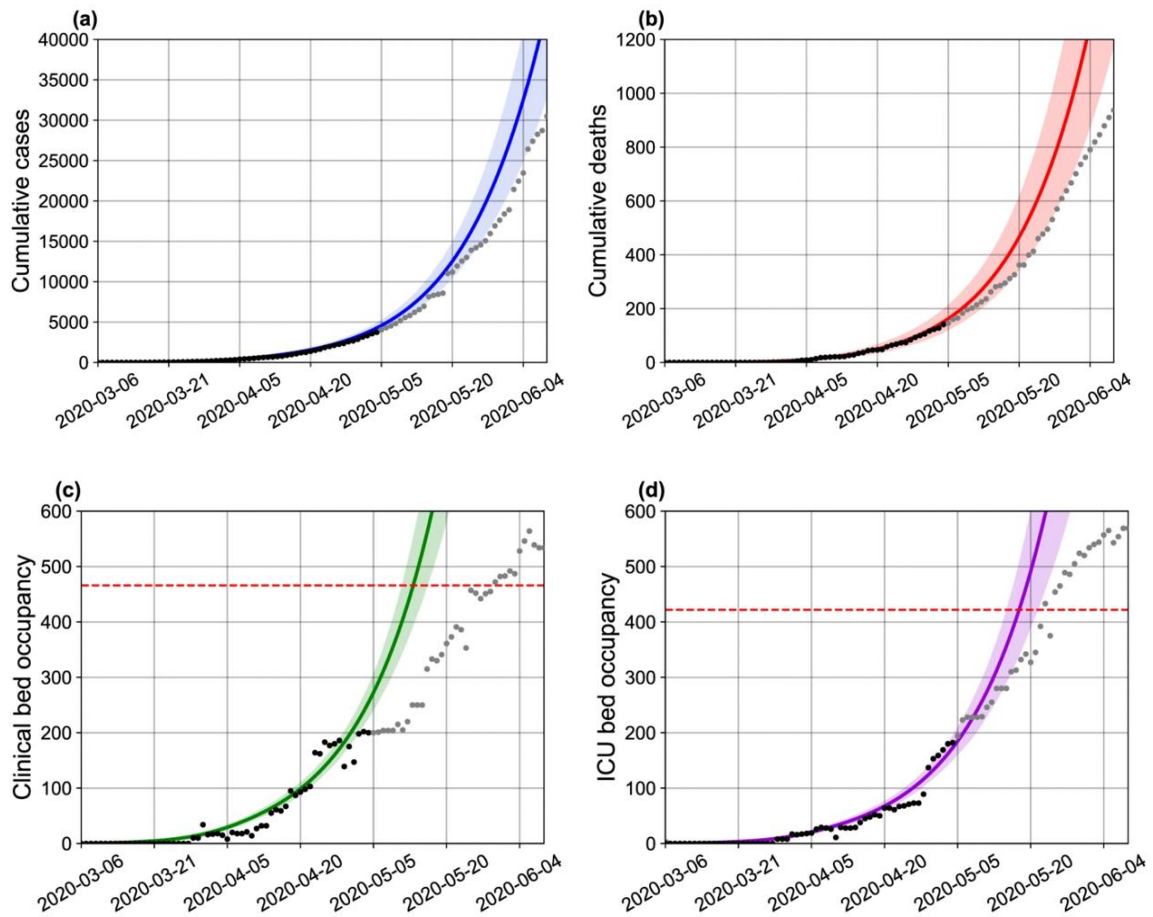


Fig. 3 (a) Cumulative cases; (b) Cumulative deaths; Bahia daily (c) clinical and (d) ICU bed needs. The model was fitted to data as of May 4, 2020, indicated by black dots. Shaded error bars represent 95% confidence intervals for the mean calculated using the weighted nonparametric bootstrapping method. Gray dots depict new data as of June 4, 2020. Horizontal red dashed lines in panels c and d represent clinical inpatient beds (466 beds) and ICU beds (422 beds) available on May 4, 2020, respectively. This

chart shows raw data from March 6 to June 4, 2020.

