Optimizing Spatiotemporal Antiviral Release Schedules in a Pandemic Influenza

by

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1 Abstract

To help the state of Texas plan pandemic influenza interventions, we build a stochastic mixed-integer program to compute time-based antiviral releases. We can derive millions of scenarios in the stochastic program from an epidemic simulator that accounts for large amount of uncertainty in the disease progression. We study techniques to solve this problem, as a direct-solve is intractable.

2 Introduction

Influenza pandemics occur when novel strains of the influenza virus emerge in human populations and spread around the globe. The primary control measures for pandemic influenza are antiviral medications and vaccines [6] as well as non-pharmaceutical interventions such as social distancing measures, school closures, and hygienic precautions [15]. Although the efficacy of influenza vaccines depends on factors such as patient age and viral type/subtype [12], they are arguably the most important intervention strategy [4]. Since the development and deployment of effective vaccines for a new influenza virus may take several months [3], antivirals and non-pharmaceutical interventions are particularly critical for early pandemic control. Antivirals are thought to reduce disease severity and duration of infectiousness in individual patients, if taken sufficiently early [6], and to protect contacts of infected individuals, if taken prophylactically [9, 10, 8]. Some studies have even suggested that aggressive treatment policies can effectively mitigate local transmission [2, 1]. In preparation for future influenza pandemics, the U.S. Department of Health and Human Services (HHS) therefore maintains a large Strategic National Stockpile (SNS) of antiviral drugs [19], and most states include SNS antivirals as a major component of their pandemic response plans [20, 17, 7, 18].

The spread of an influenza pandemic is highly stochastic. Key quantities in describing a pandemic are the disease reproduction number, R_0, and age-specific case fatality rates. These de-

termine the pandemic's transmissibility and severity, respectively. We let the term *disease scenario* refer to a specific spatiotemporal progression of the disease. Describing a pandemic using transmissibility, severity, and starting location is not sufficient to describe the disease scenario, as there are many scenarios with those starting conditions.

We build a stochastic binary optimization model for spatiotemporal antiviral releases in an influenza pandemic. We derive disease scenarios for this model from an epidemic simulator that accounts for the large degree of uncertainty in the disease progression. Since different population groups react differently to a pandemic, the optimization objective is to maximize the benefit from delivering antivirals to the population in need. Benefit can be defined as hospitalizations averted, deaths saved, or quality life years saved, for example.

At the start of a pandemic we have limited information about its origin, severity and transmission. Public health officials making decisions of spatiotemporal release of antivirals can only make their decisions based on the information they have available. To describe the available information, we classify the evolution of the disease into "information sets" — blocks of weeks containing different disease scenarios. At any time stage, a number of disease scenarios and information sets are possible. However, at any time stage a scenario can only lie within a single information set. An example of the relationship between time stages, information sets, and scenarios is provided in Figure 1.

We use Texas as a case study for our analysis, using data from the 2009 H1N1 flu. Our initial effort on developing spatiotemporal antiviral release schedules is used by the Texas Department of State Health Services (DSHS) for guidance in future pandemics [11]. We provide a screenshot of the tool in Figure 2. In the initial effort, to create a computationally tractable optimization model, we average the number of individuals who fall sick across different scenarios in the same information set. This averaging considerably reduces the problem size. In this report, we explain

the drawbacks of this approach. In addition, we describe possible reformulations and associated algorithms to make the optimization problem tractable in ways other than averaging. Finally, we provide several examples that provide insight into the modeling of antiviral release schedule optimization.

