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Modeling the Opioid Crisis in Virginia: A Differential Equations Model Assessing the Impact of Medication-Assisted Treatment on the Addicted Population

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Modeling the Opioid Crisis in Virginia: A Differential Equations Model Assessing the Impact of Medication-Assisted Treatment on the Addicted Population

by

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Project History

This thesis stems from a modeling project whose inception was September 2022. Funded through April 2023 by the Center of Undergraduate Research in Mathematics and headed by Dr. Joanna Wares, the project began with a team of students comprising Olivia Barlow (Class of 2023), Connor Gasgarth (Class of 2023), Leah Ghazali (Class of 2024), and myself. During that time, we developed an ordinary differential equations (ODE) model of the opioid epidemic in Virginia's correctional facilities. The focus of the model was to study the relationship between the size of the addicted population and these facilities' provision of Medication-Assisted Treatment (MAT) versus unmedicated treatment for opioid use disorder. For the resulting paper, we were awarded the Symposium Paper Competition Award at the Honors Convocation here at the University of Richmond.

From May 2023 onwards, the project pivoted to modeling the impacts of MAT and non-MAT for the general population of Virginia. Headed again by Dr. Joanna Wares, the team of contributors included Leah Ghazali (Class of 2024), Muskan Agarwal (Class of 2026), Gabe Greenberg (Class of 2025), and myself. For this work, we developed a new model that does not include compartments for the incarcerated populations. This ODE model simplified the original incarceration model, leading to the latter's separation into its own sub-project. I present below the analysis of the simplified model, including a conduction of sensitivity analysis to identify parameters that most affect model outcomes. In addition, I present results about policy and intervention effects on the opioid crisis.

1. Abstract

The opioid epidemic is prevalent in countless communities throughout the United States and has yet to be mitigated. Treatments for OUD (opioid use disorder) include Medication-Assisted Treatment (MAT) and treatment without medication (non-MAT), with the former being judged as more effective in terms of lower relapse rates, death rates, and criminal activity (U.S. Food & Drug Administration, 2023; SAMHSA, 2024). Motivated by the promising research on MAT, this paper models the relationship between the treatment and addicted populations using a system of ordinary differential equations. In addition to producing closed-form equilibrium solutions, the model leads to the conclusion that expanding access to MAT, while important for decreasing the addicted population, is not a sufficient policy measure in isolation. Instead, policymakers should endeavor to increase access to all forms of treatment. Furthermore, varying the rate of addiction to prescription opioids causes significantly different equilibrium populations, indicating that the prescription of opioids requires further monitoring.

2. Introduction

The U.S. opioid epidemic has its roots in the 1990s, a decade that saw a significant increase in opioid prescriptions (CDC, 2023). Since then, through opioids both legally prescribed and illicitly acquired, the epidemic has continued to cause thousands of overdose deaths every year (NIDA, 2023). Although prescriptions may have become less important as a driver of mass overdose deaths in recent years, with Medicaid opioid prescriptions to treat pain falling by 44% between 2016 and 2019 (Williams & Saunders, 2023), overdose deaths rose by 38% between 2019 and 2020. This recent wave of deaths is largely attributed to the increase in usage of synthetic opioids such as illegally produced fentanyl. Moreover, putting these deaths in a broader context, the Centers for Disease Control and Prevention reports that opioids accounted for 70%

of the 70,630 overdose deaths in 2019 (CDC, 2023). The opioid epidemic is thus a national health concern that requires meaningful attention from policymakers.

When addressing concerns about substance use disorders (SUDs), the first consideration is treatment. Individuals with OUD may receive treatment from two categories: Medication-Assisted Treatment (MAT) and unmedicated treatment (non-MAT), with the former not precluding the use of the latter. Non-MAT includes strategies such as withdrawal management, psychotherapies, and community-based treatments (Carley & Oesterle, 2021), while drug choices for MAT include three FDA-approved medications: buprenorphine, methadone, and naltrexone (Carroll, 2022). Buprenorphine and methadone, respectively a partial opioid and an opioid, regulate withdrawal symptoms such as vomiting and diarrhea while reducing cravings. A comparative benefit of these medications is their link to lower overdose death rates than naltrexone, which acts as an opioid blocker.

All three drugs, having received attention as a strategy to treat OUD, have increasingly become the subject of treatment literature. Importantly, some of the literature supports the potential of MAT, citing reduced risk of overdose death, reduced opioid use, and greater treatment retention (Pew Trusts, 2020). However, only 51% of treatment facilities surveyed in 2020 by the Substance Abuse and Mental Health Services Administration offered any type of MAT for individuals with OUD (SAMHSA, 2021). This indicates a significant barrier to effective relief for individuals who already struggle to receive any form of treatment, with treatment rates reported to be as low as 25% (Saunders & Panchal, 2023). Consequently, acknowledging the severity of the opioid epidemic and the effectiveness of MAT, one is likely to suggest that access to MAT be expanded. The fruitfulness of this solution, in addition to the proposal of increasing the general treatment rate, is central to this paper.

Prior to the creation of our model, a search for similar models revealed little mathematical modeling research on the opioid epidemic in relation to MAT. This is not to allege a complete lack of scholarly attention to epidemic– Butler (2020), similarly to our MAT model, uses the Ordinary Differential Equations (ODE) framework to model heroin and pharmaceutical opioid abuse in Maine; Phillips et al. (2021) present an ODE model of heroin and fentanyl addiction in Tennessee; Chen et al. (2019) use a system dynamics model to simulate nonmedical opioid use in the United States; Cole and Wirkus (2022) model illicit opioid and heroin use; and Rivas et al. (2021) build an ODE model accounting for addiction to four different opioids. Other methods include statistical analysis on survey data (Dickson-Gomez et al., 2022) and ARIMA modeling (Fakhrabad et al., 2023). Notably, however, none of these works contain ODE modeling specific to the use of MAT, or the use of MAT in the United States–both fundamental features of our model.

Addressing this scarcity of MAT-related modeling research, we use a system of ordinary differential equations inspired by Battista et al.'s (2019) prescription epidemic model to explore interactions between susceptible individuals, individuals with OUD, and the treatment system. We explore the feasibility of MAT as a solution to the opioid epidemic and account for several addiction- and treatment-related parameters in the model's construction.

3. Mathematical Methods: Ordinary Differential Equations

Systems of ordinary differential equations (ODEs) are frequently used in epidemic modeling, whether it be to model physical viral transmission–see, for example, Beira and Sebastião's (2021) model of COVID-19 transmission–or epidemics with non-physical transmission. An example of the latter is the ODE model of the prescription opioid epidemic

built by Battista et al. (2019), an analog to the Susceptible-Infectious-Removed (SIR) model. In their system of ODEs, susceptible individuals have either not interacted with opioids or are prescribed opioids without being addicted to them; addiction, in this case, is the "illness," and those who are addicted are the "infectious" population. Moreover, transmission is defined as the addiction rate through contact with other addicted people. The framework of ODEs is thus useful when the subject of interest involves the concept of spread, and the model presented in this thesis draws on the work of Battista et al. to study the spread of opioid use disorder (OUD) and methods of abatement. This system of ODEs enables the study of how opioid addiction spreads throughout the population of Virginia and the way in which addicted individuals cycle through treatment.

