Optimization of Non-Pharmaceutical Interventions For a Mutating Virus

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***Abstract*— International focus on the COVID-19 pandemic has caused a wealth of new mathematical models for capturing the impact of a virus. As COVID-19 seems to be approaching an endemic status, it is becoming increasingly clear that a new variant has the strong probability of becoming dominant in a short period of time from first appearance. A model with the goal of representing past data and forecasting will need the flexibility to incorporate a time-evolution of variants. In this paper we explore two methods for encompassing mutating viruses: coupled Ordinary Differential Equations (ODE) and Markov Chains and coupled ODE with Measure Differential Equations (MDE). In both approaches, ODEs are used to represent classical compartmental models. Coupled ODE-Markov chain method uses Markov chains to govern the mutation of the virus between predetermined variants. This method considers a discrete variant space allowing for more simple parameter tuning to previously recorded data. For the ODE-MDE approach, MDEs describe the virus mutations over time in a continuum space. A cost function is designed in order to study optimal decision making with respect to non-pharmaceutical interventions such as social distancing. These models will serve to highlight the importance of considering variants in the long-term decision making process.**

I. INTRODUCTION

This paper focuses on models for pandemics with time-evolution of virus variants. During the COVID-19 pandemic, a wealth of different models were proposed, thus we start with motivations and a brief review of modeling approaches.

A. The Importance of Modeling Viral Variants

To replicate, and therefore establish infection in a new host, SARS-CoV-2 (the virus causing COVID-19) must take over a host cell and duplicate itself. Errors often occur during the process of duplication resulting in virus variants that are similar but not exact copies of the original. These errors are called mutations and though subtle, could result in a new dominating variant [14]. New dominating variants cannot be predicted exactly on both temporal and structural scales, but understanding patterns of mutating viruses, such as mutation rate and genetic diversity, can shed light to make educated guesses about future mutations [29]. This information can then be used to increase the long term predictive capabilities of epidemiological models and to provide estimates of best practices for decision makers and policy writers [12].

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In the case of COVID-19, there have been a handful of dominating variants whose parameters, such as infection rate and hospitalization rate, were so different from the previous variant that the governing bodies needed to adapt their plans to mitigate risk such as increased social distancing [31], increased testing [4], and the development of an updated vaccine [8]. It is also well known that different populations can be experiencing different dominating variants of COVID-19 at the same time [34]. Especially unique populations have frequently reported different viral makeups than the rest of the world and sometimes, in the case of Alaska, even within their own countries [19].

Comparing the tenure of dominant variants using publicly sourced variant sequencing data [13] to the daily case count of COVID-19 in a population [10], one finds a strong correlation between a new variant's takeover and a spike in cases, see Figure 1. Each new dominating variant's appearance is followed shortly by a spike-then-fall in new cases.

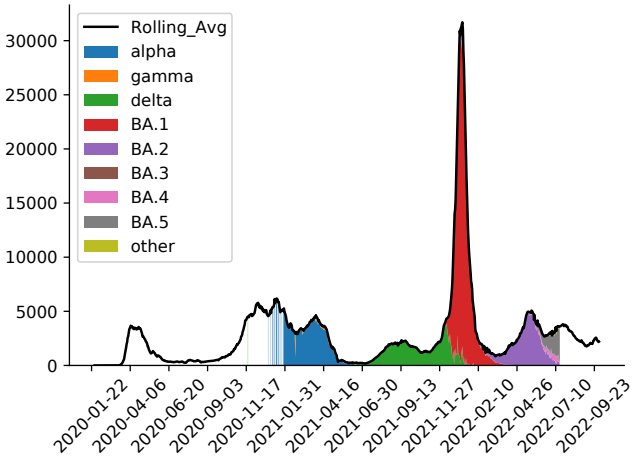

Fig. 1: Rolling average of the daily confirmed COVID-19 cases in the state of New Jersey since the pandemic onset (black contour). In color, stacked percentage of the dominant variants normalized to the daily case data. BA.1, BA.2, BA.3, BA.4, BA.5 are sub-variants of the Omicron variant.

B. Models for COVID-19

A first step in developing an epidemiological model is to choose a type of model: Agent Based Modeling (ABM) is a stochastic process which can give very granular results. For example in [30] an agent based model is updated hourly

with new interactions between susceptible and infected populations. These models can also be tuned to very small heterogeneous populations such as small towns and cities [35], [16]. Compartment based modeling is equation driven and much less computationally expensive than ABM [11]. These models can be adapted to many populations and yet retain fast run times computationally [32]. They also have the added benefit of being able to model an infectious disease well with the need for very few parameter estimates [33].

