Model-based Prediction and Optimal Control of Pandemics by Nonpharmaceutical Interventions

Reza Sameni*
Alphanumerics Lab, Department of Biomedical Informatics, Emory University School of Medicine

***Abstract*—The models and algorithms developed by the Alphanumerics Team during the XPRIZE Pandemic Response Challenge are presented. The algorithms are based on profound theories from *optimal state estimation* and *finite horizon optimal control*. The major contribution of the team is to develop a predictor and prescriptor over an *ad hoc* compartmental model for tracking the variations of the new cases and the model parameters with a *fixed-interval Kalman filter/smoother*. The solution is theoretically proved to be optimal, within the scope of the presented compartmental model. The algorithm provides both prediction and prescription, provides performance bounds and requires extremely low computational resources. The non-pharmaceutical interventions (NPI) found by this algorithm are on the *Pareto front* of the required bi-objective optimization space and the user can select the desired balance between the human factor and NPI cost by modifying a single parameter. The parameters of the model, which correspond to the human interaction and recovery rates, can be trained by using machine learning techniques. The theoretical proof of our findings and the source-codes of the implementations are available online.**

I. Introduction

The mathematical modeling of pandemic waves has significant importance for governments and decision-makers. Non-pharmaceutical interventions (NPIs) refer to actions and policies adopted by individuals, authorities or governments that help slowing down the spread of epidemic diseases. NPIs are among the best ways of controlling pandemic diseases when vaccines or medications are not yet available[1]. During the COVID-19 pandemic, several attempts have been made to categorize and quantify the various NPIs of different regions and nations. The quantification of the NPI is believed to be helpful for comparing the effectiveness of regional policies in containing the pandemic spread. By using machine learning techniques, the quantified NPI can be used to forecast the future trends of the pandemic and to simulate *"what if scenarios"* for the better management of human and medical resources, and to eventually prescribe appropriate NPI for controlling the pandemic [1]. The Oxford COVID-19 Government Response Tracker (OxCGRT) is one of the NPI tracking projects, which were launched and regularly updated during the COVID-19 pandemic [2]. Most recently, this project has been used in the machine learning community to launch data challenges for NPI-based prediction and prescription plans, including the XPRIZE Pandemic Response Challenge [3].

During this challenge, the Alphanumerics Team from the Department of Biomedical Informatics at Emory University, adopted a model-based *estimation theoretical* and *finite horizon optimal control* strategy to address the problem of weighted non-pharmaceutical interventions (NPI) prescription. Considering that the only available data were the total confirmed cases, the total confirmed deaths, and the daily NPIs, we have adopted an extension of a generic susceptible-infected (SI) compartmental model from our previous work [4], as the base model for all regions/countries. During Phase I, the proposed model parameters were trained on historic data and used to predict future trends from input NPI by using an extended Kalman filter. In Phase II, the model was integrated with a finite horizon optimal controller to find the optimal daily NPIs with arbitrary NPI weight vectors.

Algorithm 1 Summary of the proposed algorithm

Input: Historic case reports and NPI files (or an arbitrary scenario file from the *standard predictor model*)
Input: The NPI weights $\mathbf{w}(t)$, per region/country
Input: The Pareto front tuning parameter $\epsilon \in [0, 1]$.
1: **for all** Regions **do**
2: Train the compartmental model parameters over historic NPI and case reports (or the standard predictor scenario file).
3: Use EKF and EKS for prediction and prescription of finite horizon optimal control inputs $\mathbf{u}^*(t)$.
4: **end for**

II. Highlights of the Developed Algorithm

The proposed method is summarized in Algorithm 1. The major elements of this algorithm are explained in the sequel.

Before going into the details of the model and algorithm, we highlight some of its important features, which are justified in the sequel and our online source-codes[2]:

- The proposed method is based on theoretical derivations and within the scope of the proposed compartmental model accuracy (which is asymptotically accurate for region/country-level population sizes), it gives accurate *Pareto efficient* solutions.