4. Model Populations

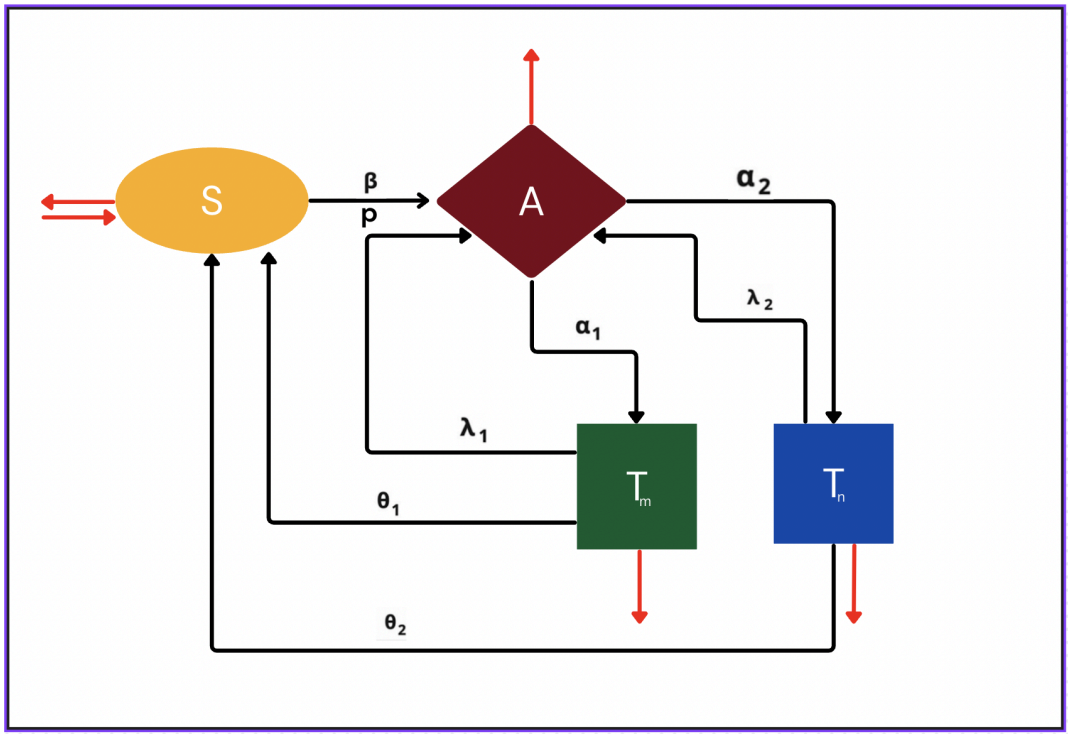

Fig. 1: Compartmental diagram. Movements between compartments are indicated by directional arrows with all parameters named except for the natural and overdose death rates.

The base MAT model (see Figure 2) is built on four populations:

1. S ("susceptible"): Individuals in the susceptible population are neither actively addicted with nor in treatment for an OUD. They may become addicted to opioids through prescriptions at a rate p or other illicit means at a rate β. Here, β is the rate that a susceptible person becomes addicted through some kind of contact with an addicted person or their drugs, here modeled as a mass action term.
2. A ("addicted"): This population represents individuals with an OUD who are not in any type of treatment program. Addicted individuals may opt for MAT or non-MAT at rates α_1 and α_2, respectively. The two remaining exit routes from *A* are opioid overdose, denoted by the rate μ^*, and death by natural causes, denoted by μ. Notably, there is no direct route to the S-population; this reflects a base assumption that T_n includes individuals who stop using opioids but are still prone to relapsing at a higher rate, and individuals from the A-population, who can move from T_n to the S-population after some time.
3. T_m ("MAT"): Those in the MAT population are currently receiving MAT for their OUD. Members of this population may die of natural causes at a rate μ, relapse into addiction and return to the A-population at a fixed rate λ_1, or recover and return to the S-population at θ_1.
4. T_n ("non-MAT"): Those in the non-MAT population are currently enrolled in treatment programs that do not utilize medication or have stopped taking opioids on their own, likely with the social support of family or friends. As in the T_m-population, there are three

routes of exit: death by natural causes at μ, relapse back into the A-population at a fixed rate λ_2, and recovery at the rate θ_2.

To simplify the the model, we assumed that the population is conserved such that $S + A + T_m + T_n = 1$. We additionally assumed that people in treatment were not taking opioids and therefore would not overdose, therefore assigning μ_* solely to the A-population. .

$$\frac{dS}{dt} = (\mu^* A) + \mu(T_m + T_n) + (\theta_1 T_m) + (\theta_2 T_n) - (\beta SA + pS)$$

$$\frac{dA}{dt} = (\beta SA + pS) + (\lambda_1 T_m) + (\lambda_2 T_n) - (\alpha_1 A) - (\alpha_2 A) - (\mu^* A)$$

$$\frac{dT_m}{dt} = (\alpha_1 A) - (\lambda_1 T_m) - (\theta_1 T_m) - (\mu T_m)$$

$$\frac{dT_n}{dt} = (\alpha_2 A) - (\lambda_2 T_n) - (\theta_2 T_n) - (\mu T_n)$$

Fig. 2: Model equations.

3. Parameters

Parameter	Parameter Description	Value	Source
β	Addiction rate due to contact with A	0.0036	Battista et al. (2019)
p	Addiction rate due to prescription	. 0.000536	Battista et al. (2019)
α_1	Rate of receiving medicated treatment once addicted	0.05	Wares et al. (2019)
α_2	Rate of receiving non-medicated treatment once addicted	0.1	Wares et al. (2019)
θ_1	Rate of medicated treatment success	0.01	Approximation
θ_2	Rate of non-medicated treatment success	0.005	Approximation
λ_1	Relapse rate of medicated treatment	0.5	Approximation; NIDA (2021)
λ_2	Relapse rate of non-medicated treatment	0.7	Approximation; NIDA (2021)
μ	Natural death rate	0.00729	Battista et al. (2019)
μ^*	Death rate of individuals with OUD	0.038415	Battista et al. (2019); VDH (2023)

Table 1: Parameter descriptions and assigned values. Citations included where applicable.

Here we explain our baseline parameter values (Table1).

1. β: Derived from Battista et. al (2019), this is the rate of addiction that occurs in proportion with the A-population. β is a mass action term that reflects pathways to addiction other than through prescription, and it may include theft of prescription opioids, purchases from street dealers, and other illicit means of drug acquisition.
2. p: The rate at which individuals become addicted to their own prescribed opioids, derived from prescription and prescription-based addiction rates provided again by Battista et al. (2019).
3. α_1: The rate at which individuals receive MAT once addicted, taken from a differential equations study of the opioid epidemic in Philadelphia (Wares et al., 2021).
4. α_2: The rate at which individuals receive non-MAT once addicted, provided by the same source for α_1.
5. θ_1: The rate at which individuals successfully complete MAT without relapsing. This was approximated by running the model with varying values of θ_1 and choosing the value which most closely resembled base model populations provided by SAMHSA (2019).
6. θ_2: The rate at which individuals successfully complete non-MAT without relapsing. The same numerical experiments were run to determine the value for θ_2 as θ_1.
7. λ_1: The rate at which individuals relapse from MAT and restart the misuse of opioids. In the absence of comprehensive OUD relapse data, λ_1 is approximated as 0.5. This is loosely justified by estimates of long-term relapse rates being estimated between 22-62% (NIDA, 2021).