We maintain the parametric conditions described in "Methods" while allowing for new transfer rate variability. New estimates show a drop in transmission rates on June 11, suggesting that Bahia's containment of the outbreak has tightened.

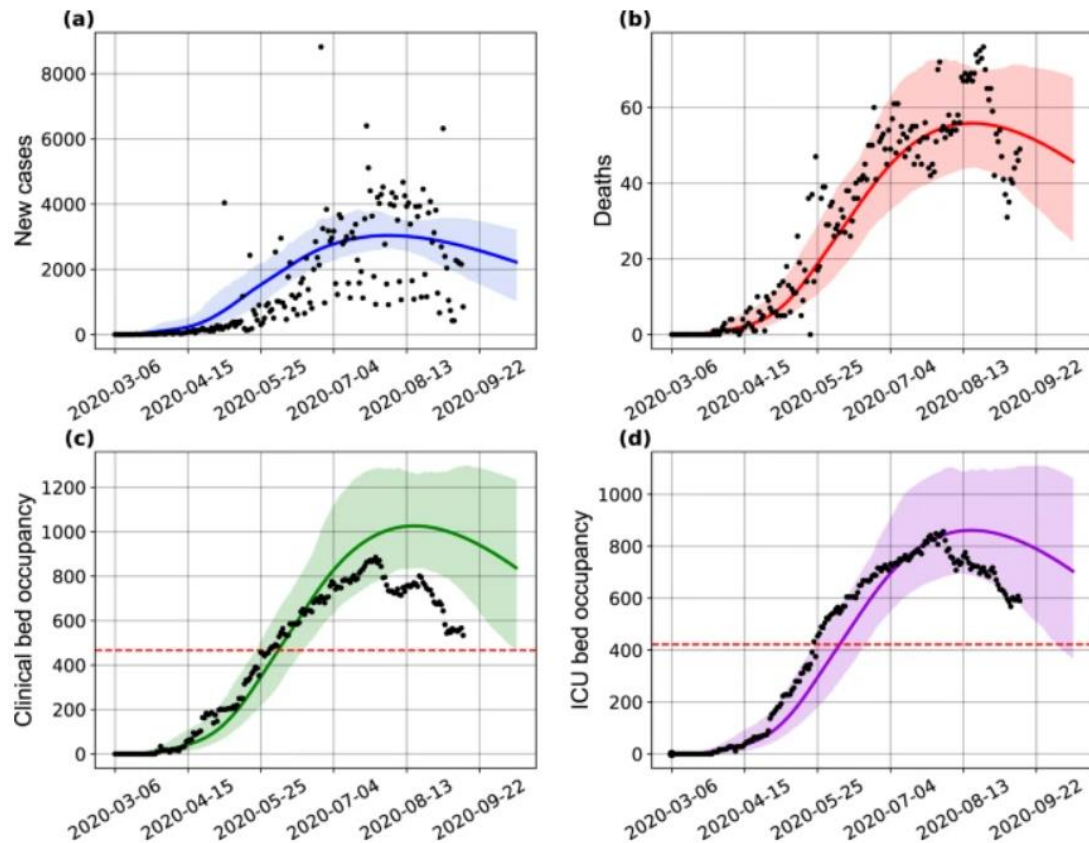


Fig. 4 Projection of the (a) number of cases, (b) deaths, (c) clinical hospitalization, and (d) ICU bed requirements with a changing transmission rate in Bahia up to September 13, 2020. The horizontal red dashed lines in plots c –d, are, respectively, the number of beds for clinical hospitalization (466 beds) and ICUs (422 beds) available on May 4, 2020. The shaded error bands represent 95% confidence intervals of the mean calculated using the weighted non-parametric bootstrap method. The assumed parameter values are shown in Supplementary Table 4.

➤ Simulations (Our results)

✓ Reproduce original model

The python model attached to github provided in the text, in which three models are established, namely Bahia (State), Salvador(city), Interior (rest 416 cities in interior), which represent areas of different sizes and are subject to policies and medical care. can have different effects, but first divide the 8 compartments, and then consider the relationship between them by data to obtain parameters, and then optimize the model through the PSO algorithm to make the model more accurate.

