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A simulation–optimization framework for optimizing response strategies to epidemics

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\textbf{Abstract}

Epidemics require dynamic response strategies that encompass a multitude of policy alternatives and that balance health, economic and societal considerations. We propose a simulation–optimization framework to aid policymakers select closure, protection and travel policies to minimize the total number of infections under a limited budget. The proposed framework combines a modified, age-stratified SEIR compartmental model to evaluate the health impact of response strategies and a Genetic Algorithm to effectively search for better strategies. We implemented our framework on a real case study in Nova Scotia to devise optimized response strategies to COVID-19 under different budget scenarios and found a clear trade-off between health and economic considerations. Closure policies seem to be the most sensitive to policy restrictions, followed by travel policies. On the other hand, results suggest that practising social distancing and wearing masks are necessary whenever their economic impacts are bearable. The framework is generic and can be extended to encompass vaccination policies and to use different epidemiological models and optimization methods.

1. Introduction

Epidemics and pandemics have become a major concern for policymakers around the world. What most people considered a distant threat turned into a catastrophic reality when the World Health Organization (WHO) declared COVID-19 a pandemic in March 2020. Around a year and a half later, and despite the drastic actions taken by governments, about 200 million COVID-19 cases and 4.2 million deaths have been reported globally. Given the enormous cost humanity has been paying due to COVID-19, experts warn that the world cannot afford to be unprepared again when the next pandemic hits [1].

It is possible to reduce the spread of an epidemic disease caused by a respiratory virus such as COVID-19 through measures that involve minimizing people’s contact, which can be achieved by implementing policies that, for example, restrict travel and ban gatherings. These policies, however, have substantial economic and societal costs if implemented for extended periods. Thus, selecting from the wide array of response policy alternatives to minimize the health impacts of an epidemic without causing disastrous side-effects on the economy and the health of people, including mental health and delayed surgeries, is a challenging task for policymakers. In the absence of systematic and evidence-based methods to develop response strategies, policymakers have no choice but to rely on ad-hoc and reactive responses, which might be far from optimum. Operations Research (OR) methods can be helpful in informing high-quality response strategies that balance health, economic, and societal considerations. However, they are yet to be used to their full potential.

Nowadays, most of the quantitative methods used by practitioners to test response policies and predict the trajectory of epidemics are based on simulation models that approximate dynamic epidemiological models like the famous susceptible–infected–recovered (SIR) model. These compartmental models are popular among practitioners due to their simplicity and intuitiveness. Other statistical (e.g., network [2]) and simulation (e.g., agent-based [3]) models have been proposed in the literature for the same purpose. While simulation models can be used for decision-making by changing input parameters and observing the change in outputs, they have well-known limitations [4]. When the number of possible alternatives is very large (as in the case when different policies could be implemented at different stages), simulation techniques can be used to evaluate and compare only a small subset of these alternatives. More importantly, these alternatives are restricted by the imagination of the model user. This issue is particularly vital when dealing with new situations like COVID-19. Another common
issue of simulation models is the difficulty of translating their outputs into useful decisions because the model provides a range of possible outputs for each set of parameters and inputs. There is often a significant overlap between output ranges of different strategies, rendering them of little value in policy formulation.

This paper proposes a novel framework for using OR tools to devise response strategies to epidemics. Our framework is a simulation-optimization that combines a compartmental model with a meta-heuristic optimization procedure to find near-optimal strategies that minimizes the number of total infections given a limit on the total economic cost of the response strategy. In particular, a simulation model based on a modified, age-stratified susceptible–exposed–infected–recovered (SEIR) compartmental model is used to evaluate response strategies, each of which defines closure, protection, and travel policies in every time period of the planning horizon. The epidemiological model captures, in detail, the contact frequencies among different age groups, the presence of co-morbidities, and the self-quarantine behaviour, among other realistic considerations. The simulation model is embedded in a Genetic Algorithm (GA) that uses the population of evaluated strategies to iteratively generate new (and hopefully better) ones through cross-over and mutation.

The research presented here was developed while working on a project with Nova Scotia Health Authority (NSHA) to build decision-support tools based on OR methods that could be used by NSHA to extract response strategies to COVID-19 and that strike a balance between health and economic objectives. Hence, we applied the proposed framework to the Canadian province of Nova Scotia (NS) as a real-life case study. It was found that when the budget is not constrained, the best response strategy is to enforce strict closures throughout the planning horizon. However, when the budget is constrained, a cyclical strategy should be employed, alternating between stricter measures to reduce spread then relaxing measures to reduce the economic impact. Unless policymakers have a very low budget, social distancing and the use of masks should always be enforced. Although the framework was developed in a specific setting, it is quite generic and can be easily tailored to be used by other jurisdictions and for other epidemics.

Throughout this paper, the term policy is used to refer to a pre-defined set of decisions specific to a single response aspect (i.e., closure, protection or travel) in a single time period. An example is restricting all international travel during a given week. The term strategy, on the other hand, refers to a series of policy tuples for the entire planning horizon, each consists of a closure, a protection and a travel policy.

The remainder of this paper is organized as follows: The next section reviews related work, highlighting the research gaps and the contributions of this paper. Section 3 describes the simulation model components, the types of response policies considered, the mathematical formulation and how the model was verified and validated. Section 4 describes the GA used to optimize response strategies. Section 5 presents the numerical results obtained by implementing the proposed framework on a real case study and draws some managerial insights. Finally, conclusions and possible extensions are provided in Section 6.

2. Related work

Before describing our approach, related work is reviewed. The first part surveys the OR methods proposed in the literature to formulate response strategies to epidemics and contrasts our work with them, highlighting research gaps and contributions. This review focuses on prescriptive, as opposed to descriptive or predictive, approaches, i.e., those which aim at informing (near-)optimal response strategies, especially when a large number of strategies could be efficiently evaluated and compared. This choice, to a great extent, excludes most simulation and statistical models commonly used in the quantitative epidemiology literature, which usually have predictive or analytical purposes. Readers interested in the classical epidemiological models are referred to the texts of Brauer [5] and Kramer [6]. The second part focuses on the COVID-19 pandemic, particularly the models proposed in the literature to evaluate its impact and aid policymakers in making decisions regarding public health interventions, and how they relate to this work. Given the sheer number of mathematical models developed for COVID-19, it is not possible to include all of them here. Interested readers are referred to the survey of Adiga et al. [7] for a detailed account.