8. λ_2: The rate at which individuals relapse from non-MAT. As with λ_1, this parameter is justified by past studies reporting relapse rates ranging widely between 38-90% (NIDA, 2021).
9. μ: The rate of natural death, taken from Battista et al. (2019).
10. μ^*: The rate of death of individuals with OUD. To calculate this, an overdose rate was estimated using data provided by the Virginia Department of Health (2023) and added to μ.

5. Results

5.1. Existence, Uniqueness, and Positivity of Solutions

5.1.1. Solutions to Initial Value Problems Exist and are Unique

The right hand side of the system of differential equations is continuously differentiable in terms of all dependent variables. Because of this, we know from the existence and uniqueness theorem, that every initial value problem for our system will have a solution and that the solution will be unique over some maximal time interval (Perko, 2001). Since our population compartments are bounded between 0 and 1 (we know they are all positive (see 5.1.2) and that they sum to unity), then we know that the right hand side of our system of differential equations (Fig 2) is globally Lipschitz (all partial derivatives are bounded) and solutions exist and are unique for all time.

5.1.2. Solutions Remain Nonnegative

Our system of differential equations is conserved, with all flows out of any compartment entering another compartment, and with the total population proportions adding to unity. We

assume that all compartment proportions begin positive, since they represent real populations that are nonzero.

We also know that solutions cannot become negative if they begin positive. Observing the right hand side of our system, if at any time one of the compartments becomes zero (which it would have to become before it becomes negative because solutions are continuous), we see that the corresponding derivative will be nonnegative. Therefore, no solution that begins positive can become negative.

5.1.3. Equilibria

Using Mathematica (Wolfram Research, Inc., 2024), we were able to find closed-form equilibrium solutions. Solving the system of ODEs resulted in two closed-form equilibria (see Appendix). As one solution was proven to produce at least one negative population value when parameters are positive (see Appendix), it was discarded. We prove below that the remaining equilibrium solution, in contrast, is always positive if the parameters are positive (which they are by realistic assumption). We then used this equilibrium to measure the model's response to varying parameters.

5.1.4 Baseline Results

While we did not have time to prove that the equilibrium solution is asymptotically stable, we ran a battery of experiments with different initial conditions in R, and all solutions tended toward the closed-form positive equilibrium solution for that set of parameter values.

As an example, using initial populations estimated from Virginia drug abuse data (SAMHSA, 2020), running the model equations through an ODE solver in R (Soetaert et al.,

2010) with the default parameter values resulted in populations that closely resemble the closed-form equilibrium solution $S \cong 0.98298$, $A \cong 0.01375$, $T_m \cong 0.00133$, and $T_n \cong 0.00193$ (Fig. 3). All numerical experiments which used numerical approximation in R, rather than the closed-form solutions, similarly approached closed-form equilibria over time.

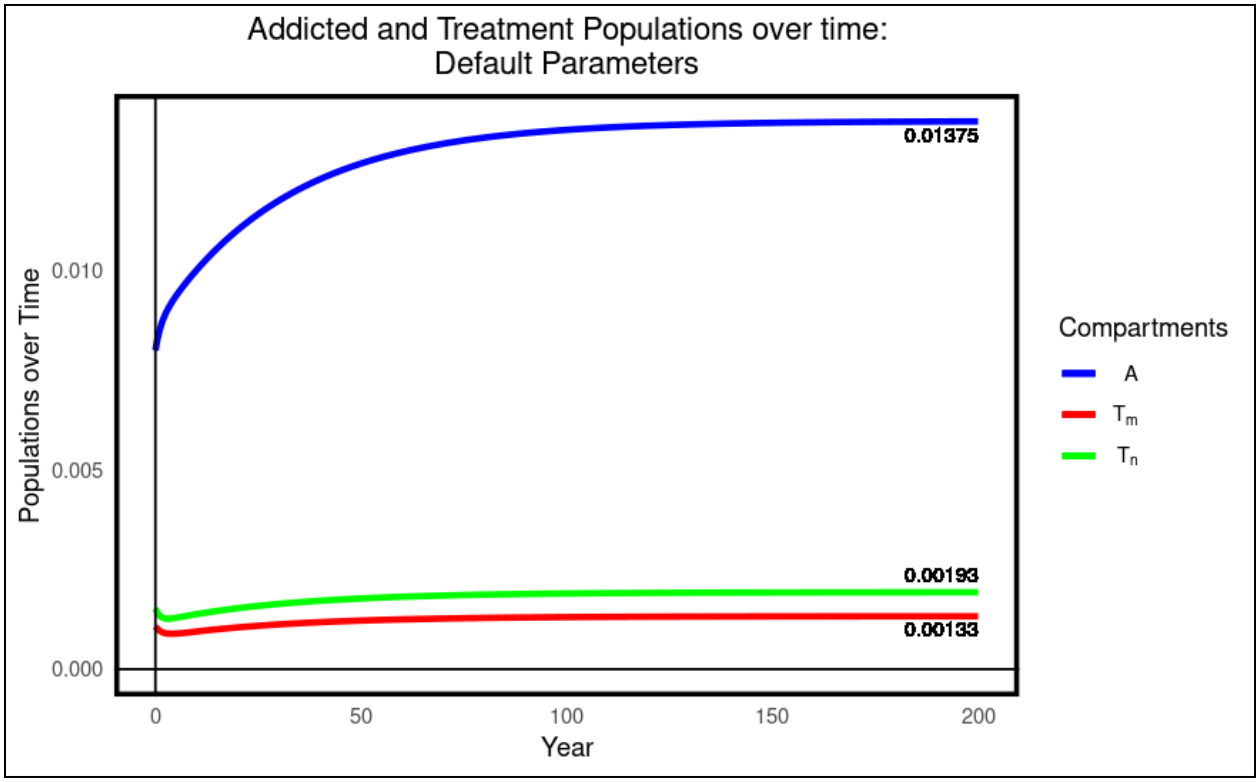

Fig. 3: Populations resulting from running the model with default parameters over a period of 200 years.

5.2. Experiments: Varying Parameters

Below, experiments are run to see the effects of different interventions on the opioid crisis. In each case, the independent variable is a particular parameter that could affect policies or interventions and the output is equilibria values for that set of parameters (the baseline parameters except for the one or more that is varied).

5.2.1. Varying Treatment Rates

In this experiment, we vary the total rate that people in the A compartment seek treatment, which keeps the proportion of those going to MAT or non-MAT constant. Fig. 4 shows the outcome on the long-term A- and T-populations when the total treatment rate increases, with the proportion of individuals going to MAT remaining the same. As more individuals are sent to treatment in general, the ending A-population decreases. Additionally, there is the intuitive result that more individuals enter treatment.