*R. Sameni is an Associate Professor of Biomedical Engineering and the director of the Alphanumerics Lab at the Department of Biomedical Informatics, Emory University School of Medicine, 101 Woodruff Circle, Atlanta, GA 30322, US (e-mail: rsameni@dbmi.emory.edu).

[1] See Centers for Disease Control and Prevention guidelines on NPIs: https://www.cdc.gov/nonpharmaceutical-interventions/.

[2] Cf. https://github.com/alphanumericslab/EpidemicModeling

- The desired point on the Pareto front can be selected by a single parameter $\epsilon \in [0, 1]$, where the corner case $\epsilon = 0$ neglects the NPI cost and $\epsilon = 1$ neglects the human factor.
- The prediction and prescription problems are integrated in a unified framework. Nevertheless, the method is applicable to both real-world data and the standard challenge predictor.
- The method can be used for *targeted pandemic control*, where strategists can target specific infection bounds that match the medical resources of a country/region, over a fixed or maximally bounded period of time. Therefore, within the proposed framework, apart from the optimal NPI and fatality rate objectives, scenarios such as this are also possible: *"how to bring the pandemic reproduction rate below 0.8, or the new cases below 100 per day in less than two months?"*
- Both the model parameters and NPI cost weights can be updated in time. Specifically, we do not assume the NPI cost weights to be constant over time. Therefore, unprecedented events such as vaccination or virus mutation effects can be integrated in the model without additional training. Following optimal control theory, optimality of future actions is independent of the past. Therefore, the prescribed optimal control strategy may be adopted at any point, regardless of the past actions of a region/nation.
- Since the Pareto front solutions are found by mathematical derivation (rather than trial and error or cumbersome searches), the computational load is minimal.
- We have developed a novel technique for solving the numerical problem of finite horizon optimal control, using an extended Kalman filter (EKF) and a finite-interval extended Kalman smoother (EKS).
- The proposed framework is extendable to pharmaceutical intervention plans and vaccinations, whenever available.
- The predictor part of the model gives confidence intervals during both the prediction and prescription steps of the algorithm. Therefore, the performance and well-function of the algorithm can be continuously monitored and adapted.

III. The Data Model

The two major classes of methods for epidemic disease spread modeling are:

1) *Compartmental models*, which split the total population of a region into various compartments (groups) such as susceptibles, exposed, infected, recovered, vaccinated, diseased, etc. These compartments are used to form differential/difference equations, which are fit onto real data and are analytically/numerically solved to predict future trends of the disease spread.
2) *Agent-based models*, which model the behaviors of individuals and their interactions at a simplified level of abstraction. Using these models, large groups of agents are generated in stochastic simulated environments as they randomly move, interact and probabilistically pass the infection to one another, recover, pass away, etc. The population-level properties are calculated by ensemble averaging over the entire population.

Each approach has its advantages and limitations. For large population sizes at regional or national levels— which was the scope of the Pandemic Response Challenge— the first approach is asymptotically accurate and is more advantageous as it can be analytically studied in a rigorous mathematical framework and combined with state estimation techniques for forecasting [4] and optimal control theories for NPI prescription. Based on this fact, we adopted the first approach, using a contact-controlled time-variant variant of the so-called *susceptible-infected (SI)* model compartmental model, as shown in Fig. 1, which is a simplified variant of the general compartmental models studied in out previous work [4]. Apparently, more accurate models can be used for the regions that further data such as the number of recovered, hospitalized, vaccinated, or the age pyramid of the population are available. However, for the current study, since the only global data provided in the Oxford dataset were the number of daily confirmed cases, total death cases, and the regional NPIs, the same SI model is used for all regions and countries.