2.1. The role of OR methods in developing epidemic response strategies

Health care has been one of the main application areas, and a prominent success story, of OR in the last four decades [8–10]. However, except for widely used simulation frameworks (system dynamics [11], discrete event [12], agent-based [3]) to model the progression of epidemics, using OR tools to devise response strategies to disease outbreaks has not received much attention prior to the COVID-19 pandemic. Among the few early attempts is the work of Lee and Pier-skalla [13], which developed a mathematical program for computing the optimal test choice and screening periods in diseases which have zero or negligible latent periods. Dimitrov et al. [14] presented a tactical optimization model for distributing a stockpile of a pH1N1 antiviral treatment, which efficiently searches large sets of intervention strategies applied to a stochastic network model of pandemic influenza transmission within and among U.S. cities. Other vaccine allocation optimization approaches proposed include stochastic programming [15, 16], derivative-free optimization [17] and heuristics [18]. Long and Brandeau [19] surveyed the application of different OR tools, including Decision Trees, Markov Models, Network Models and Linear Programming to analyse infectious disease control decisions. Probably the most related to our work is the simulation-optimization framework presented in [20] to optimize mitigation strategies for pandemics affecting several regions. It allocates a limited budget to procure vaccines and antivirals, capacities for their administration, and resources required to enforce social distancing. However, two major differences between our work and [20] are noted. First, in their framework, available budget is allocated progressively, i.e., allocation of available resources, including remaining resources from previous allocation, is performed individually for each new regional outbreak episode (epoche), as opposed to the holistic approach we use to optimize the response strategy for the entire planning horizon. Secondly, and more importantly, they select non-pharmaceutical policies (e.g., social distancing, quarantine, closure) based on static guidelines that depend on pandemic severity, in contrast to our framework that lets the optimization procedure freely decide these policies for each time period.

The emergence of COVID-19 has led to a surge in its research among the OR community. OR tools have been implemented mainly to allocate resources optimally. Risanger et al. [21] presented a facility location model to determine which pharmacies in the U.S. should be testing for COVID-19 to maximize accessibility. Mehrotra et al. [22] developed a stochastic optimization model to share ventilators across the US, aiming to minimize shortfall. More related to this work, Kaplan [23] used probability models to assess the effectiveness of case isolation of infected individuals and quarantine of exposed individuals, and found that case isolation alone is sufficient to end community outbreaks, provided that cases are detected efficiently. Rawson et al. [24] applied an optimal control framework to a modified SEIR model to investigate the efficacy of two potential lockdown release strategies. A gradual release strategy is optimized to determine how to maximize those working while preventing the health service from being overwhelmed. Although having some similarity with our framework, there is a much narrower focus on releasing a locked down population and using a simple search heuristic to identify the optimal solution. Bertsimas et al. [25] address the problem of allocating vaccine quantities among geographical areas and population groups. The problem was formulated as a bilinear, non-convex optimization model and a coordinate descent algorithm that iterates between optimizing vaccine allocations and simulating the
dynamics of the pandemic (using an extended version of an epidemiological prediction model known as “DELPHI”) was proposed to solve it. Similar to [25], we use a simulation–optimization framework that combines an epidemiological prediction model with a search algorithm. However, our work uses a GA metaheuristic to effectively cover a vast search space and has a different focus on closure, protection and travel policy rather than vaccination plans.

Our review reveals that, with the exception of few noticeable attempts, OR is yet to be utilized to its full potential to guide response strategies to epidemics and pandemics. We argue that OR methods and tools can play an important role in informing supervisor policy alternatives that formally model policymakers’ objectives, restrictions, and priorities, as opposed to the widely-used trial-and-error methods. The framework proposed in this paper is a significant step towards normalizing the use of OR methods in the area of response strategies to epidemic outbreaks. To the best of our knowledge, this is the first comprehensive OR-based framework for optimizing a multi-faceted (i.e., closure, protection, travel) pandemic response strategy over a long time horizon while trying to strike a balance between health and economic considerations. Our framework has a broader scope and higher flexibility than previous studies. Unlike the simple models used in some past studies, the detailed epidemic model used in our study adequately captures the characteristics and behaviours of the population (e.g., age groups, co-morbidities, contact patterns, quarantine, infection severity, hospital and intensive care unit (ICU) admission, introduction of new cases through travel). Furthermore, using a population-based metaheuristic like GA enables us to explore the vast search space and reach (near-)optimal strategies effectively, as opposed to the simple heuristics proposed in the literature.

2.2. COVID-19 models and response policies

COVID-19 is respiratory illness caused by a novel type of the coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which has proven to be a dangerous pathogen due to its high infectivity, long incubation period, and acute health impact on the population. Compartmental models have been used extensively to study the spread of the virus and to evaluate potential intervention policies. Among them, modified SEIR models were the most widely used since they were deemed more suitable to capture the disease profile. Two representative examples are Tuite et al. [26] and Giordano et al. [27] which utilized modified SEIR models, though with different additional compartments, to evaluate interventions such as case identification or contact tracing, case isolation, and physical distancing. Both reached the same conclusion, that contact tracing and isolation on their own are insufficient to prevent the epidemic spread and that social distancing measures are necessary to prevent over-burdening of the health system. Tuite et al. [26] also compared fixed versus dynamic strategies and showed that dynamic strategies have a comparable effectiveness in maintaining cases below ICU capacity, but result in less overall time under restrictive policies. However, neither of the models offered precise policy prescriptions in terms of how the restrictions associated with physical distancing strategies that were modelled are to be achieved. Another limitation was that policymakers must have the strategy determined beforehand to test.