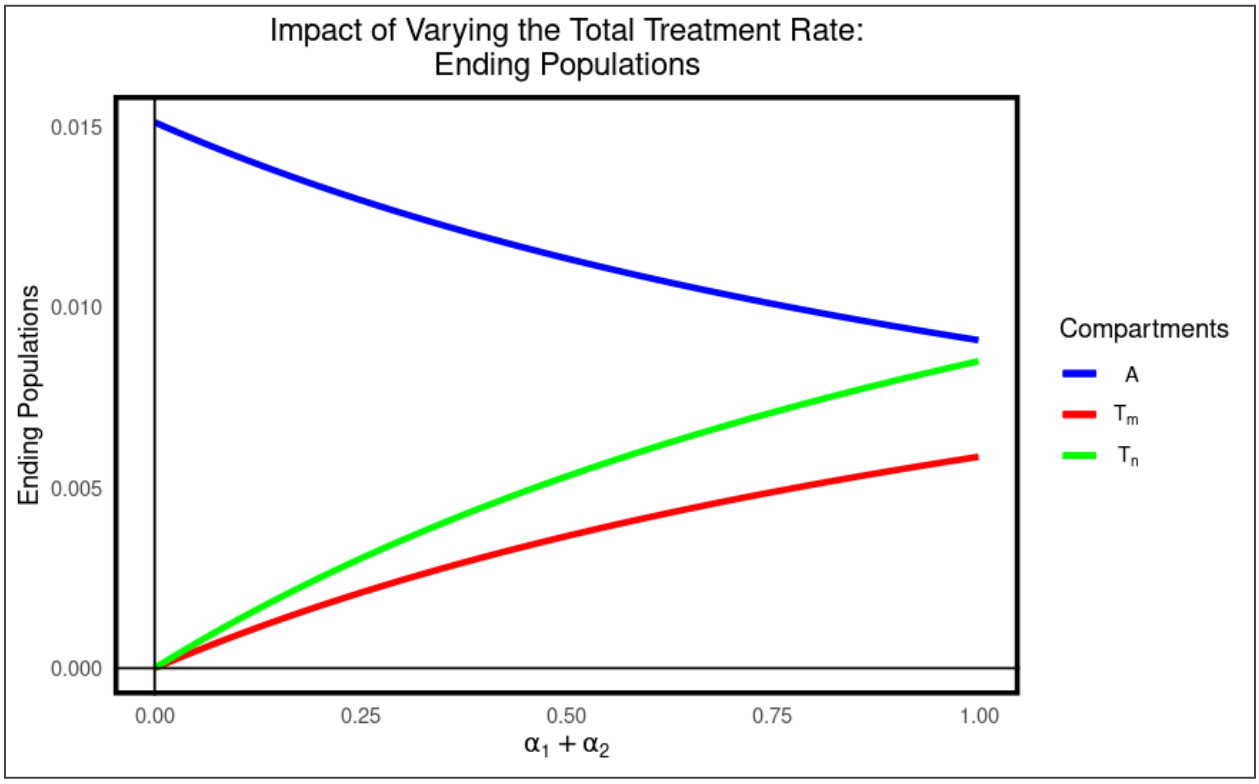

Fig. 4: End populations resulting from increasing the total treatment rate while fixing the proportion of individuals going to MAT vs. non-MAT. Note that this is accompanied by a decrease in the ending S-populations.

To further analyze the impact of treatment, the proportion of individuals with OUD going to MAT was varied with the total rate of treatment being held constant (Fig. 5). Importantly, the

direction of the relationship between MAT and the ending A-population is negative; the higher the rate of going to MAT, the lower the ending addicted population. Increasing the availability of MAT may therefore reduce the population of individuals diagnosed with OUD. However, because relapse rates are still quite high at baseline for those receiving MAT (see Table 1), this reduction is not large. For this experiment, the A-population decreased from 0.01129 to 0.01018.

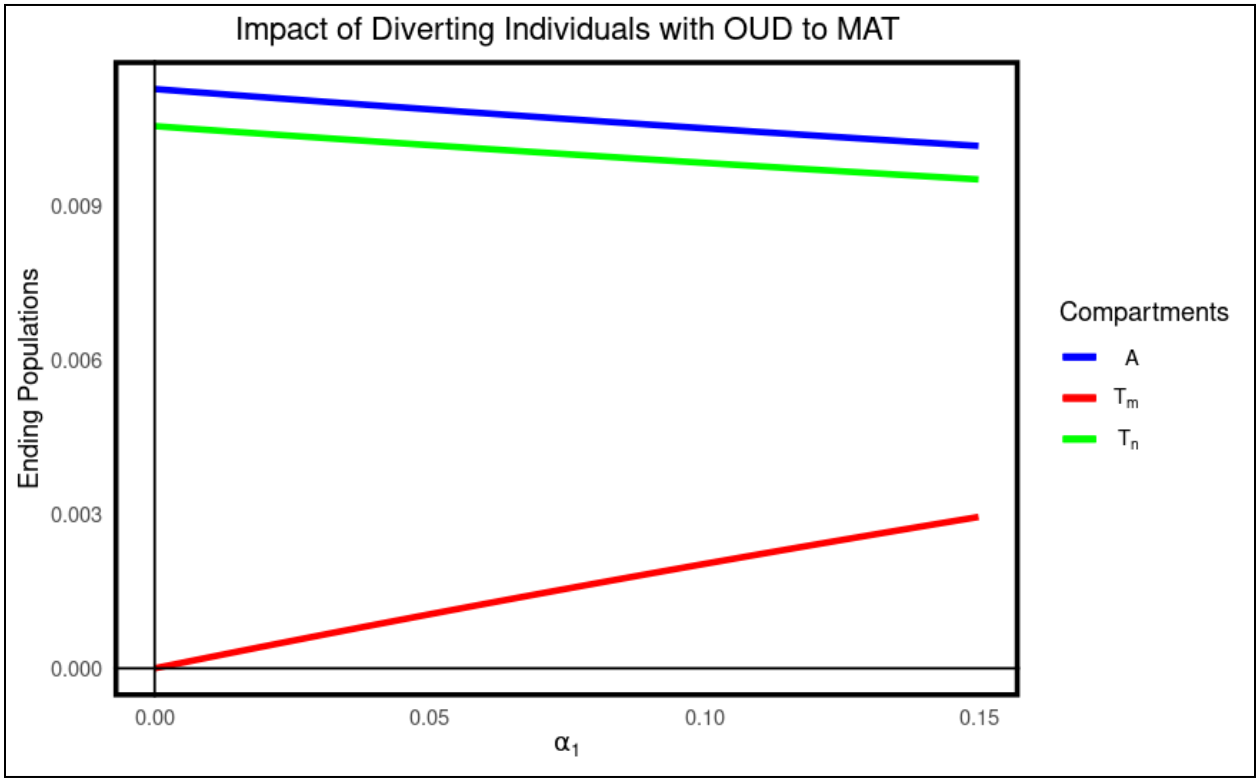

Fig. 5: End populations resulting from diverting more individuals to MAT with a fixed total treatment rate. Not depicted is the decrease in the S-population over time.