After a method is chosen, one can then decide exactly what parameters they would like to study in their model. Examples include studying an age based structure of your population [1], studying how work status could affect trajectories of a model [3], questions of vaccine allocation [25] and questions of non-pharmaceutical parameters used to mitigate risk [2]. Such parameters remain fairly constant over a smaller time-frame. When studying a longer time-frame, the characteristics of the virus itself play a factor in how these parameters change; especially in the case of COVID-19, at many stages the virus has both mutated towards infectivity [17], and away from the efficacy of the original vaccines [20].

C. Contribution of the paper

In previous work, we introduced two models to address the mutability of a virus with the goal of increasing temporal viability [36]. We did so through the coupling of a classical epidemiological model in the first case with a Markov chain (briefly MC), and in the second case with a measure differential equation (briefly MDE). Here, we expand both models and define optimal control problems for non-pharmaceutical interventions, with cost function taking into account the economic cost of lockdown, hospitalization and deaths.

II. COUPLED MODELS FOR MUTATING VIRUS

A classical method of modeling the relationship between a virus and a population is through a compartmental SIR model (Susceptible, Infected, Removed) that uses differential equations to govern the flow of population between the compartments [22]. The most basic model has the following structure: $\dot{S} = -\frac{\beta SI}{N}$, $\dot{I} = \frac{\beta SI}{N} - \gamma I$, $\dot{R} = \gamma I$, where β and γ are the infection rate and recovery rate respectively and N represents the total population. From here, one can manipulate the compartments, adding compartments/parameters in order to better represent the population that they would like to model. In the next two sections we show how to couple SIR-type models with Markov chains and time-evolving measures to model mutating viruses.

A. SIR Coupled Markov Model

The COVID-19 pandemic has been driven by a number of discrete dominant "umbrella" variants such as Alpha, Delta and Omicron [28]. A SIR model is coupled with a nonlinear discrete-time Markov chain (briefly NDMC) to govern the emergence of such virus variants in order to capture variant dynamics.

The total population of infected people $\sum_i I_i$ will follow a standard compartmental model, with $I_i/\sum_i I_i$ representing the probability of the generic infected person having contracted variant i. The SIR model with multiple variants reads:

$$\begin{cases} \dot{S} = -\sum_{i=1}^{p} \beta_i \frac{S(t)}{N} I_i(t), \\ \dot{I}_i = \beta_i \frac{S(t)}{N} I_i(t) - \gamma_i I_i(t), \\ \dot{R} = \sum_{i=1}^{p} \gamma_i I_i(t). \end{cases} \tag{1}$$

Here S is the susceptible population, $I_i(t)$ is the population infected by the i-th variant, R recovered population, N the total population, β_i and γ_i represent the infection rate and recovery rate of the i-th variant. Now the evolution of $\mathscr{I}$ can be given by an NDMC associated to a transition matrix $T = \{t(i,j)\}_{i,j=1,\dots,p}$. Assuming the time step of the MC is given by Δt, the updating term takes the following form:

$$\mathscr{I}(k\Delta t+) = \mathscr{I}(k\Delta t) \cdot T(\mathscr{I}(k\Delta t)),\ k \in \mathbb{N}. \tag{2}$$

Notice that $T = T(\mathscr{I})$ and the dependence on $\mathscr{I}$ makes it a nonlinear MC. The state of this MC is a dynamic characteristic tied to both the number of infected people with the given variant and the total infected. In the simulations to follow, we choose $T_{ii}(\mathscr{I}) = \widetilde{T}_{ii} \cdot \psi(I_i)$, where $\psi(I_i) = 1 - \eta[I_i - \bar{I}_i]_+$. Here, $\bar{I}_i$ is a chosen threshold and η depends on both the total infected and amount of infected with infection i. Lastly, reinfection is introduced carefully, as it is well known that natural immunity to reinfection is dependent on both the previous variant of infection and the new variant of exposure. To address this, the following term is included:

$$\dot{S}_{R_i} = \sigma_i R_i - \sum \beta(i,\hat{i}) * \frac{S_{R_i}}{N} * I, \tag{3}$$

where $\beta(i,\hat{i})$ is the infection rate of variant i among patients that recovered from variant $\hat{i}$ and σ is a loss of immunity rate. Lastly, a variable u is included which serves as a lockdown measure. More precisely, u can be thought of as "percent of usual interaction rates". Additional compartments are also introduced; H for hospitalized and D for deceased, thus the fully coupled model has the following structure:

$$\begin{cases} \dot{S} = -u\sum_{i=1}^{p} \beta_i \frac{S}{N} I_i \\ \dot{I}_i = u\beta_i \frac{S}{N} I_i - \sum \beta(i,\hat{i}) * \frac{S_{R_i}}{N} * I - \gamma_i I_i - \delta I_i \\ \mathscr{I}(k\Delta t+) = \mathscr{I}(k\Delta t) \cdot T(\mathscr{I}(k\Delta t)) \\ \dot{H}_i = \delta I_i - \gamma H_i - H_i d \\ \dot{R}_i = \gamma_i I_i + \gamma H - \sigma_i R_i \\ \dot{S_{R_i}} = \sigma_i R_i - \sum \beta(i,\hat{i}) * \frac{S_{R_i}}{N} * I \\ \dot{D} = \sum H_i d \end{cases} \tag{4}$$

where d represents a death rate for hospitalized patients. This is a simple death rate calculated as the total reported deaths divided by total cases giving about 0.013. Using the described equations, an MC coupled SIRS model simulates the dynamics of a virus spreading through a population while capturing the changing characteristics of the disease due to new variants appearing and taking hold over the majority of the field of infections.

B. SIR Coupled MDE Model

Where the ODE-MC model captures discrete variant dynamics, here the population of infected is represented by a measure over a space of all possible virus mutations, taking on a continuous structure. Once infection begins, the virus causing COVID-19 begins to multiply rapidly producing billions of viral particles with small copy mistakes occurring during each cycle. With about $30,000$ nucleotides in the SARS-CoV-2 genome, and with each nucleotide having one of four states, there are millions of possible variants inside of each infected person which, if sufficiently beneficial, could lead to a new dominating variant [23]. While the majority of those possible variants offer no benefit and thus have a small chance of gaining traction in a population, the number of possible mutations suggests that it may be advantageous to model the field of mutations in a continuous way.

If one assumes that the space of viral mutations can be parametrized, then it can be thought of as a continuous distribution over a closed interval. The corresponding time evolution can then be visualized as a graph in $\mathbb{R}^3$ for which each point along the x-axis represents one unique possible mutation, y-axis represents the total infected, and z-axis time. The total infected would be the area under this graph.

The distance between two variants can be assumed to hold some biological similarity significance or temporal significance, i.e. a variant of concern is close to the current dominant variant. We use the parameter α to represent the ordered mutations. Once there is a clearly defined parametrization over the pool of variants, there must be a means by which the virus can mutate. This is accomplished by considering our I to be a solution to a measure differential equation (MDE) for which each $I(\alpha)$ can be thought of as a Dirac mass of infected with variant α [27]. An MDE is defined by assigning a speed of propagation via a probability vector field (PVF). In simple words, the speed of propagation is given by a probability measure instead of a deterministic vector. Precisely, an MDE corresponding to a PVF V is defined by:

$$\dot{\mu} = V[\mu]. \tag{5}$$

where μ is a Radon measure with finite mass. The mass of μ over a set $A \subset \mathbb{R}^n$ is transported along the velocities of the support of $V[\mu]$. Therefore, we define the equation for infected population as:

$$\dot{I} = V_\varphi[I] + \frac{S}{N}\beta(\alpha)I - \gamma(\alpha)I. \tag{6}$$

Here $\dot{I}$, at each variant, is governed by the usual SIR dynamics. However, there is a new term as well, $V_\varphi[I]$ which represents the velocities, governed by some function φ, at which the infected populations mutates over the field of possible variants.

Now even though I is a parametrized continuous function, a person in S and R has either not yet come in contact with a variant of the disease, or has recovered from their interaction with the disease. We take the S population to be homogeneous, and thus consider it to be a single mass. R also need not be parametrized unless reinfection is introduced; It is well documented that viral mutation could result in heightened reinfection rates [6], so R may need parametrization if one were to investigate this further. Without reinfection, our model takes the following form:

$$\begin{cases} \dot{S} = -\frac{S}{N}\int_{\mathbb{R}} \beta(\alpha)\ dI(\alpha), \\ \dot{I} = V_\varphi[I] + \frac{S}{N}\beta(\alpha)I - \gamma(\alpha)I, \\ \dot{R} = \int_{\mathbb{R}} \gamma(\alpha)\ dI(\alpha). \end{cases} \tag{7}$$

where S and R take the usual form with the difference that, in order to correctly estimate the interactions with the full field of variants, the field of variants must be integrated over with respect to the infection rates in the case of S and the recovery rates in the case of R.