Some models in the literature attempted to evaluate and devise response strategies while considering the opposing goals of strict interventions that reduce infections and less strict interventions that reduce the economic burden and negative impact on mental wellbeing. Perkin and España [28] applied optimal control theory to determine strategies that balance the objectives of minimizing the number of deaths and minimizing the level and duration of interventions. They concluded that premature relaxation of interventions would lead to resurgences that greatly exceed healthcare capacity. Optimal control theory was also used by Năraigh and Byrne [29] with piece-wise linear controls to minimize the cost to the economy of the various control measures while keeping the number of infectious cases below a maximum threshold such that hospital capacity is not overwhelmed. Toda [30] used two separate models, an SIR compartmental model, and a stylized production-based asset pricing model, respectively, to evaluate the disease spread and economic impact. An optimal policy introducing social distancing depending on the average number of cases was determined and showed a reduction of 21.8% in peak cases. The economic model used to evaluate the intervention policy showed that while it leads to two disease peaks, its expected economic decline is moderate, amounting to 10% only compared to 50% for the single-peak base case. Guadalupe [31] also used an SIR model while measuring economic impact by looking at the time to reach steady state for different quarantine strategies. It is assumed that the faster a policy results in reaching steady state it will have a lower impact on the economy. Both models have the same limitation seen above where they do not offer detailed strategies on when to implement interventions and for how long. Popa [32] proposed a combinatorial optimization model to optimize social distancing policies while taking into consideration their impact on the economy. For a given total budget, the model determines its optimal allocation between isolating people and closing facilities. Hence, it requires a significant amount of granular data e.g., all facilities and the associated cost of closing them, as well as people and their associated cost of isolating, making it difficult to test and validate.

Other models that evaluated case management strategies included: a system of integro-differential equations [33] and dynamic transmission models based on the Erlang and Poisson distributions [34]. The models used similar interventions including lockdowns, social distancing, and contact tracing. They also had similar results stating the importance of using all interventions concurrently to ensure that health systems are not overwhelmed by cases. Furthermore, it is shown that early lockdown without additional public health interventions will result in a delayed second wave of similar magnitude once restrictions are lifted.

As COVID-19 remains to be a major threat, new models are being developed to offer insights into managing it from a policy perspective. However, a notable gap with the current models is that, while they show that public health interventions are needed to manage COVID-19 cases, they do not offer precise prescriptions that inform policymakers what level of intervention to implement and when. Moreover, these models, regardless of their accuracy and sophistication, can evaluate only the strategies pre-determined by the policymaker, but not develop new ones. Our research fills these gaps by developing a systematic approach that enable detailed and dynamic response strategies to be generated and evaluated efficiently, thus helping policymakers to make informed interventions.

3. SEIR compartmental model

In this section, we present the central component of the proposed framework, which is a modified, age-stratified SEIR model that evaluates the health impact (i.e., total number of infections) of response strategies. We begin by outlining the model structure, then describing the response policies considered, before presenting the mathematical formulation and finally showing how the model is verified and validated.

The SEIR model is a compartmental model in which the population is divided into compartments and people move between compartments at different rates of transfer [5]. It is an expanded version of the famous Kermack–McKendrick’ SIR model with an exposed compartment added. The susceptible (S) compartment contains people who are able to contract the disease. The exposed (E) compartment has people who have been infected but are not yet infectious. The infected (I) compartment consists of people who are infectious and capable of spreading the disease. The recovered (R) compartment contains people who have been infected, have immunity, or died and can no longer get the disease and spread it to others. The independent variable in
the model is time, and the rate of transfer between compartments is described mathematically as differential equations. Fig. 1 shows a flowchart representation of the SEIR model, highlighting the different compartments and the flows between them. A stock-and-flow diagram of the same model (constructed using Vensim) is shown in Fig. 2.

Like all compartmental models, the SEIR model is built on basic assumptions, including that the epidemic process is deterministic and that the number of members in a compartment is a differentiable function of time, which only becomes accurate once there are significant number of infections. It is also assumed that the time scale of the disease is much faster than births and deaths, so demographic effects are ignored. Furthermore, we make the following assumptions in our SEIR model:

1. No re-infection is possible and recovered individuals remain immune;
2. The model runs in periods of one week, meaning that a policy change can occur at a maximum of once per week;
3. An individual is only infectious during the pre-symptomatic, mild-moderate, and severe compartments;
4. Individuals have the same duration distribution in a compartment regardless of their age or health status; and

The model is based on the case study of COVID-19 in NS and all inputs are modified to accurately depict it.

### 3.1. Model parameters

The population was stratified by age and health status. There are seventeen age groups in 5-year increments using 2019 population data from Statistics Canada [35]. The health status stratification comprises of two categories, those with and those without comorbidities. A comorbidity is an underlying health condition or disease that is present within an individual. Examples of common comorbidities include: heart disease, asthma, diabetes, stroke, and cancer. It is important to understand the health characteristics of the population as it has been found that underlying conditions can have a significant impact on patient outcomes [36,37]. Statistics Canada released population health data outlining the percentage of the population by age category with at least one underlying health condition that will increase the likelihood of a severe outcome given infection with COVID-19 [38]. This data pertains only to Canadians over age 18; thus, to account for increased severity in Canadians under 18, Asthma data was used [39]. It was assumed this would be sufficient as the majority of younger people do not have
diseases such as hypertension or stroke. The parameters describing the clinical course of COVID-19 were derived from Tuite et al. [26] and can be seen in Table 1.

Given that COVID-19 is a new disease, there is still a lot of uncertainty about its parameters, transmission dynamics, and impact of policy restrictions on its spread. In general, COVID-19 parameters have a wide range of estimates in the published research, making it difficult for modellers to pick precise parameter values for their models. For example, Tuite et al. [26] estimate the latent period to be 2.5 days in their model whereas Giordano et al. [27] use a latent period of 0 days. As the knowledge and body of research surrounding COVID-19 increases, it can be noted that parameters such as infection period or proportion of severe cases change based on the population demographics, COVID-19 variant under study, and social norms within a region. This variation in data was dealt with by choosing reliable sources and reviewing parameters with NSHA experts to verify they were inline with what was being observed within NS.

3.1.1. Contact tracing

Contact tracing is a public health intervention used to control the spread of COVID-19. It is the process of identifying, assessing, and managing individuals who have been exposed to COVID-19 to prevent further transmission. In NS, once an individual is contacted, depending on their risk level, there are three potential outcomes [40]. A low risk does not require any action. A moderate risk must self-monitor for 14 days, avoid high risk people, and complete a phone assessment. A high risk must isolate for 14 days and take a COVID-19 test. Contact tracing was incorporated into the model by adding a quarantine stream. Through consultation with NSHA it was determined that their conservatively estimated ability to trace contacts was 30%. This means they are able to determine 30% of an infected persons contacts and inform them of the exposure.