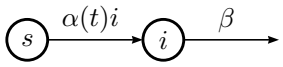


Fig. 1. The base susceptible-infected compartmental model with NPI-controlled infection rate

With this background, the nonlinear dynamic equations corresponding to the proposed model are:

$$\begin{aligned} \dot{s}(t) &= -\alpha(t)s(t)i(t) \\ \dot{i}(t) &= \alpha(t)s(t)i(t) - \beta i(t) \\ \dot{\alpha}(t) &= -\gamma\alpha(t) + \gamma h[\mathbf{u}(t)] \end{aligned} \tag{1}$$

where

- $s(t)$: the fraction of population in a region/country that is susceptible at time t (i.e., the susceptible population divided by the population size N);
- $i(t)$: the fraction of population that is infected and contagious at t (i.e., the infected contagious population divided by the population size N);
- $\mathbf{u}(t) \in \mathbb{R}^L$: the NPI vector considered as an exogenous control input ($L = 12$ during Phase II). The exact definition of the Oxford dataset NPI and the subset used during the XPRIZE Challenge are detailed in [2] and [3];
- $\alpha(t)$: the time-variant contagion rate with inverse time unit
- $h[\mathbf{u}(t)]$: a causal monotonic function of the NPI, which maps the NPI to the contagion rate;
- β: the rate of elimination from the contagious group (through quarantine, recovery, or death), assumed to be constant in the simplified case;
- γ: the *action to effect rate* (or the inverse of the NPI to individual contact rate lag).

The third equation in (1) is equivalent to $\alpha(t) = \gamma \exp[-\gamma(t - t_0)] * h[\mathbf{u}(t)]$ (for $t \geq t_0$), which is a smoothed version of $h[\mathbf{u}(t)]$. As a corner case, $\gamma \to \infty$ represents zero latency between action and effect, resulting in $\alpha(t) = h[\mathbf{u}(t)]$. The parameters β, γ and the function $h[\mathbf{u}(t)]$ require learning using the observed variables, as detailed in Section VI. Furthermore, in [4], we showed that the infection *reproduction rate* $\mathcal{R}_t$ can be calculated from $\alpha(t)$ and β.

It is later shown that the model parameters and variables in (1) can be identified by (noisy) observations of the *new*

cases fraction: $n(t) = \alpha(t)s(t)i(t)$, or the total *confirmed cases* fraction: $c(t) = 1 - s(t)$.

IV. Finite horizon optimization

A. Cost function and problem statement

In (1), the total number of new infections over an arbitrary time window $[t_0, t_1]$ is:

$$J_0(\mathbf{u}) = \int_{t=t_0}^{t_1} \alpha(t)s(t)i(t)dt, \tag{2}$$

the total cost of NPIs over the same time period is

$$J_1(\mathbf{u}) = \int_{t=t_0}^{t_1} \mathbf{w}(t)^T\mathbf{u}(t)dt \tag{3}$$

where $\mathbf{w}(t)$ is the NPI weight vector given as input (cf. [3] for the definition of the NPI weights), and the set of admissible inputs for the system is

$$\Gamma = \{\mathbf{u} | \mathbf{u}^{\min} \leq \mathbf{u}(t) \leq \mathbf{u}^{\max}, \forall t \in [t_0, t_1]\} \tag{4}$$

where $\mathbf{u}^{\min}$ and $\mathbf{u}^{\max}$ are (element-wise) the minimum and maximum ranges of each NPI from the Oxford dataset.

The optimization problem can be now formulated as a bi-objective optimization problem, with total cost:

$$J(\mathbf{u}) = (1-\epsilon)J_0(\mathbf{u}) + \epsilon J_1(\mathbf{u}) \quad \text{s.t. } \mathbf{u} \in \Gamma \tag{5}$$

where $\epsilon \in [0, 1]$ is a free parameter that compromises between the human factor (J_0) and the NPI cost (J_1). For a given weight pair $\{\epsilon, \mathbf{w}(t)\}$, the objective is to find $\mathbf{u}^*(t)$ for all $t \in [t_0, t_1]$, such that:

$$J(\mathbf{u}^*) = \min_{\Gamma}(J(\mathbf{u})) \tag{6}$$

B. The Pareto optimal solution

Any input which satisfies (6) is *Pareto optimal (efficient)*. The problem can be solved by *finite horizon optimization* [5]. In fact, for an arbitrary weight vector $\mathbf{w}(t)$, by sweeping ϵ over $[0, 1]$, the *Pareto-optimal front* of the optimization problem is found, from which strategists can select the desired free parameter ϵ and its corresponding optimal input $\mathbf{u}^*(t)$.