Combining the previous experiments, a simulation was run that both increased the general treatment rate and sent more individuals to non-MAT. From this, we observed that increasing the general treatment rate has a greater impact on mitigating the epidemic, i.e. decreasing the A-population, when individuals are sent to MAT rather than its counterpart. However, as Fig. 6 shows, the difference made by sending more individuals to MAT is negligible

at lower levels of total treatment. The greatest change in the A-population instead comes from increasing the total treatment rate; the implications of this result are discussed in the conclusion of this paper.

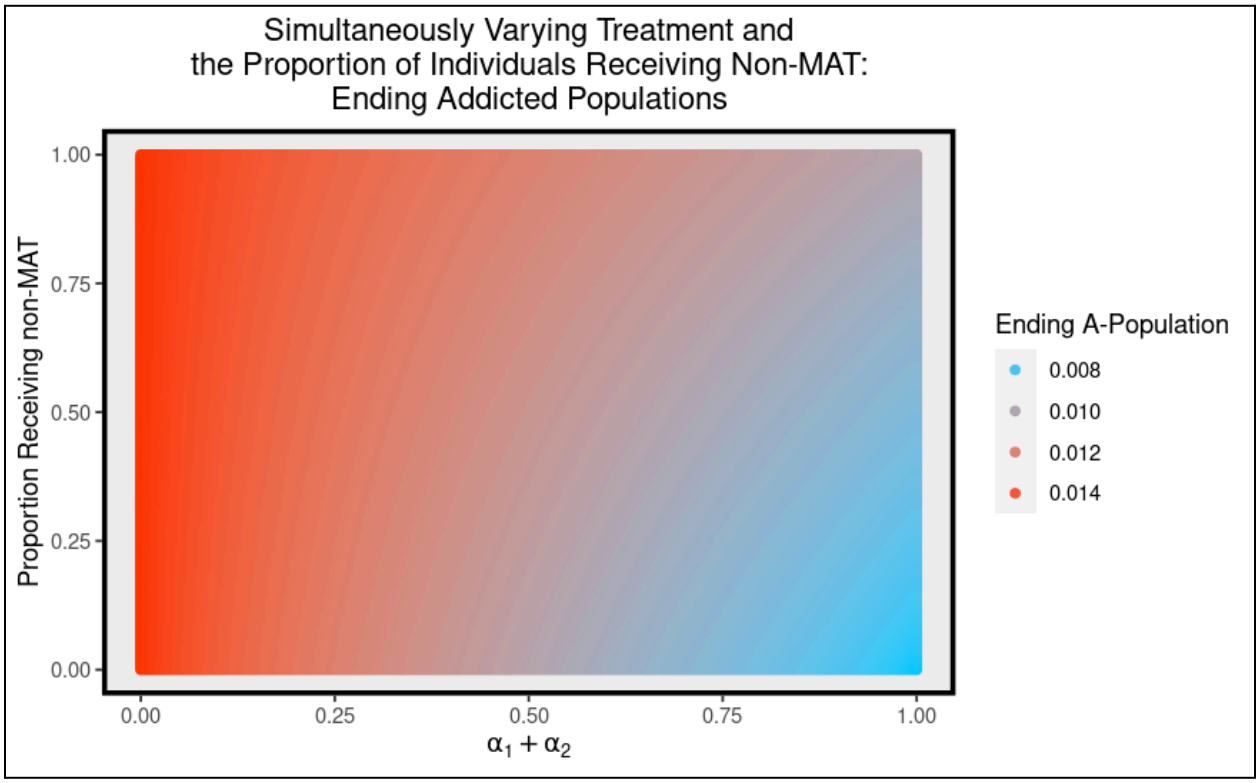

Fig. 6: Ending A-populations resulting from sending more individuals with OUD to treatment, but diverting them away from MAT to non-MAT.

5.2.2. Varying Addiction Rates

Turning to rates of addiction, Fig. 7 and Fig. 8 demonstrate the impacts of increasing the values of two parameters: addiction via contact, and addiction through one's own prescription(s). Varying them over the same range, we make three main observations. First, the ending A- and T-populations increase over the range of values; second, at high values of β and p, the A-population curve is approximately concave; and third, while the overall trajectory of the populations is the same in both experiments, β differs from p in that its short-term variations

yield convex A- and T-curves. In other words, increasing the values of both parameters eventually raises the A- and T-populations at a decreasing rate, but variations in p demonstrate more consistently concave behavior than variations in β.

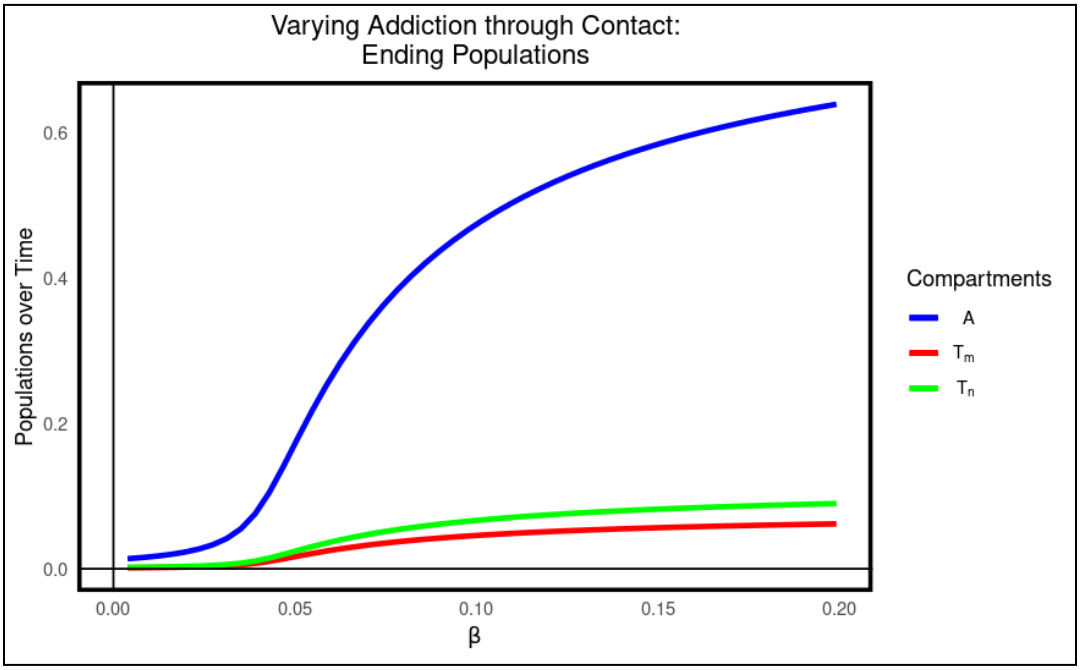

Fig. 7: Ending populations resulting from increasing the rate of addiction via contact. Not depicted is the decrease in the ending S-populations.