3.1.2. Case importation

Travel restrictions are another public intervention that can be implemented to manage infections and the transmission of COVID-19. By restricting travel, the opportunity for introduction of new cases is limited, which minimizes the likelihood of community spread and increased cases. Travel restrictions have clear benefits when the region has few or no cases, as seen in NS [41]. There are four different levels of travel policies in the model: No travel, Atlantic Canada travel, National travel, and International travel. For each travel policy the estimated number of daily imported COVID-19 cases was determined. The purpose of separating domestic travel into National and Atlantic was due to the implementation of the Atlantic bubble. The Atlantic bubble was the agreement among Atlantic Canadian provinces that permitted free movement between them without the need for isolation [42].

Statistics Canada provides data for the number of international and domestic travellers that visited NS in 2017 and 2018 [43,44]. This data was used to estimate the number of people that visit NS from within Canada and from outside of Canada, respectively. A simplifying assumption was that the travellers are evenly distributed throughout the year. The yearly estimate was used to determine the number of incoming travellers per day. The international travel data from Statistics Canada reported the top 13 countries international travellers come from. The prevalence of COVID-19 was then estimated in cases per million for each country [45]. Bhatia and Klausner [46] determined the probability that a random community contact has COVID-19 in the United States. A ratio of cases per million between the United States and the remaining 12 countries was used to determine the probability of a random traveller having COVID-19 for each country. A weighted average probability for an international traveller was determined, with the United States accounting for 78.05% of travellers and an average of the remaining 12 countries for the other 21.95% of travellers. The probability of a traveller having COVID-19 dependent on the country of origin in combination with the daily traveller data allowed for the calculation of the number of daily incoming travellers with COVID-19.

In the model, the imported cases were defined in terms of the subscripts: age group and health status. Statistics Canada describes an age distribution of people that travel domestically in Canada. This data was then applied to each case importation rate to determine the distribution of incoming COVID-19 cases. When cases are imported, they come directly from the existing susceptible population and move into the exposed compartment because the model uses a closed population. The assumption is that infected travellers will interact with the NS population and cause new infections.

3.1.3. Transmissibility

A contact with an infected individual does not necessarily mean transmission of infection. The transmission rate is a combination of the contact rate and the probability of transmission upon contact [47], referred to as transmissibility. This probability is dependent on several factors, including the closeness and duration of the contact, infectivity, and susceptibility. Transmissibility can be impacted by public health interventions such as social distancing, which reduces the likelihood of transmitting the disease. The transmissibility value with no interventions was estimated to be 15.6% [48] from a study in Thailand that quantified the number of contacts of a confirmed case that had become infected. Our SEIR model includes two factors that impact disease transmissibility: masks and social distancing. Chu et al. [49] studied the impact of different interventions, including social
distancing, wearing eye protection, or wearing masks on the reduction in spread of respiratory diseases. The study found that incorporating social distancing resulted in a reduction in transmission of 10.2%, with a 95% CI of [0.11.5, %7.5], and wearing masks alone resulted in a reduction of transmission of 14.3%, with a 95% CI of [0.15.9, %10.7]. The transmission reduction of 10.2 points was used because the authors estimated moderate certainty in the social distancing results versus low certainty in the mask results. Therefore, the transmissibility with public health interventions in place was estimated to be 5.4%. A limitation with the estimate is that we are assuming 100% compliance, which results in a full reduction in transmissibility.

### 3.1.4. Contact matrices

Transmission of COVID-19 is driven by individuals’ social contacts. The typical SEIR framework assumes homogeneous mixing, which does not accurately represent population mixing dynamics. To mitigate the impact, mixing was stratified by age. Mossong et al. [50] determined contact patterns for different age groups to help understand the spread of respiratory diseases. The study collected data from 8 countries: Poland, Belgium, Germany, Finland, Great Britain, Italy, The Netherlands, and Luxembourg. An average of the age–age contacts for all countries was used to determine the contact matrix. The contact matrix was calibrated using the transmissibility parameter to get an acceptable basic reproduction number ($R_0$) of 3.47 [51], where $R_0$ represents the number of secondary infections cause by a single infected member into a completely susceptible population. Its value determines whether a disease will cause an epidemic (when $R_0 > 1$) or the infection dies (when $R_0 < 1$).

### 3.2. Response policies to epidemics

Governments and health authorities can implement different policies to contain, and hopefully eradicate, epidemic outbreaks like COVID-19. Examples include setting limits on gathering sizes, imposing travel restrictions, quarantining symptomatic and high-risk individuals, conducting contact tracing, and promoting or mandating PPE usage. Each policy has multiple levels of strictness and scopes of implementation in terms of duration, geographical boundaries and/or target population. For instance, gathering limitations can be very mild (e.g., allowing up to 50 people to gather in one place) or very strict (a total curfew), can extend for hours or months, and cover few communities or the entire country. Each policy alternative has quantifiable effects on the spread on the disease, along with economic and social costs. In general, one can expect that the stricter the policy is and the longer it is applied, the greater the effect it has in reducing the spread, albeit the higher it costs. A rational decision maker would try to maximize the positive spread reduction effects of the implemented policies while minimizing their costs, giving rise to a multi-objective problem. It is not easy to develop an exhaustive list of response policies that could be used during epidemic outbreaks. However, this paper focuses on closure, protection and travel policies.

The policies used in our model were derived by reviewing the policies implemented within NS from March through July 2020. This allowed for review of a large variety of policies of different strictness. Generally speaking, policies implemented during March and April imposed strict restrictions on the population, whereas the policies from May through July gradually relaxed some restrictions. Examples of
these restrictions include: closing child care facilities, stopping elective surgeries, closing personal services, and online public school. The list was consolidated into three overarching categories, closure, protection, and travel, and each category was narrowed down into policies which were assumed to have a significant impact. The main closure components are gathering limitations and closure of public schools, universities or colleges, daycare facilities, businesses such as restaurants and stores, and public outdoor facilities. These policies focus on reducing the average number of daily contacts of an individual. There are five different closure levels which all have different strictness ranging from keeping everything open to sheltering in place. Protection policies focus on reducing transmissibility, and account for the implementation of social distancing and masks. Two protection policy alternatives are considered: enforced and not enforced. The travel restriction policies account for the limitations on travellers to prevent case importation. There are four travel policies, where level one is allowing all travel including international and domestic and level four is disallowing all travel. A summary of each policy class and their levels can be seen in Table 2.