The following six pictures (Fig. 5-7) are the forecasts from 2020/05/04 to 2021/01/04 simulated by the model, which is the number of infections and deaths in Bahia, Salvador, and Interior cities respectively.

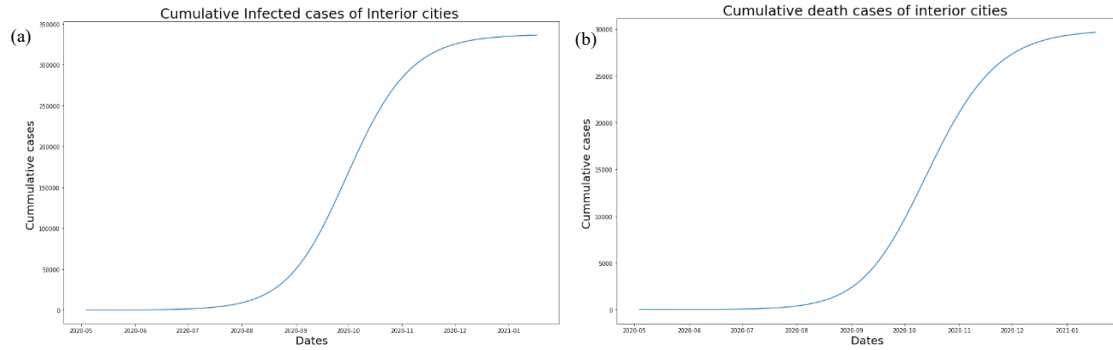


Fig. 5 The simulations of model reproduction. (a) represents that the cumulative infected cases of interior cities have reached close to 350,000. (b) represents that the cumulative death cases of interior cities have reached nearly to 30,000.

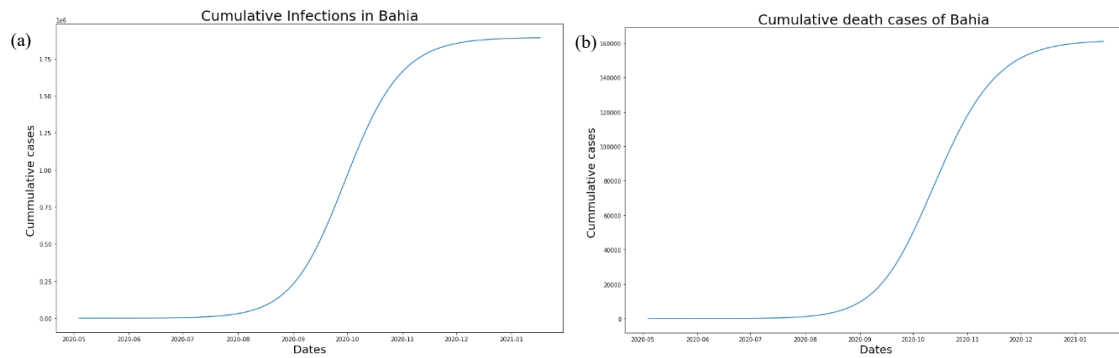


Fig. 6 The simulations of model reproduction. (a) represents that the cumulative infected cases of Bahia have reached over than 1.75×10^6 . (b) represents that the cumulative death cases of Bahia have reached nearly to 160,000.