One goal of this paper is to not only provide a route for a SIR model to capture viral mutation, but also show that such a model is capable of showing nuanced characteristics of the system which may be helpful for policy makers. Therefore, the system of equations has the following structure:

$$\begin{cases} \dot{S} = \left(-\frac{S}{N}\int_{\mathbb{R}} \beta(\alpha)\ dI(\alpha)\right)u, \\ \dot{I} = V_\varphi[I] + u * \frac{S}{N}\beta(\alpha)I - \gamma(\alpha)I - \delta(\alpha)I, \\ \dot{H} = \int_{\mathbb{R}} \delta(\alpha)\ dI(\alpha) - \nu * H - d * H, \\ \dot{R} = \int_{\mathbb{R}} \gamma(\alpha)\ \mathscr{I}(\alpha) + \nu * H, \\ \dot{D} = d * H. \end{cases} \tag{8}$$

where δ is the hospitalization rate of a given variant (note this is also parametrized because severity of disease is tied strongly to the nature of the variant), u quantifies the lockdown measures as before, and d the death rate.

III. OPTIMAL CONTROL PROBLEM

In this section we consider optimal control problems for the systems (4) and (8) with the control representing the "severity" of lockdown measures. The cost function will be designed to take into account the lockdown effects on both the pandemic dynamics and the economy. More precisely the cost function in USD is defined as:

$$cost = C_1 + C_2 + C_3 \tag{9}$$

where C_1, C_2, and C_3, are given by:

$C_1 = c_1 S(1-u)$	$c_1 =$	70,	social distancing,
$C_2 = c_2 h$	$c_2 =$	2700,	hospitalization,
$C_3 = c_3 d$	$c_3 =$	1500000	death

Here c_1, c_2, and c_3 are estimates for the cost of social distancing from [26], [7], [21], Hospitalization from [15] and death from [9]. The model input parameters are based on New Jersey data with the goal of optimizing a strategy over the economic cost of pandemic management under various conditions. The optimal control problem considered here is in Bolza form over a fixed time horizon $[0,T]$. We indicate by X the state variable with dynamics given by (4) or (8) and consider the optimal control problem:

$$\min_{u(\cdot)\in\mathscr{U}} \int_0^T C(X,u)\,dt \tag{10}$$

where $u \in [0,1]$ is the control and $\mathscr{U}$ the set of admissible control functions, e.g. measurable functions since the control set is compact. Notice that we are using a slight abuse of notation for X. More precisely, for the dynamics (4) we have $X = (S, I_i, H_i, R_i, S_{R_i}, D)$ belongs to a Euclidean space as in classical control systems, while for (8) we have $X = (S, I, H, R, D)$ with $S \in \mathbb{R}$ but the other components being Radon measures.

New rules introduced by government to impose social distancing measures are not immediate and there has even been observed lag effect between implementation of a new rule and societal compliance with regards to COVID-19 regulations [5]. We choose 30 days as an estimate of the minimum switching time mid-pandemic for the government to identify a shift in the populations relationship with the virus, choose a plan of action, write the plan into legislature, and have the public be informed and compliant with the new rules. In other words, our controls are piecewise constant with switching times every 30 days. Therefore the set $\mathscr{U}$ is finite dimensional and compact so we obtain the following:

Theorem 1: There exists a solution for the optimal control problem (10) with dynamics (4) or (8)

The proof is straightforward for (4), while for (8) we can apply results from [18].

A. Numerics for Optimization

To solve optimal control problems as (10) one generally chooses between direct and indirect methods. Here we use a direct method, since the optimal control problem proposed involves some state constraints and the set of admissible controls is compact. The direct method is based on standard Runge-Kutta schemes to discretize the ODE part of the systems (SIR model) and on discrete sums of Dirac masses for the measures called Lattice Approximate Solutions, see [27] for details. Due to space constraint we will present only results for the system (4). To initialize our optimization, we create a vector, u of length "total days of run" divided by 30, with values initialized between 0 and 1. The "law-maker" is then given the ability to change the lockdown percent at each interval to simulate decision making.

B. Optimization of a Lockdown With Viral Mutation Dynamics Using ODE-Markov model

There are some universal results which can be expected regardless of viral mutation, examples such as Figures 2 and 3 show the detriment of a lag time in the government initially identifying the pandemic. Both simulations are run using the same parameters. In Figure 2, the pandemic begins on day one, and the first government lockdown decision happens on day 90. In Figure 3, the first government intervention does not happen until day 150. We see from the figures that this two month lag results in not only a much stricter requisite lockdown, but also a much larger economic cost. The difference in total cost after 400 days is around 15%.

With our optimal control problem defined, we implement our SIR-Markov model to study how variant dynamics can affect the minimization of an intervention such as lockdown.