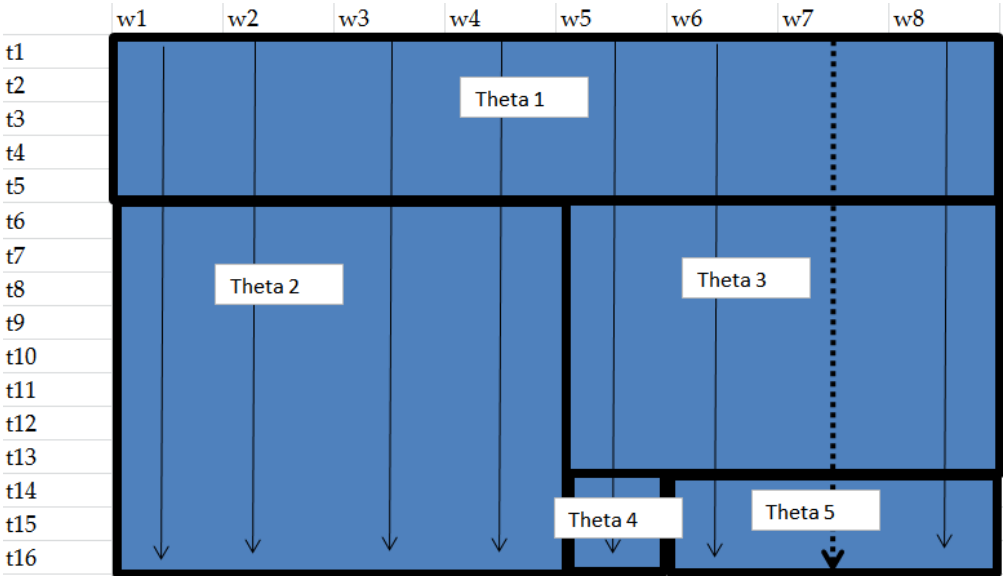

Figure 1: An example of the relationship between time stages, information sets, and scenarios. At any time stage, a number of disease scenarios and information sets are possible. However, a scenario can only lie within a single information set at a given time stage. Here ω_7 is the true unknown disease scenario, indicated in dotted lines. An information set is a group of disease scenarios for a group of time stages. Public health officials cannot differentiate between the disease scenarios in an information set, and thus have to pick one spatiotemporal strategy for each information set.

3 Modeling Framework

In this section we explain how we create disease scenarios, and describe the optimization model for antiviral releases. Disease scenarios are created using an influenza simulator, as described in Section 3.1. Section 3.2 describes a mixed integer program for computing an optimal release schedule.