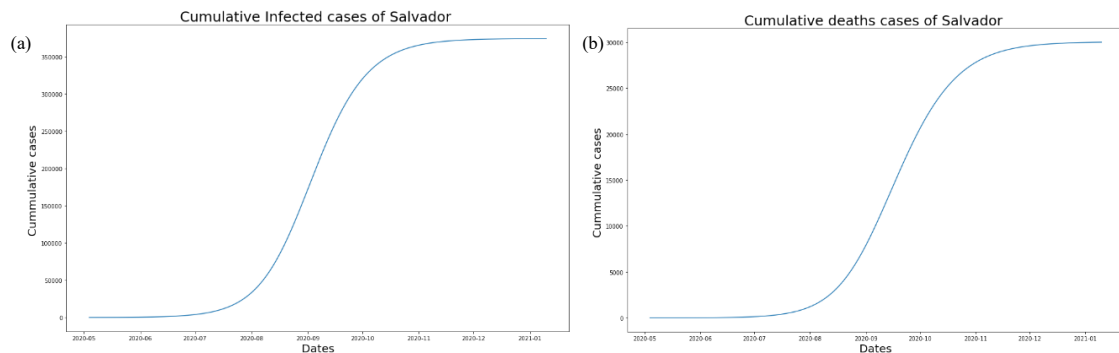


Fig. 7 The simulations of model reproduction. (a) represents that the cumulative infected cases of Salvador have reached over than 350,000. (b) indicates that the cumulative death cases of Salvador have reached nearly to 30,000.

✓ Particle Swarm Optimization

Hereinafter referred to as PSO, PSO is a random search algorithm originally developed to graphically analogize the graceful and

unpredictable movements of flocks of birds. Observations of animal social behavior reveal that social sharing of information in groups provides an evolutionary advantage and serves as the basis for developing algorithms. PSO can effectively search for problems with huge solution space and find candidate solutions without knowing too much problem information, but at the same time, it does not guarantee that the best solution it finds is the real best solution. Therefore, it is used as an algorithm for optimizing parameters in this paper.

✓ **Revise the model**

We used the SIR (3-compartment) model learned in the classroom, representing susceptible, infected, and death, respectively, and modified the parameters to compare with the results of the 8 compartments, which read the data of the paper, and Predict the number of infected people from 2020/05/04 to 2021/01/04, the Fig. 8 is the graph made by the prediction.

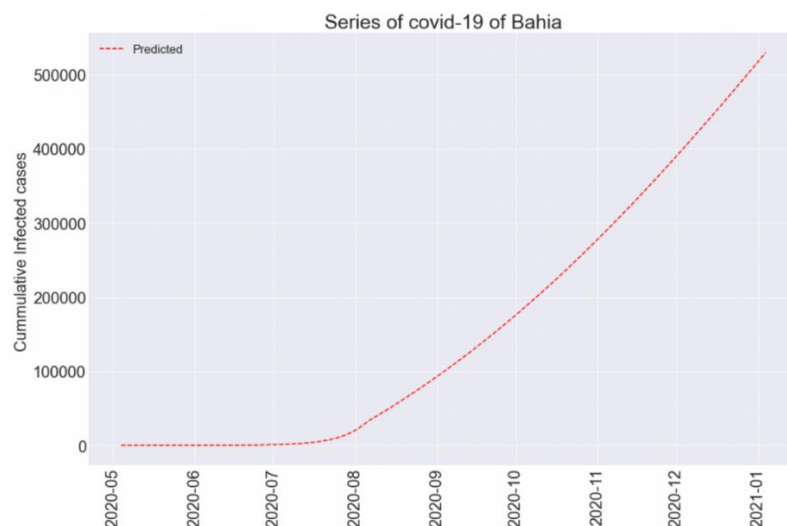


Fig. 8 We use the SIR model learned in the classroom to simulate the local data provided by this paper

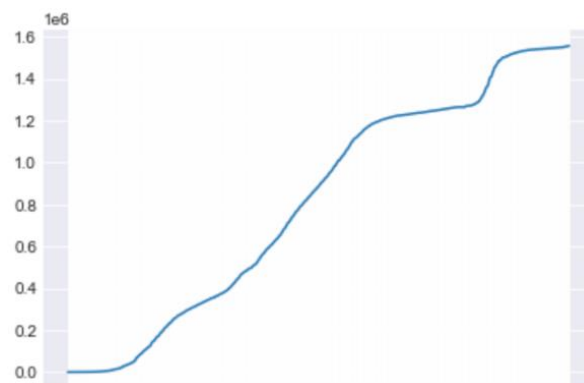


Fig. 9 This is provided by the paper. In Bahia, Brazil, the local data from May 4, 2020 to January 4,