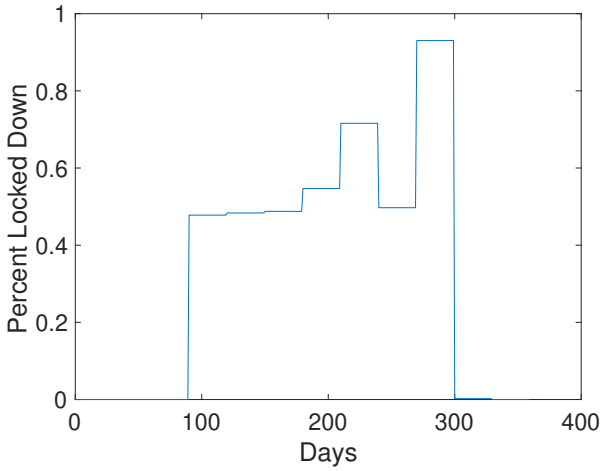

Fig. 2: Government updates lockdown policy every 30 days with the first update occurring on day 90. Total cost over time horizon is 8.1597e10.

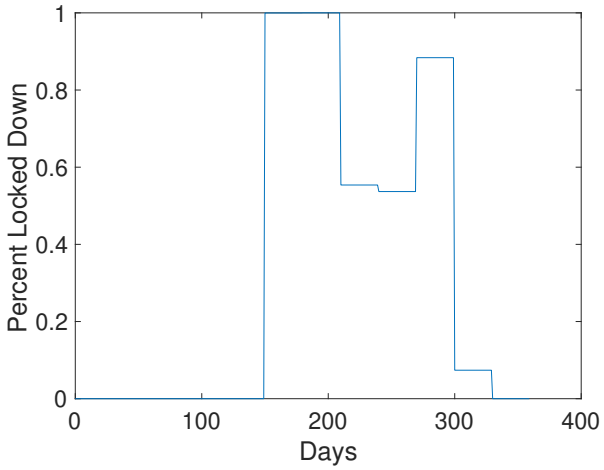

Fig. 3: Government updates lockdown policy every 30 days with the first update occurring on day 150. Total cost over time horizon is 9.3472e10.

In the three years since the COVID-19 began, there have been $3-5$ dominating variants depending on the population being considered, namely the original variant, the Alpha variant, Delta and Omicron. Therefore, for the purposes of this model, we will consider four variants.

In Figure 4 we see the daily cases of our model with no lockdown imposed. We see that as the virus progresses through the population, the different variants take over the state-space as dominant variant, sometimes even being the sole variant contributing to the system. We also see the characteristic fluctuations in cases with peaks seen each time a new variant has completely taken over. This is an exciting and validating result as these fluctuations correlate strongly with the real data visualized in Figure 1. In our simulations, we wish to see a progression from first variant to fourth over our time horizon, so we define our $\hat{\beta}$ in such a way that variant one can only mutate towards variant two which

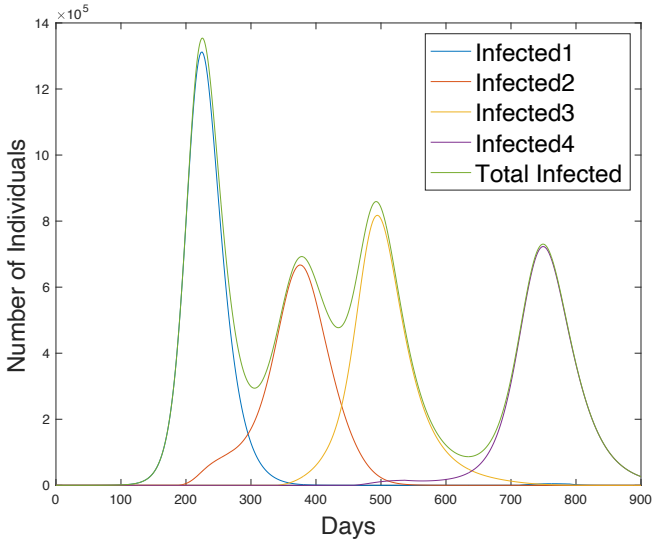

Fig. 4: Evolution of daily case rate for a simulation of our SIR-MC model with four variants. The total cost with no lockdown is 1.2371e+11.