In order to solve (6), first the corresponding *Hamiltonian* function is formed [5, Ch. 2]:

$$\begin{aligned}\mathcal{H} = \quad & (1-\epsilon)\alpha(t)s(t)i(t) + \epsilon\mathbf{w}(t)^T\mathbf{u}(t) \\ & -\lambda_1(t)\alpha(t)s(t)i(t) \\ & +\lambda_2(t)[\alpha(t)s(t)i(t) - \beta i(t)] \\ & -\gamma\lambda_3(t)\{\alpha(t) - h[\mathbf{u}(t)]\}\end{aligned} \tag{7}$$

where $\lambda_1(t)$, $\lambda_2(t)$ and $\lambda_2(t)$ are known as *co-states*. According to *Pontryagin's minimum principle*, the co-states and the optimal solution $\mathbf{u}^*$ satisfy [5, Ch. 6]:

$$\begin{aligned}\dot{\lambda}_1(t) &= -\frac{\partial\mathcal{H}}{\partial s} = [\lambda_1(t) - \lambda_2(t) - (1-\epsilon)]\alpha(t)i(t) \\ \dot{\lambda}_2(t) &= -\frac{\partial\mathcal{H}}{\partial i} = [\lambda_1(t) - \lambda_2(t) - (1-\epsilon)]\alpha(t)s(t) + \beta\lambda_2(t) \\ \dot{\lambda}_3(t) &= -\frac{\partial\mathcal{H}}{\partial \alpha} = [\lambda_1(t) - \lambda_2(t) - (1-\epsilon)]s(t)i(t) + \gamma\lambda_3(t) \\ \boldsymbol{\nabla}_{\mathbf{u}}\mathcal{H}(\mathbf{u}^*) &\leq \boldsymbol{\nabla}_{\mathbf{u}}\mathcal{H}(\mathbf{u}), \quad \forall \mathbf{u} \in \Gamma\end{aligned} \tag{8}$$

where $\boldsymbol{\nabla}_u\mathcal{H}$ denotes the Hamiltonian gradient with respect to the input vector $\mathbf{u}$, and the inequality should hold element-wise. The optimal solution can now be found by solving (8) and the state equations (1), with initial conditions for the states and appropriate boundary conditions (also known as the *transversality conditions*) on the co-states and the Hamiltonian:

$$\lambda_1(t_1) = 0, \quad \lambda_2(t_1)[i(t_1) - i_{\max}] = 0, \quad \lambda_3(t_1) = 0 \tag{9}$$

The first and last conditions in (9) are the general free end-point conditions of finite horizon optimization problems, and the second condition is based on the assumption that the objective of any NPI policy over a reasonable time period $[t_0, t_1]$ (long enough to make the NPIs effective) is to bring the number of active cases down to $i(t_1) \leq i_{\max}$, where $i_{\max}$ is some target fraction of active cases (ideally zero). These conditions match the Challenge scenario during the prescription phase. Alternative transversality conditions that can be studied within the proposed framework are:

1) The end time t_1 is not fixed, but we require that $i(t_1)$ reaches below $i_{\max}$ (*infinite horizon* scenario). This requires: $\mathcal{H}(t_1) = 0$;
2) $i(t_1)$ drops below $i_{\max}$ any time before a maximum end time t_f, which requires $(t_1 - t_f)\mathcal{H}(t_1) = 0$.

C. The NPI to inter-human contact map

The solution of the optimization problem depends on the choice of $h[\mathbf{u}(t)]$, i.e., the NPI to inter-human contact mapping model. We study the following two cases, which lead to closed form solutions for the optimal input, as functions of the model co-states:

1) *Linear regression model*: $h[\mathbf{u}(t)] = \mathbf{a}^T[\mathbf{u}^{\max} - \mathbf{u}(t)] + b$, where $\mathbf{a}$ is a vector of *input influence weights* and b is a constant bias (intercept value). The LASSO model, with or without a constraint, falls into this category. In this case:

$$\boldsymbol{\nabla}_{\mathbf{u}}\mathcal{H}(\mathbf{u}) = \epsilon\mathbf{w} - \gamma\lambda_3(t)\mathbf{a} \tag{10}$$