The weekly economic cost was determined for each policy. The closure policy costs were determined using the Canadian Gross Domestic Product (GDP) [52]. The GDP in February 2020 was taken as a baseline (i.e., level 1) while the GDP in April 2020 was used for the strictest closure policy (i.e., level 5). The three policies in between were scaled based on the estimated average daily contacts. The protection policy costs were estimated based on the GDP specifically for restaurants and accommodations [52]. The GDP in February 2020 was taken as the baseline while the GDP in July/August was used for level two. The reasoning is that April 2020 had the most significant drop at 18%; however, as businesses began opening with restrictions, it increased and levelled off in July and August prior to the second wave. The travel policy costs were based on the estimated loss of tourism GDP [53]. It was estimated that 20% of tourism is from international visitors while 80% is from domestic visitors [54]. Combining the GDP loss and visitor estimates, a cost was determined for each level. A limitation of the policy costs were based on the estimated loss of tourism GDP [53]. It was estimated that 20% of tourism is from international visitors while 80% is from domestic visitors [54]. Combining the GDP loss and visitor estimates, a cost was determined for each level. A limitation of the approach used to estimate cost data is that it ignores the potential interaction between the costs of different interventions.

3.3. Model formulation

Table 3 depicts the notations used to formulate the compartmental model. The model consists of the system of Eqs. (1)-(15), which describe the flow of individuals with age group $i$ and co-morbidity status $k$ between the different compartments in the simulation model. The flows are later approximated using algebraic (difference) equations in the discrete-time simulation model by replacing $dt$ with $\Delta t$, where $\Delta t$ is the simulation step size. The notations $c_{i,j,t}$, $\beta_i$, $\lambda_{i,t}$, $\alpha_{i,k}$, and $\gamma$ represent the values of their corresponding parameters during period $t$. Most equations are self-explanatory, though a few clarifications are warranted. As shown in Fig. 1, the flow from the Susceptible compartment splits into two streams depending on whether the case is discovered and isolated or not. Both streams go through the same steps and merge again in the Hospitalized and Recovered compartments. Also, all cases introduced through travel are assumed to be in the exposed phase, thus are added to the Exposed compartments (with or without quarantine, depending on the policy applied) and deducted from the Susceptible compartment to keep the total population unchanged. It is clear that the flows are dependent on selection of the closure, protection, and travel policies.

### Table 2

| Policy alternatives. | Level | Description |
|----------------------|-------|-------------|
| Closure              | 1     | No closures |
|                      | 2     | Mild restrictions |
|                      | 3     | Moderate restrictions |
|                      | 4     | Severe restrictions |
|                      | 5     | Shelter in place |
| Protection           | 1     | No interventions |
|                      | 2     | Masks required and social distancing |
| Travel Restrictions  | 1     | International travel |
|                      | 2     | Domestic travel |
|                      | 3     | Atlantic travel |
|                      | 4     | No travel |

### Table 3

| Model notations. |
|------------------|
| **Indices**      |
| $i,j$             | Age group, $i,j = 1, \ldots, J$ |
| $k$               | Co-morbidity status, $k = 1, \ldots, K$ |
| $t$               | Time period, $t = 1, \ldots, T$ |
| $l$               | Closure policy, $l = 1, \ldots, L$ |
| $p$               | Protection policy, $p = 1, \ldots, P$ |
| $q$               | Travel policy, $q = 1, \ldots, Q$ |
| **Parameters**    |
| $n_{ik}$          | Population of age group $i$ with co-morbidity status $k$ |
| $c_{i,j,t}$       | Contact rate for a person in age group $i$ with people in age group $j$ under closure policy $l$ |
| $v_{i,j,t}$       | Contact rate for a quarantined person in age group $i$ with people in age group $j$ |
| $a_i$             | Average exposure duration |
| $a_{i,s}$         | Average pre-symptomatic duration |
| $a_{i,h}$         | Average infection duration |
| $a_{i,hs}$        | Average hospital duration |
| $a_{i,ICU}$       | Average ICU duration |
| $\sigma_i$        | Proportion contacts traced |
| $\sigma_{i,f}$    | Probability of severe infected, given infected |
| $\sigma_{i,h}$    | Probability hospitalized, given severe infected |
| $\sigma_{i,P}$    | Probability ICU, given hospitalized |
| $\sigma_{i,c}$    | Probability death, given ICU |
| $\beta_i$         | Rate of new cases introduced by travel policy $q$ |
| $\gamma_i$        | Force of infection |
| $\lambda_i$       | Quaran time force of infection |
| $\gamma$          | Transmissibility under protection policy $p$ |

| **Compartments**  |
|-------------------|
| $S_{i,k}$          | Number of susceptible of age group $i$ with co-morbidity status $k$ |
| $E_{i,k}$          | Number of exposed of age group $i$ with co-morbidity status $k$ |
| $I_{P,k}$          | Number of infected pre-symptomatic of age group $i$ with co-morbidity status $k$ |
| $IM_{i,k}$         | Number of infected mild-moderate of age group $i$ with co-morbidity status $k$ |
| $IS_{i,k}$         | Number of infected severe of age group $i$ with co-morbidity status $k$ |
| $I_{PQ,k}$         | Number of infected pre-symptomatic quarantined of age group $i$ with co-morbidity status $k$ |
| $IMQ_{i,k}$        | Number of infected mild-moderate quarantined of age group $i$ with co-morbidity status $k$ |
| $ISQ_{i,k}$        | Number of infected severe quarantined of age group $i$ with co-morbidity status $k$ |
| $H_{i,k}$          | Number of hospitalized of age group $i$ with co-morbidity status $k$ |
| $I_{ICU,k}$        | Number of ICU of age group $i$ with co-morbidity status $k$ |
| $R_{i,k}$          | Number of recovered of age group $i$ with co-morbidity status $k$ |
| $D_{i,k}$          | Number of dead of age group $i$ with co-morbidity status $k$ |
before being added-up iteratively until the entire model is assembled. built in small sub-modules that were tested and debugged individually led to the same results. Furthermore, in the Vensim case, the model was tested on several instances and ensured that the three platforms that was eventually used in the simulation–optimization framework. Vensim (Fig. 2) stock-and-flow model, and a computer code on

3.4. Model verification and validation

In what follows, we provide a brief explanation on how the compartmental model was verified and validated. By verification, we mean ensuring that the system accurately describes reality.