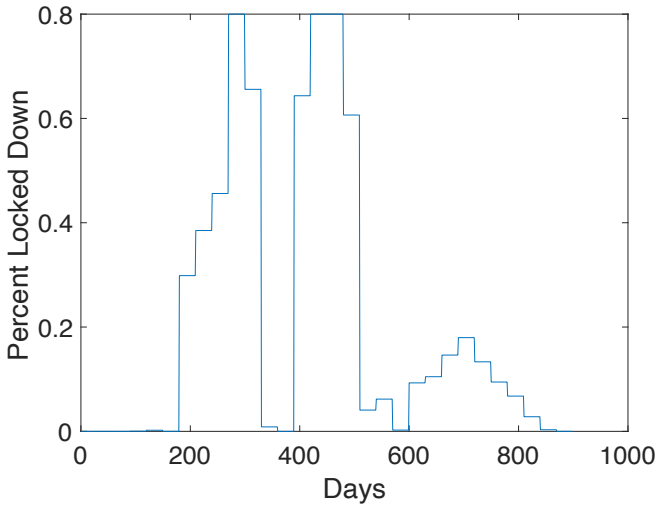

Fig. 5: Optimal lockdown schedule fo the SIR-MC model with maximum lockdown 80%. The infectivity of variants is, respectively, $1.5, 2, 2.5, 3$. The total cost is 7.0316e+10.

can only mutate towards variant three etc. In Figure 5 we represent the optimal lockdown schedule for the evolution with four variants with increasing level of infectivity and lockdown limited to 0.8 (80% closure of economy). Notice that the total cost for the controlled case is around half of the not controlled case despite the bound on the control and strong lockdown exerted only for around 200 days our of 1000. An interesting finding which can be seen in Figure 5 is that for a virus which will inevitably mutate, the optimal solution is to allow the virus to grow unchecked until the first mutation at which time we begin implementing a lockdown. We see the first intervention takes place on day 180 which coincides with the area of time in which the second variant begins taking hold in Figure 4 where the first replication rate is also 1.5. We then see a peak between days 400 and 500 corresponding with the dip in cases between variants 2 and 3, and lastly another small peak between days 600 and 700 corresponding with the last dip in cases before the end of the simulation. This suggests that in long term virus mitigation, the "time to strike" with regards to an intervention that would drive costs down may be during the period of time in which the dominant variant is in a transitional period.

In many large countries, an 80% lockdown in the middle of the pandemic could be considered unrealistic. Therefore, if we only allow for at most a 50% lockdown, the optimal lockdown schedule transforms into the schedule seen in Figure 6. A one time lockdown as shown in the figure is not surprising and has been observed in previous studies [24]. What is interesting here is that once again, the lockdown begins after the first variant has run its course and the second variant is becoming more prevalent, as seen in Figure 7.

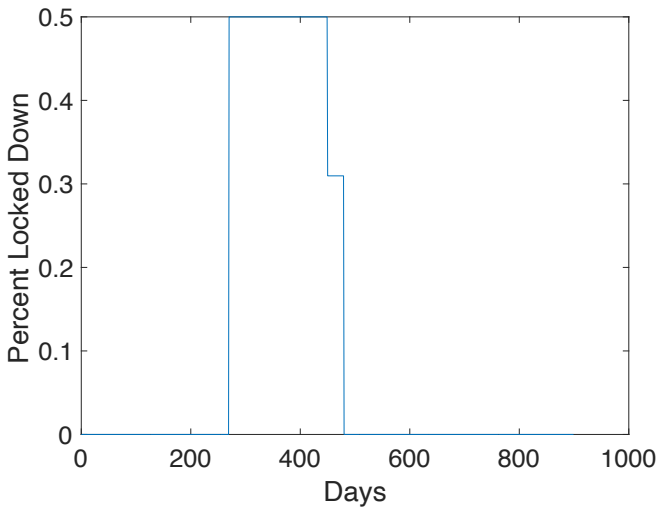

Fig. 6: Optimal lockdown schedule for a simulation of our SIR-MC model with maximum lockdown of 50%. The total cost is 8.5316e+10.

IV. CONCLUSION

SIR models have been widely used in order to predict best strategies for short term policy making. A mutating virus can drastically change both biologically and in its relationship to the population it is infecting. To capture these changes, we develop two frameworks: A Markov chain coupled ODE system which takes on a discrete set of viral mutations, and an MDE coupled ODE system which takes on a continuum of viral mutation. We then couple these models with an optimal control problem in order to elucidate possible connections between optimal policy decision making surrounding non-pharmaceutical interventions. As expected, any level of lockdown significantly decreases the cost over the time horizon, suggesting that continued vigilance is key in the mitigation of viral impact. In fact, earlier first government intervention itself can result in a much less drastic lockdown schedule