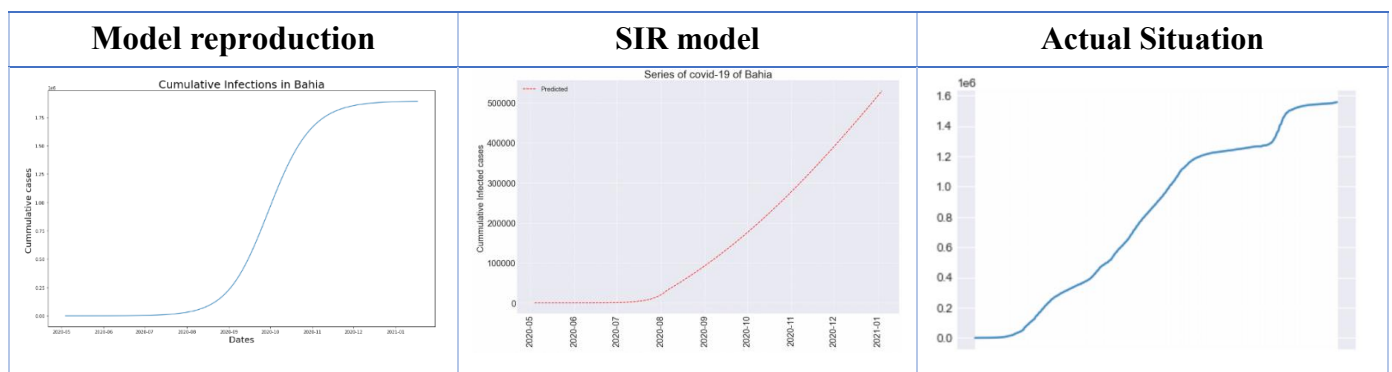
2021, we simulated it

➤ Discussion

✓ Comparison

To better discuss the original model and the revised model results, we use the data of Bahia as a comparison. The predicted time is from 2020/05/04 to 2021/01/04. The actual results are obtained from the Brazilian database, and we use the modified SIR as our model. Comparing the conclusions of the reproduced model in the paper as a comparison, the actual cumulative confirmed number of people as of 2021/01/04 is about 1.75 million, and the reproduced model of the paper predicts the result is also about 1.75 million. while our result predicted by the SIR model is about 500,000 people, which is very different from the precious two results as shown below.

We conjecture that the possibility of wrong results is the incompleteness of the data, and the provided data contains data of non-medical behaviors, such as the decree issuing time, the number of hospital beds and even the quantitative value of medical capacity. In the SIR model, our data is not complete due to not including the remaining 5 compartments, which is the main reason we believe the forecast is inaccurate.



✓ Conclusion

The results of this study show that the intervention of government quarantine orders will effectively reduce the rate of virus transmission.

This paper reinforces the negative impact of healthcare resources associated with the cycle of asymptomatic/mild cases, where policies aimed at easing the current level of social distancing measures in a situation where diagnostic testing is not available for the majority of the population could potentially give an already limited health system a boost. Infrastructure brings additional burdens.

The findings suggest that non-pharmaceutical measures should be implemented to reduce the rate of disease transmission to buy time for the

creation of new hospitals, access to protective equipment and materials, and safeguarding of human resources.

Long-term predictions are hampered by the inherent complexity of epidemic development, in which human behavior, the timing of deployment and cancellation of government policies, and associated parameters cannot be fully expressed through modeling strategies alone. Ultimately, these will all be reflected as changes in transfer rates over time.

➤ **Acknowledgements**

We would like to thank the professor for her teaching this semester and the contribution of the teaching assistant. The number of students in this semester is relatively small, so we both feel that we are often cared by the professor during the class. Thank the professor for her enthusiastic teaching. We have learned various models of biological systems, but we believe that these learning experiences can help us better understand how to analyze a whole system, or even a model, and let us learn the ability to solve problems.