3.4.1. Verification

Model verification was primarily performed by comparing the results obtained from three computer programs written based on the conceptual model using different platforms: an Excel spreadsheet, a Vensim (Fig. 2) stock-and-flow model, and a computer code on Julia that was eventually used in the simulation–optimization framework. We tested on several instances and ensured that the three platforms led to the same results. Furthermore, in the Vensim case, the model was built in small sub-modules that were tested and debugged individually before being added-up iteratively until the entire model is assembled. The remaining parameters have a smaller impact on model output into consideration the potential inaccuracy in the model output if these values are not accurate. The parameters should also be updated as new information becomes available on the transmission of COVID-19.

3.4.2. Validation

Model validity was established by, first and foremost, determining its structure in consultation with health policy experts at NSHA and obtaining its data from high-credible sources. Moreover, a sensitivity analysis was performed to understand the uncertainty around the input parameters and their impact on cumulative infections. Two sensitivity analyses were performed: univariate and multivariate. The univariate analysis was completed by changing one parameter, sampling within a random uniform distribution, and holding all other parameters constant. The uniform distribution limits for each parameter was ± 10% of the nominal/mean value. There were 200 simulations performed for each parameter. Fig. 3 displays the resulting range of cumulative infections over 100 days. The minimum and maximum cumulative infections for each of the 200 simulations are summarized in Table 4.

The results of the univariate analysis show that changes in the transmissibility and contact rate have the most significant impact on the models cumulative infections. The users of the model should take into consideration the potential inaccuracy in the model output if these values are not accurate. The parameters should also be updated as new information becomes available on the transmission of COVID-19. The remaining parameters have a smaller impact on model output than transmissibility and contact rate, and therefore do not need to be scrutinized or updated to the same degree.

The multivariate analysis was completed by changing all parameters simultaneously. There were 200 simulations performed, each with a different combination of parameters within the uniform random distributions. Fig. 4 displays the range of cumulative infections over 100 days. The multivariate analysis results show that there are interaction effects between the parameters and changing them simultaneously results in significant variation in the model output. The minimum

\[ \frac{dI_{PQ,k}}{dt} = \left( \frac{1}{a_1} \right) EQ_{i,k} - \left( \frac{1}{a_2} \right) I_{PQ,k} \]

\[ \frac{dIM_{Q,k}}{dt} = \left( 1 - \sigma_{i,k} \right) \left( \frac{1}{a_3} \right) I_{PQ,k} - \left( \frac{1}{a_3} \right) I_{MQ,k} \]

\[ \frac{dIS_{Q,k}}{dt} = \left( 1 - \sigma_{i,k} \right) \left( \frac{1}{a_4} \right) I_{PQ,k} - \left( \frac{1}{a_4} \right) IS_{Q,k} \]

\[ \frac{dH_{i,k}}{dt} = \sigma_{i,k} \left( \frac{1}{a_3} \right) IS_{i,k} - \left( \frac{1}{a_3} \right) H_{i,k} \]

\[ \frac{dI_{i,k}}{dt} = \sigma_{i,k} \left( \frac{1}{a_4} \right) H_{i,k} - \left( \frac{1}{a_4} \right) I_{i,k} \]

\[ \frac{dD_{i,k}}{dt} = \sigma_{i,k} \left( \frac{1}{a_4} \right) I_{i,k} \]

\[ \frac{dR_{i,k}}{dt} = \left( \frac{1}{a_3} \right) \left( IM_{i,k} + 1M_{i,k} + 1S_{i,k} \right) \]

\[ \lambda_{ij} = \gamma_i \sum_{j=1}^{K} \sigma_{ij} \left( \sum_{k=1}^{K} \left( 1P_{i,k} + 1M_{i,k} + 1S_{i,k} \right) \right) \]

\[ \lambda_{q,i} = \gamma_i \sum_{j=1}^{K} c_{q,i} \left( \sum_{k=1}^{K} \left( 1P_{i,k} + 1M_{i,k} + 1S_{i,k} \right) \right) \]

### Table 4

| Parameter                  | Minimum       | Maximum       | Range |
|----------------------------|---------------|---------------|-------|
| Transmissibility           | 549,683       | 901,984       | 47%   |
| Contact Rate               | 574,184       | 875,188       | 43%   |
| Contact Rate Quadrantine   | 812,042       | 829,335       | 2%    |
| Probability Tracing        | 759,003       | 860,514       | 14%   |
| Exposure Duration          | 784,656       | 847,144       | 8%    |
| Pre-symptomatic Duration   | 802,829       | 836,403       | 4%    |
| Infection Duration         | 732,640       | 870,382       | 18%   |
| Initial Infected           | 813,278       | 827,236       | 2%    |
and maximum number of infections obtained from the multivariate sensitivity analysis were 130,239 and 938,060 people, respectively.

Lastly, the model output was retrospectively compared to the initial infection wave that occurred in NS. The policies were combined and implemented following a similar timeline to what was actually enforced. The model was run for a period of 120 days starting on March 1st, 2020. It resulted in 1070 cumulative infections with a peak daily cases of 429, while NS had 1087 cumulative infections with a daily peak of 422. Fig. 5 shows the results obtained from the model and the actual numbers for NS. Although this model predicted a faster spread and an earlier peak of the epidemic than reality, the differences in cumulative infections and daily peaks were 1.56% and 1.57% only, leading to the conclusion that the model is valid. The delayed peak in the outbreak data compared to the model output can, possibly, be explained by the nonuniform COVID-19 spread in NS during the first wave, which had several localized outbreaks in long-term care (LTC) homes, and the ineffective testing and case reporting protocols implemented at the early stage of the pandemic. With high-quality outbreak data, however, the model parameters could have been “fine-tuned”, e.g., through nonlinear least-squares model fitting, to minimize the deviation between the model output and the data.