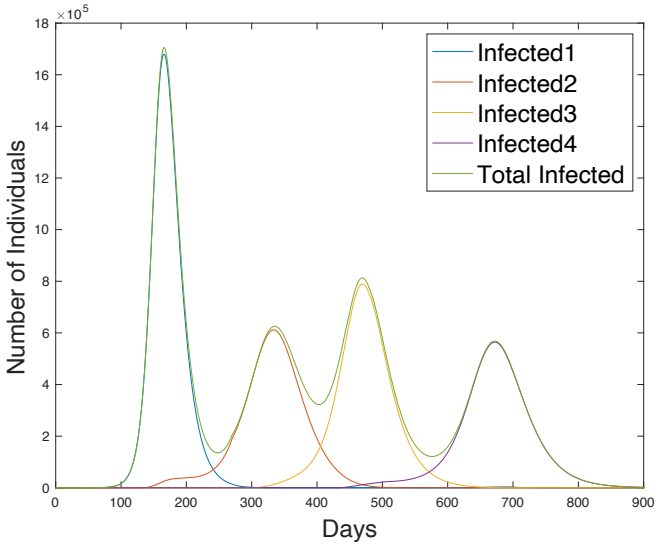

Fig. 7: Infected dynamics for simulation shown in Figure 6

while still finding a lower cost. An interesting finding is that if the mutation of the virus is inevitable, the optimal solution seems to be to implement a more strict lockdown during times where two variants are having an exchange of power. Moreover, limiting lockdown intensity increases modestly the total cost.

References

[1] Daron Acemoglu, Victor Chernozhukov, Iván Werning, and Michael D Whinston. Optimal targeted lockdowns in a multigroup sir model. *American Economic Review: Insights*, 3(4):487–502, 2021.

[2] Nikhil Anand, A Sabarinath, S Geetha, and S Somanath. Predicting the spread of covid-19 using sir model augmented to incorporate quarantine and testing. *Transactions of the Indian National Academy of Engineering*, 5(2):141–148, 2020.

[3] Erhan Bayraktar, Asaf Cohen, and April Nellis. A macroeconomic sir model for covid-19. *Mathematics*, 9(16):1901, 2021.

[4] Akshaya Srikanth Bhagavathula, Philip M Massey, and Jagdish Khubchandani. Covid-19 testing demand amidst omicron variant surge: Mass hysteria or population health need? *Brain, Behavior, and Immunity*, 101:394, 2022.

[5] Zilin Bian, Fan Zuo, Jingqin Gao, Yanyan Chen, Sai Sarath Chandra Pavuluri Venkata, Suzana Duran Bernardes, Kaan Ozbay, Xuegang Jeff Ban, and Jingxing Wang. Time lag effects of covid-19 policies on transportation systems: A comparative study of new york city and seattle. *Transportation Research Part A: Policy and Practice*, 145:269–283, 2021.

[6] Ewen Callaway. The coronavirus is mutating–does it matter? *Nature*, 585(7824):174–178, 2020.

[7] US census. Us and world population clock. https://www.census.gov/popclock/, 2020.

[8] Santenna Chenchula, Padmavathi Karunakaran, Sushil Sharma, and Madhavrao Chavan. Current evidence on efficacy of covid-19 booster dose vaccination against the omicron variant: A systematic review. *Journal of Medical Virology*, 94(7):2969–2976, 2022.

[9] The Apothecary Chris Conover. How economists calculate the costs and benefits of covid-19 lockdowns. https://www.forbes.com/sites/theapothecary/2020/03/27/how-economists-calculate-the-costs-and-benefits-of-covid-19-lockdowns/?sh=44a20e846f63, 2020.

[10] Jonathan M Clarke, Azeem Majeed, and Thomas Beaney. Measuring the impact of covid-19, 2021.

[11] Özden O Dalgıç, Osman Y Özaltın, William A Ciccotelli, and Fatih S Erenay. Deriving effective vaccine allocation strategies for pandemic influenza: Comparison of an agent-based simulation and a compartmental model. *PloS one*, 12(2):e0172261, 2017.

[12] GE Dever. An epidemiological model for health policy analysis. *Social indicators research*, 2(4):453–466, 1976.

[13] S Elbe and G Buckland-Merrett. Data, disease and diplomacy: Gisaid's innovative contribution to global health. glob chall. 2017; 1 (1): 33-46.

[14] W Robert Fleischmann Jr. Viral genetics. *Medical Microbiology. 4th edition*, 1996.

[15] The Henry J. Kaiser Family Foundation. Hospital adjusted expenses per inpatient day, 2019.