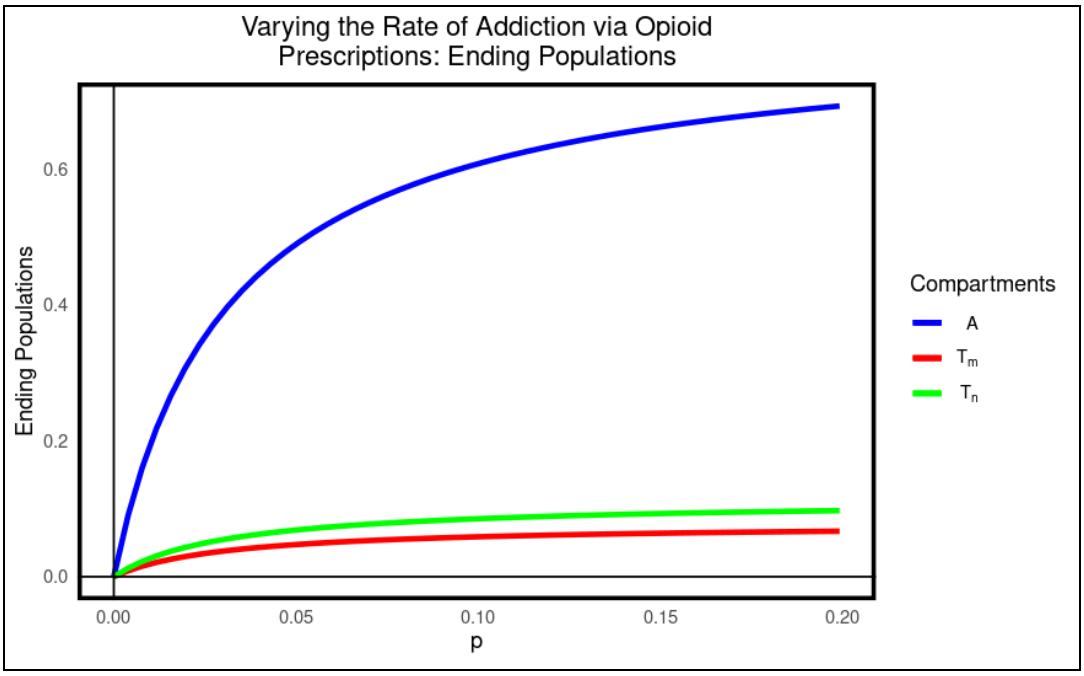

Fig. 8: Ending populations resulting from increasing the rate of addiction via contact. Not depicted is the decrease in the ending S-populations.

5.2.3. Varying Relapse Rates

Finally, we turn towards the success and relapse rates of both treatment options. Fig. 9 shows the difference in results when the recovery rate of MAT is varied versus when the recovery rate of non-MAT is varied. This difference is relatively subtle, with the end population curves being similarly shaped (convex) but yielding smaller A-populations when non-MAT is more effective. However, this may stem from the base values of α_1 and α_2; with more individuals receiving non-MAT for OUD, it is intuitive that the success of the more commonly used treatment would cause greater population differences.α_1 and α_2; with more individuals receiving non-MAT for OUD, it is intuitive that the success of the more commonly used treatment would cause greater population differences.

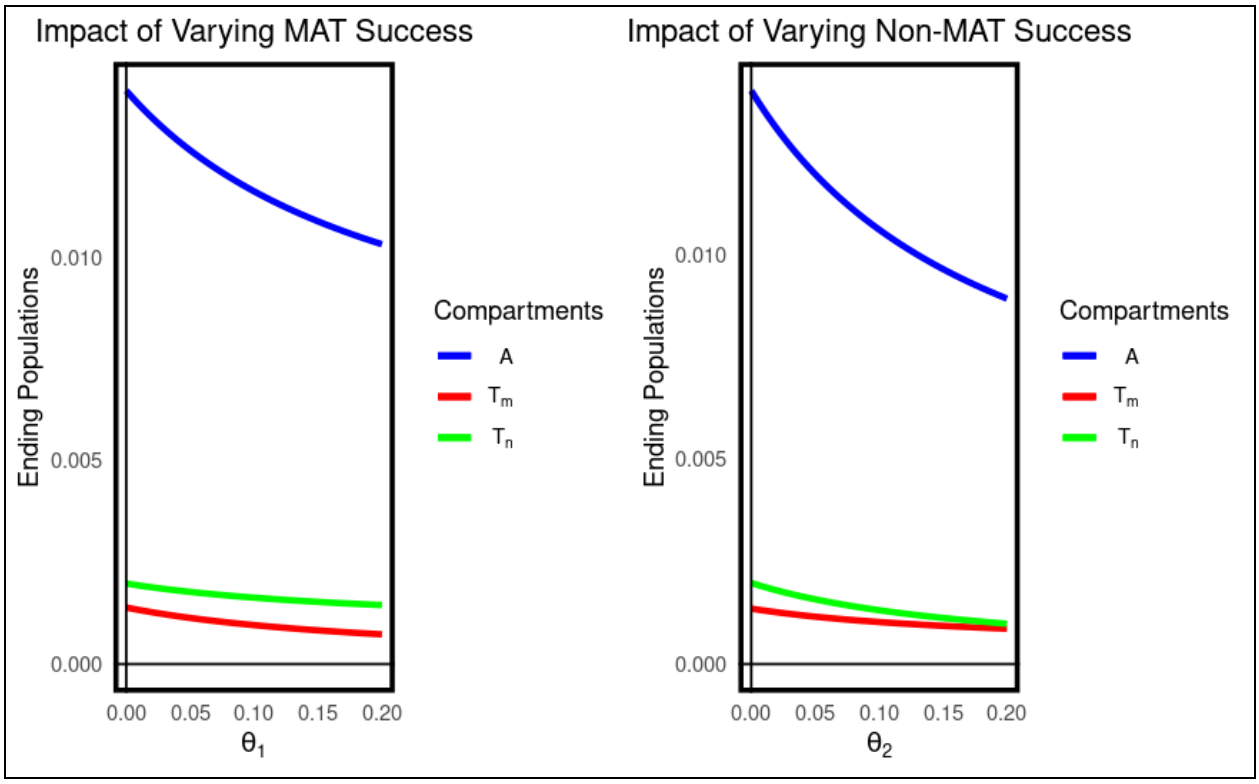

Fig. 9: Populations resulting from increasing the success rates of MAT and non-MAT, respectively. Not depicted in either graph is the increase in the ending S-populations.

Unlike θ_1 and θ_2, the relapse rates of MAT and non-MAT affect model outcomes in significantly different ways (Fig. 10). When the relapse rate of MAT increases, the ending A-population increases with greater magnitude than when the relapse rate of non-MAT increases. The A-population in the latter simulation remains lower at every value in the chosen range. Moreover, increasing each relapse rate results in greater populations of individuals in their associated treatments. Explained differently, this means that higher MAT relapse leads to more people entering MAT, while higher non-MAT relapse leads to more people entering non-MAT. The reasons behind this difference require further analysis.