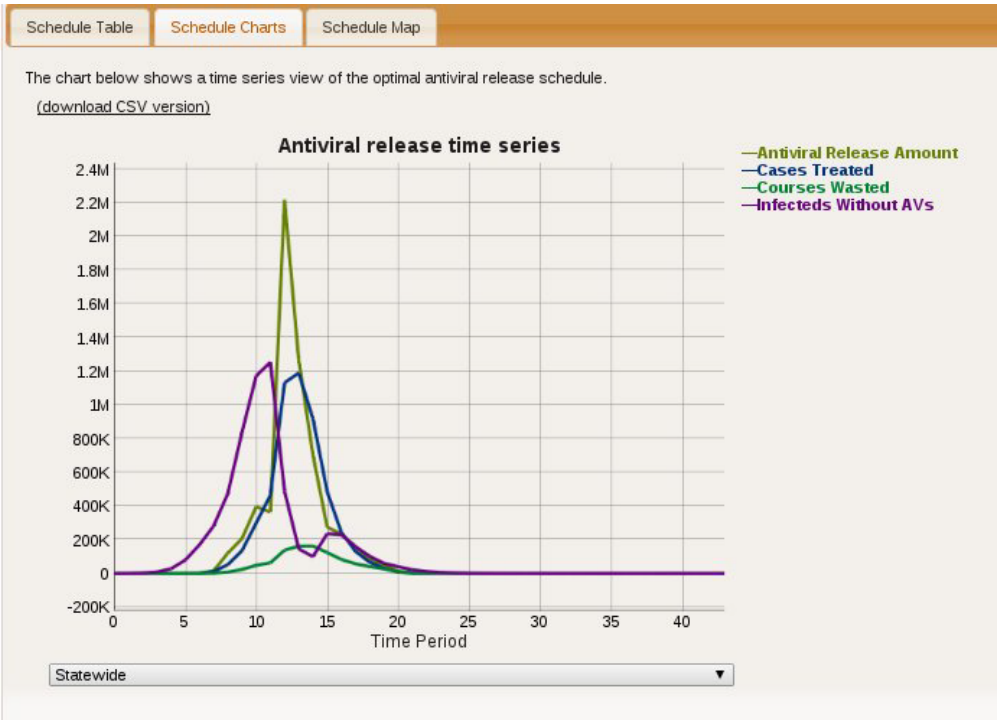

Figure 2: Screenshot of Texas Antiviral Release Scheduling Tool [11]. The x-axis denotes bi-weekly time stages, and the y-axis denotes the number of antivirals released. Some quantity of antivirals are wasted on individuals who think they are sick, but are not. This wastage happens even under an optimal release schedule.

3.1 Disease Scenarios

We use the Texas Pandemic Flu Exercise Tool, available at http://flu.tacc.utexas.edu/exercise/, to create a library of disease scenarios. The scenarios in the library are grouped by their type; i.e., severity and transmissibility, and geographic initial condition. We simulate five historical epidemics and three geographic initial conditions, for a total of 15 scenario groups. Each group includes 150 individual scenarios, for a library total of 2250 scenarios. We summarize the transmissibility and severity parameters in Table2, while Table 2 summarizes the geographic initial conditions.

Given the transmissibility, severity, and geographic initial condition parameters specified in the Tables 2 and 2, we create a disease scenario in the following way. For each scenario, the reproduction number, R_0, is uniformly drawn from a range of specified values. Case fatality rates are set to the reported point estimates. Each scenario is initialized with a small number of cases. We first select a uniform random number between 1 and 10 to determine the number of counties that contain initial cases. We choose these many counties based on the geographic conditions specified in Table 2. To determine the number of cases in each county, we choose a uniformly random number between 1 and 20 for each county.

	Case-fatality rates					Reproduction numbers	
Pandemic type	0-4 years	5-24 years	25-49 years	50-65 years	65+ years	Lower	Upper
2009-like	0.000092	0.000168	0.000343	0.000253	0.000037	1.4	1.55
1968-like	0.000096	0.000134	0.000222	0.001377	0.010019	1.55	1.75
1957-like	0.0001	0.0001	0.0001	0.0025	0.02	1.55	1.75
1928-like	0.0087	0.0011	0.003	0.0098	0.0403	1.75	2.3
1918-like	0.0196	0.0156	0.016	0.0068	0.0151	1.75	2.3

Table 1: Parameters of five historical influenza pandemics. Age-specific case-fatality rates are available for the 2009-like pandemic from [14], for the 1968-like and 1957-like pandemics from [13], and for the 1928-like and 1918-like pandemics from [5].

3.2 Optimization Model

We summarize the notation for our different optimization models as follows:

Indices / Sets

$t \in T$	time stages
$\theta \in \Theta$	information sets about the disease
$c \in C$	counties
$\omega \in \Omega$	disease scenarios
$t \in T_\theta$	time stages at which information θ is available
$\omega \in \Omega_\theta$	disease scenarios in information set θ
$anc(\theta, t)$	the information θ' such that $t \in T_{\theta'}$ and $\Omega_\theta \subseteq \Omega_{\theta'}$. Intuitively, the information set of the decision maker at time t, if currently the decision maker is in θ.

Data

s_{ct}^{ω}	population in scenario ω, county c, stage t, that is seeking antivirals

Geographic region	Number of counties chosen	Location criteria	Number of initial cases
Random	$\mathbb{U} \sim (1, 10)$	uniformly random	$\mathbb{U} \sim (1, 20)$
Random-weighted	$\mathbb{U} \sim (1, 10)$	uniformly random by population weight	$\mathbb{U} \sim (1, 20)$
Migration-weighted	$\mathbb{U} \sim (1, 10)$	uniformly random from counties bordering Mexico, weighted by migration rates	$\mathbb{U} \sim (1, 20)$

Table 2: Initial geographic conditions of influenza pandemic simulator. We choose three different criteria for selecting the locations (counties) of the initial outbreak: random, proportional to population size, and proportional to cross-border migration rates [16]. In each case, the number of initial counties is selected uniformly from 1 to 10 counties, and in each county, the number of initial cases is selected uniformly from 1 to 20 cases.