[16] Navid Mahdizadeh Gharakhanlou and Navid Hooshangi. Spatio-temporal simulation of the novel coronavirus (covid-19) outbreak using the agent-based modeling approach (case study: Urmia, iran). *Informatics in Medicine Unlocked*, 20:100403, 2020.

[17] Carmen Elena Gómez, Beatriz Perdiguero, and Mariano Esteban. Emerging sars-cov-2 variants and impact in global vaccination programs against sars-cov-2/covid-19. *Vaccines*, 9(3):243, 2021.

[18] Xiaoqian Gong and Benedetto Piccoli. A measure model for the spread of viral infections with mutations, 2022.

[19] Tracie J Haan, Lisa K Smith, Stephanie DeRonde, Elva House, Jacob Zidek, Diana Puhak, Logan Mullen, Matthew Redlinger, Jayme Parker, Brian M Barnes, et al. A repeat pattern of founder events for sars-cov-2 variants in alaska. *medRxiv*, 2022.

[20] Azizul Haque and Anudeep B Pant. Mitigating covid-19 in the face of emerging virus variants, breakthrough infections and vaccine hesitancy. *Journal of Autoimmunity*, page 102792, 2022.

[21] The Wall Street Journal. State shutdowns have taken a quarter of u.s. economy offline, 2020.

[22] William Ogilvy Kermack and Anderson G McKendrick. Contributions to the mathematical theory of epidemics. ii.—the problem of endemicity. *Proceedings of the Royal Society of London. Series A, containing papers of a mathematical and physical character*, 138(834):55–83, 1932.

[23] Kai Kupferschmidt. Evolving threat, 2021.

[24] Sean T McQuade, Ryan Weightman, Nathaniel J Merrill, Aayush Yadav, Emmanuel Trélat, Sarah R Allred, and Benedetto Piccoli. Control of covid-19 outbreak using an extended seir model. *Mathematical Models and Methods in Applied Sciences*, pages 1–26, 2021.

[25] Chantal Nguyen and Jean M Carlson. Optimizing real-time vaccine allocation in a stochastic sir model. *PloS one*, 11(4):e0152950, 2016.

[26] Federal Reserve Bank of St. Louis. Bullard discusses impact of economic shutdown during a u.s. chamber of commerce event, 2020.

[27] B. Piccoli. Measure differential equations. *Archive for Rational Mechanics and Analysis*, 233(3):1289–1317, 2019.

[28] Angel Manuel Ramos, María Vela-Pérez, Miriam R Ferrández, AB Kubik, and Benjamin Ivorra. Modeling the impact of sars-cov-2 variants and vaccines on the spread of covid-19. *Communications in Nonlinear Science and Numerical Simulation*, 102:105937, 2021.

[29] Rafael Sanjuán and Pilar Domingo-Calap. Mechanisms of viral mutation. *Cellular and molecular life sciences*, 73(23):4433–4448, 2016.

[30] Md Shamil, Farhanaz Farheen, Nabil Ibtehaz, Irtesam Mahmud Khan, M Sohel Rahman, et al. An agent-based modeling of covid-19: validation, analysis, and recommendations. *Cognitive Computation*, pages 1–12, 2021.

[31] Raphael Sonabend, Lilith K Whittles, Natsuko Imai, Pablo N Perez-Guzman, Edward S Knock, Thomas Rawson, Katy AM Gaythorpe, Bimandra A Djaafara, Wes Hinsley, Richard G FitzJohn, et al. Non-pharmaceutical interventions, vaccination and the delta variant: epidemiological insights from modelling england's covid-19 roadmap out of lockdown. *medRxiv*, 2021.

[32] Simone Sturniolo, William Waites, Tim Colbourn, David Manheim, and Jasmina Panovska-Griffiths. Testing, tracing and isolation in compartmental models. *medRxiv*, 2020.

[33] Juliana Tolles and ThaiBinh Luong. Modeling epidemics with compartmental models. *Jama*, 323(24):2515–2516, 2020.

[34] Ingrid Torjesen. Covid-19: Delta variant is now uk's most dominant strain and spreading through schools, 2021.

[35] Agnieszka Truszkowska, Brandon Behring, Jalil Hasanyan, Lorenzo Zino, Sachit Butail, Emanuele Caroppo, Zhong-Ping Jiang, Alessandro Rizzo, and Maurizio Porfiri. High-resolution agent-based modeling of covid-19 spreading in a small town. *Advanced theory and simulations*, 4(3):2000277, 2021.

[36] Ryan Weightman, Anthony Sbarra, and Benedetto Piccoli. Coupling compartmental models with markov chains and measure evolution equations to capture virus mutability. *Mathematical Models and Methods in Applied Sciences*, 2022.