It should be highlighted that the results found in this work are based on previous parameter estimates found in the literature, and that the results and inferences are significantly impacted by the accuracy of these parameters. To ensure the usefulness of the model outputs, the parameters should be updated to reflect the most accurate estimates to date.

4. A simulation–optimization approach

The compartmental model described in the previous section is embedded in an optimization procedure. This simulation–optimization framework enables a large number of response strategies to be evaluated effectively and accurately, which makes it a favourable alternative to both pure simulation (compartmental) and mathematical programming methods. Table 5 summarizes the pros and cons of each approach.
We use the well-known solutions, that can be presented to the policymaker [55]. The goal of solving such problems is usually to obtain a set of non-dominated solutions, also known as the response strategy implemented. The formulation of the optimization problem is provided in (16)–(24).

\[\sum_{t=1}^{T} \gamma_t = \sum_{p=1}^{P} \gamma_p X_{ij} t = 1, \ldots, T\]  
\[\beta_t = \sum_{p=1}^{P} \beta_p X_{ij} t = 1, \ldots, T\]  
\[\sum_{l=1}^{L} X_{il} = 1 t = 1, \ldots, T\]  
\[\sum_{p=1}^{P} X_{ij} = 1 t = 1, \ldots, T\]  
\[\sum_{q=1}^{Q} X_{ij} = 1 t = 1, \ldots, T\]  
\[\sum_{l=1}^{L} \left( \sum_{j=1}^{J} C_l X_{ij} + \sum_{p=1}^{P} C_p X_{ip} + \sum_{q=1}^{Q} C_q X_{iq} \right) \leq B\]  
\[X_{ij}, X_{ip}, X_{iq}, \in \{0,1\} l = 1, \ldots, L, p = 1, \ldots, P, q = 1, \ldots, Q, i = 1, \ldots, T.\]  

The GA is used as the optimization procedure as it enables effective exploring of the feasible region by gradually evolving towards a superior feasible solution. The algorithm attempts to find a solution that minimizes the total number of infections, evaluated using the compartmental model, within a pre-defined budget. Each strategy (chromosome) is encoded as a matrix of size 3×T, where each columns is a tuple (l, p, q) of closure, protection and travel policies respectively. The GA functions by performing a random crossover, gene by gene, then randomly mutating the children solutions. The stopping rule is defined as a set number of iterations without improvement in the fitness function. For our case study, and as presented in Table 2, we have \(n = 50\) and the mutation rate \(d\) is 0.001. A pseudocode of the GA is provided in Table 6.

The problem under consideration naturally gives rise to a multi-objective optimization that has two conflicting objectives: minimizing the total number of infections and minimizing the economic cost of the response strategy implemented. The goal of solving such problems is usually to obtain a set of non-dominated solutions, also known as Pareto-optimal solutions, that can be presented to the policymaker [55]. We use the well-known \(\epsilon\)-constraint method which transforms the multi-objective problem into a constrained single objective optimization problem by keeping one objective while turning all other objectives into constraints [56]. By minimizing the cumulative infections and converting the cost objective into a constraint we were able to determine an optimal solution without assigning a monetary value to human life, which is not always palatable to policymakers. This technique also allows the decision-maker to set a personalized budget for policy strategies and review alternatives of different budgets. The mathematical formulation of the optimization problem is provided in (16)–(24).

\[\min f(X_{ij}, X_{ip}, X_{iq}, t = 1, \ldots, T)\]  
\[\text{s.t} \ c_{ij} = \sum_{l=1}^{L} c_{ijl} X_{ij} i = 1, \ldots, I\]  

### Table 5

| Methodology Comparison | Strengths | Limitations |
|------------------------|-----------|-------------|
| Compartmental          | High accuracy and flexibility | Few solutions tested |
| Mathematical Programming | Easy to use | Cannot explore new strategies |
| Simulation-Optimization | Guaranteed optimality | Computationally expensive |
|                        | All solutions considered | |

### Table 6

A pseudocode of the Genetic Algorithm.

| Inputs | |
|--------|---|
| Population size \(n\) | Number of iterations without improvement \(h\) |
| Number of high fitness parents selected \(a\) | Number of low fitness parents selected \(b\) |
| Mutation rate \(d\) | |

| 1 | Set \(\text{counter} = 1\) |
| 2 | Randomly generate initial population of size \(n\) |
| 3 | Evaluate the fitness of each solution in the population |
| 4 | While \(\text{counter} < b\) do |
| 5 | Select \(a\) parents from the 50% most fit and \(b\) parents from the 50% least fit solutions |
| 6 | Randomly pair parent solutions |
| 7 | Generate two children from each pair using uniform crossover |
| 8 | With probability \(d\), mutate the genes of the children |
| 9 | Evaluate the fitness of the children solutions |
| 10 | if max\((\text{population fitness}) \geq \text{max(children fitness)}\) then |
| 11 | \(\text{counter} = \text{counter} + 1\) |
| 12 | end if |
| 13 | Replace the worst \((a + b)\) solutions in the population with the children solutions |
| 14 | end while |
| 15 | Return best solution |

The binary variables \(X_{ij}, X_{ip}, X_{iq}\), respectively, take values 1 if closure policy \(l\), protection policy \(p\) and travel policy \(q\) are used in week \(t\), and 0 otherwise. The objective function \(f(.)\), which counts the cumulative infections, is evaluated through the compartmental model for given values of the decision variables. Constraints (17)–(19) link the decision variables with their corresponding policy selections to obtain the compartmental model parameters \(c_{ijl}, \gamma_t\) and \(\beta_t\) in every week. Constraints (20)–(22) stipulate that in each week, exactly one closure, protection and travel policy level are selected. Constraint (23) states that the total cost of the strategy over the entire planning horizon must not exceed the budget \(B\), where the parameters \(C_l, C_p\) and \(C_q\) denote the cost of implementing closure policy \(l\), protection policy \(p\) and travel policy \(q\), respectively, for one week. Note that this constraint
Table 7

| Budget | Closure | Protection | Travel |
|--------|---------|------------|--------|
| $1.6B  | 2 2 2 2 | 1 2 2 1 2 | 1 2 1 |
|        | 1 1 1 1 | 1 1 1 1   | 1 1 1 1|
| $3.2B  | 2 2 2   | 1 2 2 1 2 | 1 2 1 |
|        | 1 1 1 1 | 1 1 1 1   | 1 1 1 1|
| $7.5B  | 2 2 2 2 | 1 2 2 1 2 | 1 2 1 |
|        | 1 1 1 1 | 1 1 1 1   | 1 1 1 1|

is incorporated into the fitness function of the GA using a linear penalty. Finally, (24) is a domain constraint.