B^{ω}_{ct} benefit of providing antivirals in scenario ω, county c, stage t
p^{ω} probability that scenario ω occurs; $\sum_{\omega \in \Omega} p^{\omega} = 1$
a_t antivirals available for release at stage t

Decision Variables
sh^{ω}_{ct} number of antivirals on shelf in scenario ω, county c, stage t
f^{ω}_{ct} fraction of population who receive antivirals in scenario ω, county c, stage t
x^{ω}_{ct} 1 if entire population in need does not receive antivirals in scenario ω, county c, stage t; 0 otherwise
$r_{\theta ct}$ number of antivirals released under information θ, in county c, stage t

Formulation

$$
\begin{aligned}
z^* = \max \quad & \sum_{t\in T, c\in C} \mathbb{E}_\omega[B^\omega_{ct} f^\omega_{ct}] && \text{(1a)}\\
\text{s.t.} \quad & sh^\omega_{ct} = sh^\omega_{c,t-1} - f^\omega_{c,t-1} s^\omega_{c,t-1} + r_{\theta,c,t}, \forall \theta \in \Theta, \omega \in \Omega_\theta, c \in C && \text{(1b)}\\
& \sum_{c\in C, t':t'\le t} r_{anc(\theta,t'),c,t'} \le \sum_{t':t'\le t} a_{t'}, \quad \forall t \in T_\theta, \theta \in \Theta && \text{(1c)}\\
& f^\omega_{ct} s^\omega_{ct} \le sh^\omega_{ct}, \quad \forall t \in T, \omega \in \Omega, c \in C && \text{(1d)}\\
& 1 - x^\omega_{ct} \le f^\omega_{ct}, \quad \forall t \in T, \omega \in \Omega, c \in C && \text{(1e)}\\
& f^\omega_{ct} \ge \frac{sh^\omega_{ct}}{s_{c,t,p}} - M\,(1 - x^\omega_{ct}), \quad \forall t \in T, \omega \in \Omega, c \in C && \text{(1f)}\\
& x^\omega_{ct} = \{0, 1\}, \quad \forall t \in T, \omega \in \Omega, c \in C && \text{(1g)}\\
& 0 \le f^\omega_{ct} \le 1, \quad \forall t \in T, \omega \in \Omega, c \in C && \text{(1h)}\\
& sh^\omega_{ct}, r_{\theta ct} \ge 0, \quad \forall t \in T_\theta, \theta \in \Theta, \omega \in \Omega_\theta, c \in C. && \text{(1i)}
\end{aligned}
$$

The objective function in equation (1a) maximizes the sum of the expected benefit derived from antiviral pickups. The constraint (1b) computes antivirals on the shelf by considering roll-over from the previous stage, pickups, and new releases. Specifically, the quantity $f^\omega_{ct} s^\omega_{ct}$ is the number of antiviral pickups in county c at stage t under scenario ω. The constraint (1c) bounds the number of antivirals that can be released at any stage with those that are available. The constraint (1d) analogously bounds the antivirals that get picked up at any stage, the left hand side of the constraint, with antivirals on shelf. The constraint (1e) says that if all population groups do not receive exactly the antivirals they seek (i.e., $f < 1$) then x is 1. When $x = 1$, constraint (1f) says all antivirals on the shelf get picked up. When $x^\omega_{ct} = 0$, constraint (1f) is vacuous, but $f^\omega_{ct} = 1$ via constraints (1f) and constraint (1h). Intuitively, constraints (1e)-(1h) prevent the model from having antivirals on the shelf that are not picked up by people who want them. They are required because sometimes, the benefits of picking up antivirals are negative, for example if antivirals are needed by a group of worried individuals who are not sick.