Since $\boldsymbol{\nabla}_{\mathbf{u}}\mathcal{H}(\mathbf{u})$ is independent of $\mathbf{u}$, we can conclude that the minimum of the Hamiltonian occurs at one of the extreme ends, depending on the sign of $\boldsymbol{\nabla}_{\mathbf{u}}\mathcal{H}(\mathbf{u})$. This gives

$$u_k^*(t) = \begin{cases} u_k^{\min}: & \text{if } \lambda_3(t) \leq \dfrac{\epsilon w_k}{\gamma a_k} \\ u_k^{\max}: & \text{if } \lambda_3(t) > \dfrac{\epsilon w_k}{\gamma a_k} \end{cases} \tag{11}$$

2) *Quadratic regression:* $h[\mathbf{u}(t)] = \frac{1}{2}[\mathbf{u}^{\max} - \mathbf{u}(t)]^T\mathbf{S}[\mathbf{u}^{\max} - \mathbf{u}(t)] + \mathbf{a}^T[\mathbf{u}^{\max} - \mathbf{u}(t)] + b$, where $\mathbf{S} \in \mathbb{R}^L$ is a positive semi-definite matrix. Quadratic programming can be used to find $\mathbf{S}$, $\mathbf{a}$ and b from historic NPI and case-report data. In this case:

$$\boldsymbol{\nabla}_{\mathbf{u}}\mathcal{H}(\mathbf{u}) = \epsilon\mathbf{w} - \gamma\lambda_3(t)\{\mathbf{a} + \mathbf{S}[\mathbf{u}^{\max} - \mathbf{u}(t)]\} \tag{12}$$

which using Pontryagin's minimum principle in (8), gives

$$u_k^*(t) = u_k^{\max} - \min\{\Delta u, \max[0, \mathbf{S}^{-1}(\frac{\epsilon\mathbf{w}}{\gamma} - \lambda_3(t)\mathbf{a})]\} \tag{13}$$

where $\Delta u \triangleq u_k^{\max} - u_k^{\min}$ and $k = 1, \ldots, L$.

V. A UNIFIED PREDICTOR AND PRESCRIPTOR

For an ideal model, the state and co-state dynamic equations detailed in Section IV can be solved with numerical toolboxes for finite horizon control. However, in practice, there are some major issues, which limit the numerical performance, including: 1) model inaccuracies, 2) noisy observations (case reports), 3) unknown or variable parameters, 4) incorporation of the boundary conditions.

Due to these issues, we have developed a novel technique, based on optimal state estimation. Accordingly, we have integrated the finite horizon NPI optimizer and the new-case predictor in a classical EKF and EKS scheme [6]. Using (1) and (8), the unified dynamic equations for the EKF are as follows:

$$\begin{aligned}
&\dot{s}(t) = -\alpha(t)s(t)i(t) + w_s(t)\\
&\dot{i}(t) = \alpha(t)s(t)i(t) - \beta i(t) + w_i(t)\\
&\dot{\alpha}(t) = -\gamma\alpha(t) + \gamma h[\mathbf{u}^*(t)] + w_\alpha(t)\\
&\dot{\lambda}_1(t) = [\lambda_1(t) - \lambda_2(t) - (1-\epsilon)]\alpha(t)i(t) + \eta_1(t)\\
&\dot{\lambda}_2(t) = [\lambda_1(t) - \lambda_2(t) - (1-\epsilon)]\alpha(t)s(t) + \beta\lambda_2(t) + \eta_2(t)\\
&\dot{\lambda}_3(t) = [\lambda_1(t) - \lambda_2(t) - (1-\epsilon)]s(t)i(t) + \gamma\lambda_3(t) + \eta_3(t)\\
&n(t) = \alpha(t)s(t)i(t) + v(t)
\end{aligned} \tag{14}$$

where the first six equations are the state and co-state dynamics, the last equation is the observation equation and $h[\mathbf{u}^*(t)]$ is the impact of the optimal control calculated from (11) or (13). The terms $w_s(t)$, $w_i(t)$, $w_\alpha(t)$, $\eta_1(t)$, $\eta_2(t)$ and $\eta_3(t)$ in (14) represent process noises, and $v(t)$ is observation noise. For an estimation based on the total number of confirmed cases, the last observation equation in (14) can be replaced with

$$c(t) = 1 - s(t) + v(t) \tag{15}$$

The discretized and linearized versions of (14), which are required for the discrete-dime implementation of the EKF and EKS are available in our online available MATLAB implementations.