5. Results and analyses

In this section, we present and discuss the results obtained from implementing the proposed framework on the case study under consideration. For the purpose of demonstrating the applicability of the proposed framework and to show the trade-off between health and economic considerations, we find the optimal response policies over a 50-week period with three levels of budget: High budget ($7.5B), medium budget ($3.2B) and low budget ($1.6B). Table 7 depicts the optimal strategies in all tested cases.

We notice that in the high budget scenario (which effectively places no restriction on the budget), the model chooses to impose strict policies to keep the number of infections at a very low level, below 100. Throughout nearly the entire planning horizon, the closure policy cycled between 3, 4, and 5, while spending the most time in 5 (i.e., shelter in place). Furthermore, social distancing and wearing masks were enforced in most weeks (35/50). When it comes to travel policies, the model almost always selected stricter policies, cycling between 3 (Atlantic) and 4 (no travel). Figs. 6 and 7, respectively, show the progress of infections and spending over time for the high budget scenario.

When the budget is cut to $3.2B in the medium budget scenario, the closure policies become more dynamic and proactive. Instead of the strict closures, the model recommended alternating between strict and lenient closure policies. In particular, a no-closure policy is implemented for a week or two, followed by a partial closure for another week or two. This pattern clearly demonstrate an attempt to contain outbreaks as they reach a critical level, then relaxing the closure policy to salvage the economy, a strategy that might be suitable for countries with modest financial resources. Interestingly, the “shelter in place” closure policy was not selected frequently, probably due to its high cost. It is also interesting to notice that even when the budget is significantly reduced, the protection policy remained unchanged: practice social distancing and wear masks. This policy has low financial impacts as it does not force businesses to close but modify their operations and capacity to ensure patrons are able to social distance. It also has a high impact on spread because it reduces the transmissibility from 15.6% to 5.4%. Therefore, having people social distance and wear masks should always be enforced. Finally, travel policies oscillated between all four
levels with some negative correlation between the travel and closure policies, meaning that international and domestic travel is more likely to be allowed during closure weeks and prevented when there is no closure. Figs. 8 and 9, respectively, show the progress of infections and spending over time for the medium budget scenario. One can see that the proactive interventions recommended kept the growth in infections almost linear, as opposed to the exponential growth expected without them. The cumulative infections remained below 1300.

Finally, the low budget scenario recommended a no-closure policy in 27 out of the 50 weeks with a few partial closure interruptions to bring the outbreak under control. This is expected since closures are extremely expensive. Unlike the two other scenarios, social distancing and wearing masks were recommended in only 7/50 weeks. It employs the protection policy in a cyclical pattern in the first half of the planning horizon, likely in an effort to prevent exponential growth as long as possible. The travel policies recommended are generally more relaxed than in the other scenarios, ranging between international travel and national travel. Figs. 10 and 11, respectively, show the progress of infections and spending over time for the low budget scenario. Spending sprees were observed whenever a strict closure policy was implemented. The cumulative infections increased more than 200 times compared to the medium budget case. The strategic interventions implemented were sufficient to reduce infections, however, exponential growth was still observed.

The results obtained can, to a great extent, explain the pandemic pattern observed in NS, where a high value was placed on minimizing infections and ensuring that cases did not exceed healthcare capacity. The economic impact was considered secondary to the healthcare impact. This is evidenced by the strict long term policy strategy put in place while there were few identified cases and maintained until the total active cases began to drop. Between March 4 and 22 the Government of NS implemented various restrictions limiting interactions until finally declaring a provincial state of emergency. At this point, there was a maximum limit of five people gathering, several businesses were closed or limited to contactless service, and movement outside the home was greatly restricted. These measures remained in place until May when restrictions began to relax. The responsiveness and strict policy strategy was able to drive the total active cases from a peak of 422 on April 24 to zero by June 22.

6. Conclusions and possible extensions

In this paper, we presented a simulation–optimization framework for optimizing response strategies to epidemics and applied it to devise response strategies in NS to the COVID-19 outbreak. The proposed framework combines a modified, age-stratified SEIR compartmental model to evaluate dynamic response strategies that include different levels of closure, protection, and travel policies with a GA that iteratively searches for better strategies. Response strategies were evaluated based on both their health and economic impact, represented, respectively, by the total number of infections and their economic cost. Implementation results showed a clear trade-off between health and economic objectives, and the model proposed totally different closure strategies depending on the available budget. Under the high budget scenario tested, strict closure policies were recommended throughout nearly the entire planning horizon, whereas under low and medium budget scenarios, it swung between no closure and partial closures, trying to suppress disease outbreaks while giving the economy some room to breathe. Social distancing and wearing masks were recommended under medium and high budgets. The travel policy was always enforced in an oscillating pattern but was less sensitive to the budget when strict closure policies were in place. Besides prescribing (near-)optimal strategies under budget constraints, our tool can also help policymakers leverage existing capacity and plan for peak cases.

The proposed framework is quite generic and can be easily tailored for other epidemics or jurisdictions. Furthermore, other epidemiological models might be utilized, along with alternative optimization techniques. A potential, and quite interesting, extension of the model is to include vaccination, which has recently become a viable alternative at the disposal of policymakers for the COVID-19 pandemic. This can
be done by adding a direct flow from the Susceptible to the Recovered compartments that is regulated through a vaccination policy to be selected. Finally, a more accurate calibration of the economic burden of policies can be performed to capture issues like the interactions between different classes of policies and the nonlinear cost as a function of the implementation duration of a given policy.

CRediT authorship contribution statement

Melissa Gillis: Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. Ryley Urban: Software, Validation. Ahmed Saif: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. Noreen Kamal: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Supervision, Project administration, Funding acquisition. Matthew Murphy: Validation, Investigation, Resources, Funding acquisition.

Declaration of competing interest

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