We note that $f^\omega_{ct} = \min\{1, \frac{sh^\omega_{ct}}{s^\omega_{ct}}\}$. In other words, if the antivirals on the shelf exceed the

population seeking them, i.e., $sh^{\omega}_{ct} > s^{\omega}_{ct}$, then the entire population picks up antivirals. If the antivirals on the shelf are short of the population seeking them, i.e., $sh^{\omega}_{ct} < s^{\omega}_{ct}$, then all antivirals are picked up.

4 Analysis

Our modeling framework resembles that of a stochastic programming model with relatively complete recourse. The first stage deterministic decision variables are how many antivirals to release spatiotemporally, across different information sets; i.e.,$r_{\theta ct}$. After the disease scenario is realized, the model decides how many antivirals would be on the shelf, sh^{ω}_{ct}, and how many antivirals would get picked up by different population groups, $f^{\omega}_{ct}s^{\omega}_{ct}$. The following lemma makes these statements precise.

Lemma 4.1. *Given the values of* $r_{\theta ct}, \forall \theta \in \Theta, c \in C, t \in T$*, the variables* sh^{ω}_{ct} *and* f^{ω}_{ct} *are completely determined* $\forall \omega \in \Omega_{\theta}, \theta \in \Theta, c \in C, t \in T$.

Proof. We prove this by induction on t. We start with the base case, $t = 1$. From constraint (1b), we have $sh^{\omega}_{c1} = r_{\theta c1}$. Given sh^{ω}_{c1}, we determine f^{ω}_{c1} via $f^{\omega}_{ct} = \min\{1, \frac{sh^{\omega}_{c1}}{s^{\omega}_{c1}}\}$, and hence the base case is true. Next, as the inductive hypothesis, we assume that the lemma is true for stage $t-1$, and we will show that it is also true for stage t. Again, via constraint (1b), we have $sh^{\omega}_{ct} = sh^{\omega}_{c,t-1} - f^{\omega}_{c,t-1}s^{\omega}_{c,t-1} + r_{\theta,c,t}$. However, $sh^{\omega}_{c,t-1}$ and $f^{\omega}_{c,t-1}$ are determined by the release variables, $r_{\theta c1}, r_{\theta c2}, \ldots r_{\theta ct-1}$, by the induction hypothesis. Hence sh^{ω}_{ct} is also determined as a function of the release variables. Given sh^{ω}_{ct}, we can further determine f^{ω}_{ct} via $f^{\omega}_{ct} = \min\{1, \frac{sh^{\omega}_{ct}}{s^{\omega}_{ct}}\}$, and hence the lemma holds for stage t. □

Even in the absence of integer restrictions on the release and shelf variables, model (1) is

intractable due to the large number of scenarios, $\omega \in \Omega$, a large number of binary variables x_{ct}^{ω}, and the M in constraint (1f). We study methods to solve this problem.

4.1 Some reformulations

An LP relaxation of model (1) does not provide an optimal solution. Model (1) forces $f_{ct}^{\omega} = \min\{1, \frac{sh_{ct}^{\omega}}{s_{ct}^{\omega}}\}$; i.e., if an antiviral is available in a (c, t, ω) triplet then it gets picked up even if it corresponds to a negative benefit, B_{ct}^{ω}. An LP relaxation of model (1) instead chooses to wait to have antivirals picked up until a positive benefit exists. We illustrate this via the following example.