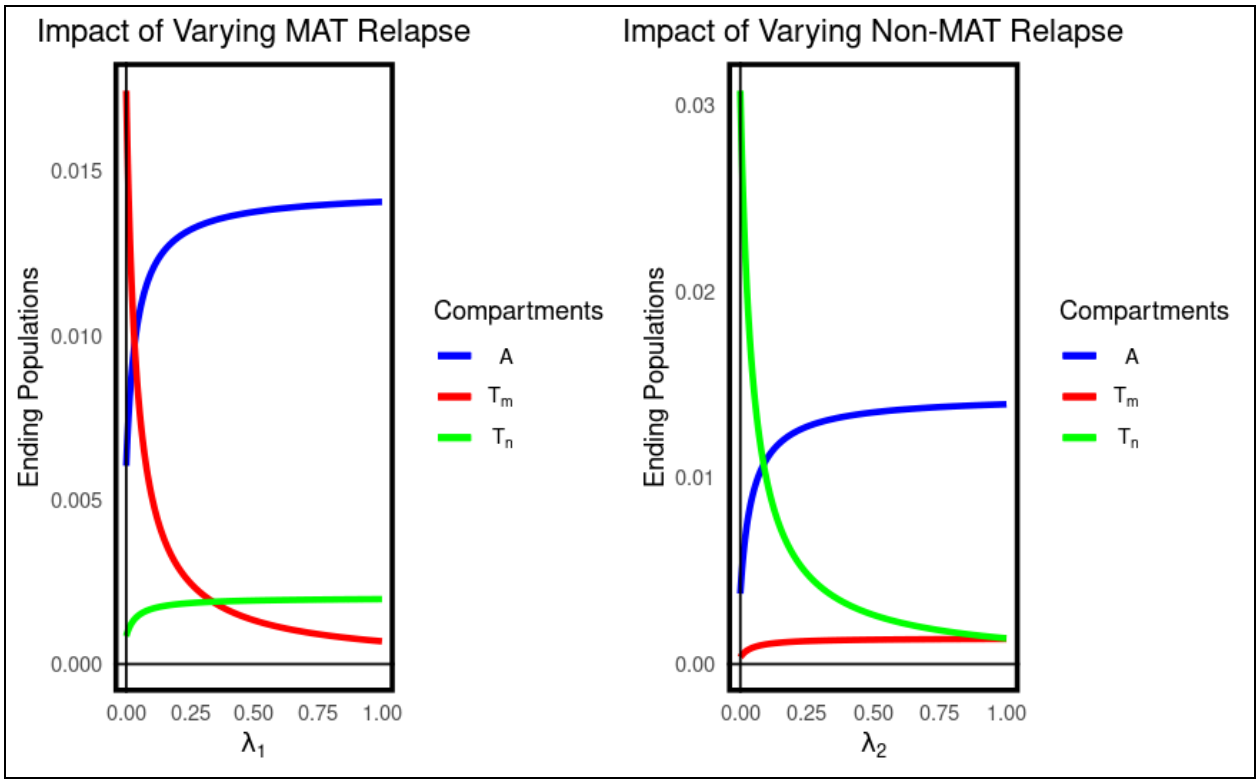

Fig. 10: Populations resulting from increasing the relapse rates of MAT and non-MAT, respectively. Not depicted in either graph is the increase in the S-populations.

6. Sobol Sensitivity Analysis

To measure the model's sensitivity to different parameters, Sobol's method of sensitivity analysis was performed using R (Puy et al., 2022) . First-order indices produced by this method formally quantify the impact of each parameter by its associated variation in model outcomes; the greater the first-order index value, the greater the change in populations when the parameter is varied. For this process to be carried out, numerous experiments were run to record parameters values that kept the A-population under 5%. These values created justifiable ranges on which Sobol's method was conducted (Table 2).

Parameter	Parameter Description	Sobol Range
β	Addiction rate due to contact with A	[0, 0.0562]
p	Addiction rate due to prescription	[0, 0.0024]
α_1	Rate of receiving medicated treatment once addicted	[0, 1]
α_2	Rate of receiving non-medicated treatment once addicted	[0, 1]
θ_1	Rate of medicated treatment success	[0, 1]
θ_2	Rate of non-medicated treatment success	[0, 1]
λ_1	Relapse rate of medicated treatment	[0, 1]
λ_2	Relapse rate of non-medicated treatment	[0, 1]
μ	Natural death rate	[0, 0.2]
μ^*	Death rate due to addiction	[0, 1]

Table 2: Parameter ranges chosen for Sobol sensitivity analysis.

Preliminary results of applying Sobol's method are shown in Fig. 11. Denoted by *Si*, the first-order indices are the greatest for α_1 and p. Following these parameters closely are μ^* and α_2. This has several implications within the universe of this model.α_1 and p. Following these parameters closely are μ^* and α_2. This has several implications within the universe of this model.

We first recall that α_1 is negatively associated with the ending A-population (Fig. 5). This means that, by its first-order value, increasing the rate of MAT not only results in fewer individuals diagnosed with OUD, but outweighs the impact that greater non-MAT reception has on increasing the addicted population. α_1 is negatively associated with the ending A-population (Fig. 5). This means that, by its first-order value, increasing the rate of MAT not only results in fewer individuals diagnosed with OUD, but outweighs the impact that greater non-MAT reception has on increasing the addicted population.

Secondly, non-MAT relapse has a greater effect on the model than MAT relapse. This indicates that if the former relapse rate falls, then the ending A-population will fall by a greater magnitude.

Thirdly, the model is more sensitive to θ_2 than θ_1. Consequently, increasing the success rate of non-MAT would more significantly change the A-population than if MAT were to become more effective.θ_2 than θ_1. Consequently, increasing the success rate of non-MAT would more significantly change the A-population than if MAT were to become more effective.

Fourthly, we observe that p creates greater model variation than β, its counterpart addiction rate. This suggests that higher rates of addiction to prescription opioids would increase the ending A-population more than addiction to illicitly sourced opioids. This, too, is an intuitive result due to β being an interaction term between the S-population and the smaller A-population. p creates greater model variation than β, its counterpart addiction rate. This suggests that higher rates of addiction to prescription opioids would increase the ending A-population more than addiction to illicitly sourced opioids. This, too, is an intuitive result due to β being an interaction term between the S-population and the smaller A-population.

Lastly, changes in the death rate of individuals with OUD causes greater population variation than changes in the natural death rate.