VI. MODEL TRAINING

The model parameters $h[\mathbf{u}(t)]$, β, γ and the EKF/EKS parameters (initial/final states and covariance matrices) require region-wise training or fact-based selection. For this study, we used classical techniques for *Kalman filter engineering* [7, Ch. 8], based on monitoring the properties of the *innovations process* of the Kalman filter and adapting them automatically over time.

The mapping $h[\mathbf{u}(t)]$ was trained over the Oxford dataset historic cases and NPIs starting from January 1, 2020 to Feb 7, 2021 [2]. For this, the developed EKS was first applied to the historic data by assuming $h[\mathbf{u}(t)]$. Referring to (14), this assumption is practically equivalent with considering the input-driven fluctuations of $\alpha(t)$ inside the process noise $w_\alpha(t)$. This gives us a primary estimate of $\alpha(t)$ over the training period, which is given to a constrained LASSO or quadratic programmer (for the linear and quadratic forms presumed in Section IV, respectively), to estimate $h[\mathbf{u}(t)]$ using the historic NPI data. The trained model $h[\mathbf{u}(t)]$ together with the historic data is used in a second round of EKS, this time by using the historic NPI and apparently a smaller *a priori* assumption for the variance of $w_\alpha(t)$. After the secondary EKS, the new estimates of $\alpha(t)$ are once more used to refine the model parameters of $h[\mathbf{u}(t)]$. The refined parameters are stored per country/region for utilization during the test phase (over real or synthetic scenarios).

We should add that the LASSO coefficients were constrained to be positive, to guarantee a monotonic relationship between the input NPI $\mathbf{u}(t)$ and the contact impact $h[\mathbf{u}(t)]$. This constraint can be achieved in most optimization software by variants of constrained least squares optimization.

The *action to effect rate* parameter γ was selected intuitively. From different social experiences, it is reasonable to expect a smooth transition in α due to any change in the NPI. In other words, imposing any policy on a complex social system is never abrupt. Although the transition is region and NPI dependent, in order to reduce the model complexity, we have fixed γ=1/(7 days)=0.1429 days^{-1}, for all regions/countries.

The recovery parameter β was selected by educated guesses from the CDC reports (https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html) regarding recovery and contagion periods. According in multiple scientific studies worldwide, it has been reported that an exposed subject is no longer *infectious* after 3 to 4 weeks. This is evidently a stochastic range. To clarify, with an exponential model such as the SI mode, in absence of new infected cases ($\alpha = 0$), we find $l \triangleq i(t_0 + T)/i(t_0) = \exp[-\beta T]$, which can be interpreted as an exponential law for the probability of infectiousness after T time units (days). Combining the model with the CDC reports, we derive the following rule for setting β:

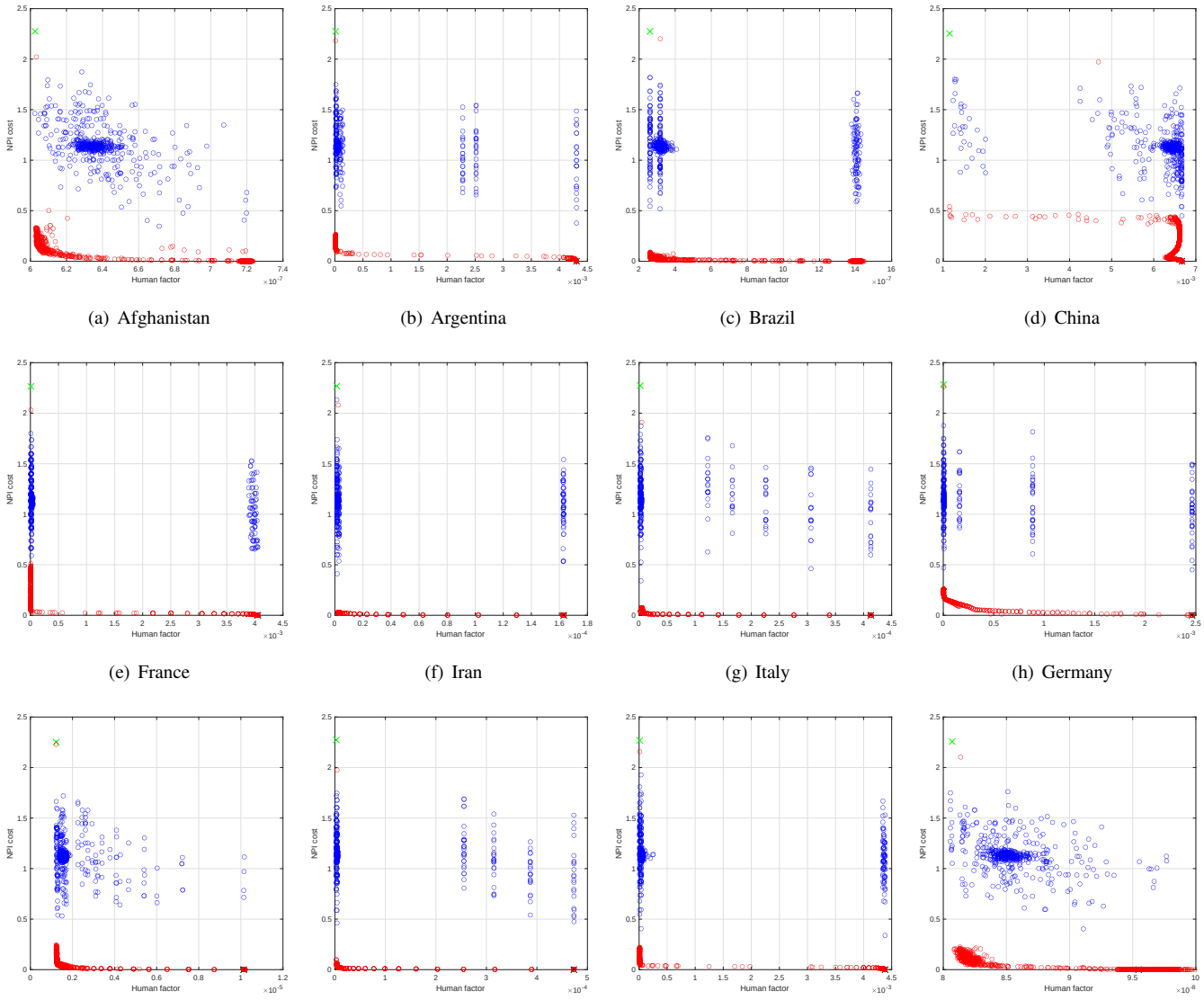
$$\beta = \frac{-\log(\text{probability of contagion after } T \text{ time units})}{T} \tag{16}$$

For the later presented results, we have taken the probability of contagion 0.01 and T=21 days, resulting in β=0.2193 days^{-1}. Note that one of the advantages of the EKF/EKS framework is that the model parameters can also be considered as state variables and be *state augmented* with the other equations to be estimated (or updated over time). This approach can be used for both γ and β to refine the initial educated guesses, detailed above.

Finally, the regional/national population sizes, as required for normalizing the total and new contaminated cases to the normalized variables of the SI model were obtained from public global population datasets and assumed fto remain fix over the study (i.e., immigration, inter-border travels, natural birth/deaths have been neglected in the current model).