Example For model (1), consider $|C| = |T| = |\Theta| = 1, |T| = 3, |\Omega| = 2$, and, $p^{\omega_1} = p^{\omega_2} = 0.5, a_{t_1} = 11, a_{t_2} = a_{t_3} = 0$, and other relevant data inputs as provided in Table (3). The optimal solution to this problem is $r_{t_1} = 1, r_{t_3} = 10$, with an objective function value of 25. The solution to the LP relaxation is $r_{t_1} = 10, r_{t_3} = 1$, but with an objective function value of 74.99. The LP model allows only a small number of antivirals to get picked up at (ω_2, t_2) which has a negative benefit, thus having $f_{t_1}^{\omega_1} = f_{t_3}^{\omega_2} = 1$. This is not possible in the original model which forces $f_{t_1}^{\omega_1} = f_{t_2}^{\omega_2} = 0.1, f_{t_3}^{\omega_2} = 1$, despite the negative benefit of t_2. Intuitively, the LP relaxation allows roll-over on the shelf, without people who want antivirals, picking up available antivirals.

Table 3: Example data showing LP relaxation of model (1) and Algorithm (1) may not provide an optimal solution. The table entries provide values for $(B_{c,t}^{\omega}, s_{c,t}^{\omega})$, respectively.

Scenario/Time	t_1	t_2	t_3
ω_1	100, 10	1,10	0,0
ω_2	0,0	-100,10	50,10

In the initial study performed for DSHS [11], we average the population seeking antivirals within an information set across all scenarios. Thus, instead of having decision variables for each

scenario we have them only for information sets. We call this as the *aggregated model*. We illustrate the aggregated model via an example, which also shows a potential drawback of this approach.

Example For model (1), consider $|C| = |T| = |\Theta| = 1, |\Omega| = 2$, and, $s_{ct}^{\omega_1} = 10, s_{ct}^{\omega_2} = 1, a_t = 10, p^{\omega_1} = p^{\omega_2} = 0.5, B_{ct}^{\omega_1} = 10, B_{ct}^{\omega_2} = 1$. The optimal value of this model is 5.5 with all ten antivirals being released, and $f = 1$ for both scenarios. In the aggregated model, we have $s_{ct}^{\theta} = \frac{10+1}{2} = 5.5$. The optimal value is again 5.5, but with only 5.5 antivirals being released. Thus, in the aggregated model under scenario ω_2 the model creates a shortage of antivirals for 4.5 people. Ultimately, a state health agency is interested in the antiviral release schedule, and typically prefers covering individuals to the negative effects of wasting antivirals. As such, the antiviral release schedule from the aggregated model does not perform as well as possible.

Finally, we also provide a robust formulation for model (1) in model (2).

$$
\begin{aligned}
z^* = \max \quad & y && \text{(2a)}\\
\text{s.t.} \quad & y \leq \sum_{c \in C, t \in T} B_{ct}^{\omega} f_{ct}^{\omega}, \forall \omega \in \Omega && \text{(2b)}\\
& (1b), (1c), (1d), (1e), (1f), (1g, (1h), (1i). && \text{(2c)}
\end{aligned}
$$

Model (2) is a standard way for modeling a worst-case approach. However, this formulation does not provide a useful solution for antiviral release schedules. In the presence of even a single scenario with negative benefits in all (county, time stage) pairs, the robust model would release no antivirals for the entire information set. This behavior does not capture the kinds of optimization sought by a public health agency. Specifically, an agency might lean entirely the other way, where they prefer to release antivirals even if only a single scenario has positive benefits. We are studying alternate worst case formulations which would have more suitable interpretations.

4.2 An Algorithm

Algorithm 1 describes a possible method to compute antiviral release schedules. The intuition behind the algorithm is to release a single antiviral to the (county, time stage) pair with the maximum myopic benefit, defining benefit as the expected benefit across all scenarios. This single antiviral is released from the closest preceding time stage where antivirals are available. The algorithm stops releasing antivirals when we have distributed all available antivirals or when there are no more (county, time stage) pairs left with a positive benefit.

This greedy scheme is optimal for releasing a single antiviral. This method either presents a heuristic, or can be guaranteed to produce correct solutions under some conditions. We have not yet verified the conditions under which it produces correct solutions. On the other hand, we have tested the algorithm on several random instances and it provides optimal release schedules in those instances. For sufficiently small instances of the problem—with few (county, time stage) pairs—we can run the algorithm as well as the optimization model on a laptop.

In an effort to prove the conditions under which the algorithm produces optimal solutions, we have created an example where it fails. This example provides intuition that the algorithm fails when the instance has large negative benefits for some scenarios. We are currently working on a proof based on this intuition.

Example For model (1), consider $|C| = |T| = |\Theta| = 1, |T| = 1, |\Omega| = 2$, and, $p^{\omega_1} = p^{\omega_2} = 0.5, a_{t_1} = 3, B^{\omega_1}_{c_1,t_1} = -20, B^{\omega_2}_{c_1,t_1} = 27, s^{\omega_1}_{c_1,t_1} = 2$, and $s^{\omega_2}_{c_1,t_1} = 3$. The optimal solution to to release three antivirals, for an objective function value of 3.5. The algorithm, however, myopically sees that releasing one antiviral gives a benefit of -1, and thus stops at the first iteration. Algorithm 1 releases antivirals only when a non-negative benefit can be realized.

Algorithm 1 Antiviral Release algorithm

Initialize:
$r_{ct\theta} \leftarrow 0, \forall \theta \in \Theta, t \in T, c \in C$
$sh^{\omega}_{ct} \leftarrow 0, \forall \omega \in \Omega, t \in T, c \in C$
$D_{ct} \leftarrow 0, \forall c \in C, \forall t \in T$
while $a_t \neq 0 \, \forall t \in T$ or $D_{ct} \geq 0 \forall c \in C, t \in T$ **do**
  for $c \in C, \theta \in \Theta, \omega \in \Omega, t \in T_\theta$, **do**
    $t' = \min \{k | k \geq t, sh^{\omega}_{ck} < s^{\omega}_{ck}, s^{\omega}_{ck} > 0\}$
    if $t' \neq \emptyset$ **then** $d^{\omega}_{ct} \leftarrow B^{\omega}_{ct'}$;
    else $d^{\omega}_{ct} \leftarrow 0$
    end if
  end for
  $D_{ct} = \mathbb{E}(d^{\omega}_{ct}), \forall c \in C, t \in T$
  $(c^*, t^*) \leftarrow \text{argmax} D_{ct}$
  $t'' = \max \{k | k \leq t^*, a_k > 0\}$
  Update:
  $a''_t \leftarrow a''_t - 1$
  $sh^{\omega}_{c^*t^*} \leftarrow sh^{\omega}_{c^*t^*} + 1 \, \forall \omega \in \Omega$
  $r_{c^*t^*\theta} \leftarrow r_{c^*t^*\theta}$
end while

4.3 Computation

We use GAMS to model all of our work. We created and tested random instances of model (1) to test our work, and provide insightful examples presented above. Thus, we concluded that the aggregated model, the LP relaxation, and the robust model all lead to solutions that are not typically applicable to antiviral release schedules. In addition to running the small examples we describe on a laptop, we ran larger instances on the supercomputers available at the Texas Advanced Computing Center (TACC). One larger instance had sets of size $|C| = 254, |T| = 451$ to describe daily antiviral releases Texas counties over 15 months. In reality, weekly release schedules would be more appropriate for the application, but we consider this large instance to push the computational boundaries of the model. Even with only two disease scenarios, the resulting model builds up to a size of around 11 GB of memory and crashes. This illustrates the need for a tractable

formulation or for efficient heuristics.

5 Future work

We are studying the hardness of model (1). This can be done by a reduction from a known $\mathbb{NP}$ hard problem. We are also investigating conditions under which the algorithm produces optimal solutions, in addition to the use of sophisticated data structures for optimizing the running time of the algorithm. We continue to seek tractable formulations of the proposed optimization models, and we continue to test possible solutions on the supercomputers available at the TACC. Finally, we seek to provide guidelines from our models to the state of Texas for deciding future antiviral releases.

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