VII. RESULTS

We trained and applied the proposed finite horizon optimal controller to all regions/countries with arbitrary NPI cost weights. As proof of concept, examples of the bi-objective optimization space are shown in Fig. 2 for several countries, and compared with 1) minimal stringency $\mathbf{u}(t) = \mathbf{u}^{\min}$, 2) maximal stringency $\mathbf{u}(t) = \mathbf{u}^{\max}$, 3) random constant stringency $\mathbf{u}(t) = \boldsymbol{\kappa}$, $\boldsymbol{\kappa} \in [\mathbf{u}^{\min}, \mathbf{u}^{\max}]$, and 4) random variable stringency $\mathbf{u}(t) \in [\mathbf{u}^{\min}, \mathbf{u}^{\max}]$.



(a) Afghanistan (b) Argentina (c) Brazil (d) China

(e) France (f) Iran (g) Italy (h) Germany

(i) South Africa (j) Spain (k) UK (l) US

Fig. 2. Biobjective optimization space for sample countries. Blue: random inputs; Red: optimal input for 2000 $\epsilon \in [0, 1]$; Green: Full stringency; Black: No stringency. $h[\mathbf{u}(t)]$ was found by linear regression over historic NPI from Jan 1, 2020 to Feb 7, 2021, using a LASSO with positive coefficients constraint.

A. *Processing load*

The MATLAB version of the codes applied to all regions and countries (235 in total), take less than 30 s to train over the historic cases and NPI on a MacBook Pro laptop with 2.3 GHz Quad-Core Intel Core i7 and 32GB of memory, without notable optimizations. The run-time on the test scenarios takes about 15 s in total (since it contains only one EKS stage during the test period). Therefore, the proposed framework is extremely efficient. This permits the combination of the proposed method with other machine learning methods, to reduce the search space and to improve the accuracy on other datasets and under more complicated models such as the Long short-term memory (LSTM).

VIII. Conclusion and Future Work

In this study, a model-based approach was used for the prediction and prescription of weighted-NPIs that best balance between the NPI cost and the number of new cases. The proposed algorithm and the prescribed NPI are proved to be Pareto optimal, to the extent of the accuracy of the utilized compartmental model. Software implementations of the proposed algorithms are online available at: https://github.com/alphanumericslab/EpidemicModeling.

In future studies, different aspects of the method can be extended and improved, including:

- Using advanced machine learning algorithms for learning the NPI to contact rate function $\mathbf{h}(\cdot)$. The LSTM is a promising approach.
- For regions with additional data (e.g., the number of hospitalized, number of vaccinated, fatality rate of the virus, the population age pyramid, etc.), more accurate models such as the fatal susceptible-exposed-infected-recovered (SEIR) [4] can be used. Adding additional reports such as the death reports as an observed variable will also help to increase

the EKF/EKS accuracies.

- Theoretical aspects of the proposed EKF/EKS frameworks, including stability conditions, parameter identifiability and robustness require further study.

REFERENCES

[1] R. Miikkulainen, O. Francon, E. Meyerson, X. Qiu, E. Canzani, and B. Hodjat, "From Prediction to Prescription: Evolutionary Optimization of Non-Pharmaceutical Interventions in the COVID-19 Pandemic," 2020. [Online]. Available: https://arxiv.org/abs/2005.13766

[2] Thomas Hale and Sam Webster and Anna Petherick and Toby Phillips and Beatriz Kira, *Oxford COVID-19 Government Response Tracker*, 2020, Blavatnik School of Government. [Online]. Available: https://github.com/OxCGRT/covid-policy-tracker

[3] XPRIZE, *The XPRIZE Pandemic Response Challenge*, Oct 2020 – Feb 2021. [Online]. Available: https://xprize.org/pandemicresponse

[4] R. Sameni, "Mathematical Modeling of Epidemic Diseases; A Case Study of the COVID-19 Coronavirus," 2020. [Online]. Available: https://arxiv.org/abs/2003.11371

[5] D. S. Naidu, *Optimal control systems*. CRC press, 2003.

[6] B. D. O. Anderson and J. B. Moore, *Optimal Filtering*. Dover Publications, Inc., 1979.

[7] M. S. Grewal, L. R. Weill, and A. P. Andrews, *Global positioning systems, inertial navigation, and integration*. John Wiley & Sons, 2007.