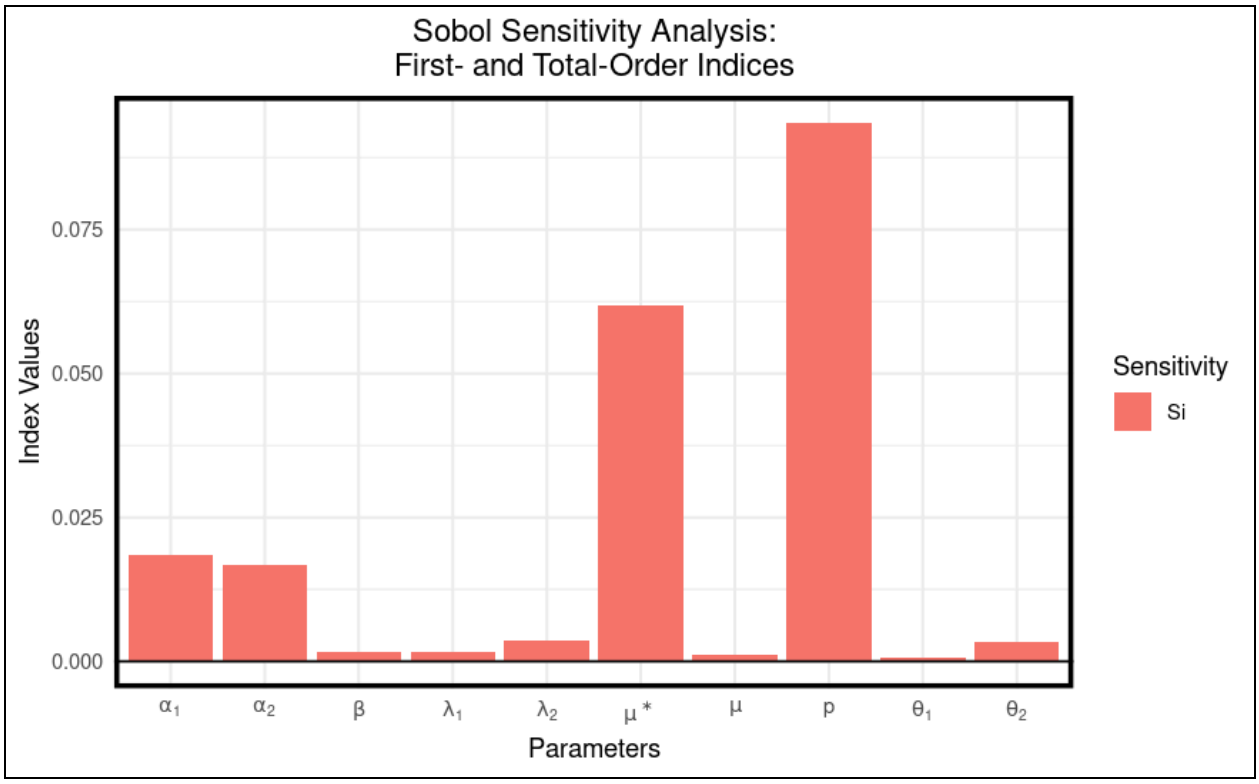

Fig 11: First-order indices of model parameters over 786,432 experiments.

7. Conclusion

Our analysis of the model produced several intuitive results–such as the higher the addiction rates, the higher the ending A-populations; the higher the A-population death rate, the lower the ending A-population. However, multiple experiments produced results worthy of further analysis.

For movement in and out of the T-populations, we observe that sending more individuals seeking OUD treatment to non-MAT than MAT consistently ends in higher A-populations. Moreover, increasing the non-MAT relapse rate yields lower A-populations than when fewer people relapse from MAT, and greater non-MAT success results in fewer cases of addiction than greater MAT success. Sensitivity analysis using Sobol's method provides the additional information that the rate of going to MAT causes greater variation in the ending A-population,

the relapse rate of non-MAT is more impactful than the relapse rate of MAT, and and the success rate of non-MAT causes greater model variation than the success rate of MAT.

When analyzed in combination, these results may suggest the importance of MAT in the opioid epidemic. Although the success of non-MAT appears to have a greater effect on model outcomes, the processes that produced this result used the default treatment parameters $\alpha_1 = 0.05$ and $\alpha_2 = 0.1$. To repeat a previous statement, this outcome may then be attributed to far fewer individuals receiving MAT for OUD than non-MAT, rather than the former's insignificance as a treatment measure. This reasoning may additionally explain the model's greater sensitivity to non-MAT relapse rates.$\alpha_1 = 0.05$ and $\alpha_2 = 0.1$. To repeat a previous statement, this outcome may then be attributed to far fewer individuals receiving MAT for OUD than non-MAT, rather than the former's insignificance as a treatment measure. This reasoning may additionally explain the model's greater sensitivity to non-MAT relapse rates.

However, Fig. 6 opposes MAT expansion as a sole policy measure. Although the A-population decreases when more people receive this treatment, this reduction is less impactful when the overall treatment rate is low. Therefore, policymakers should consider ensuring access to treatment in general rather than focus entirely on making MAT more available. This could involve subsidizing treatment costs for clients, advertising and funding existing treatment centers, disseminating information about OUD for those who may not realize they are struggling with a treatable disorder, and related measures.

In addition to improving the accessibility of treatment, policymakers may observe the model's high sensitivity to p and determine interventions surrounding prescription opioids. This may include restricting the prescription of opioids to cases in which there is no suitable–and non-addictive–alternative, or more careful checks on patient compliance. The latter suggestion is

broad and may involve pill-counting, frequent checks of pharmacy records, and similar measures to ensure that clients do not attempt to request more prescriptions than are medically necessary. p and determine interventions surrounding prescription opioids.

Finally, based solely on Sobol's first indices, the death rate of individuals with OUD causes greater variation in model outcomes than the natural death rate. While this could support the suggestion to mitigate the risk of overdose death, it is accompanied by uncertainty that is described in the next section.

In summary, examining the model under different parameter conditions leads to two policy suggestions: expanding access to treatment, and regulating the use of prescription opioids. While the latter suggestion has its own complexities, the nuance of increasing treatment opportunities is particularly relevant to the motivation of this paper; spending resources exclusively on expanding access to MAT is unlikely to be the best method to reduce addiction unless more individuals have access to treatment in general. For example, introducing medication to all existing non-MAT programs would not lessen the severity of the epidemic to a satisfactory degree. These programs, along with all currently available treatments, must be made accessible to those diagnosed with OUD.

8. Discussion and Limitations

The model presented in this paper is limited in predictive ability by a number of factors. Firstly, there is a scarcity of data on several parameters. This severely impacts the accuracy of the model's population outcomes. Further limiting accuracy is that some parameter values were approximated based on model experiments alone, and it is difficult to verify their accuracy due to a lack of verifiable benchmarks.

In addition to lacking quality data, the model is limited by its simplifying assumptions. For example, we assume that individuals do not have access to opioids while in treatment and therefore cannot die of overdose unless they are untreated; one may argue that this is too far-reaching of an assumption, as patients in treatment may gain access to opioids from a variety of illicit sources. This may particularly be true for treatment that does not require the patient to stay at a treatment facility.

Furthermore, the model ignores the issue of intersectionality. As it assumes a homogenous population, it is absent of race as an identifier. This is incompatible with the reality that Black communities are less likely to receive prescriptions for opioids and more likely to experience overdose deaths (Gondré-Lewis et al. 2022). The model additionally does not distinguish between genders, and it is reported that at least 75% of individuals with OUD in 2022 were white men (Davis 2022). Therefore, without explicitly accounting for the epidemic's unequally distributed consequences, the model cannot provide a comprehensive analysis of it.

Rather than serving to predict outcomes for addicted populations, then, it is a preliminary exploration of the role that MAT may play in the epidemic. It is our hope that it will encourage further scholarship on MAT that is not only intersectional, but accounts for the effects of overdose in treatment and other variables that would support sound policy recommendations.

9. Appendix

9.1. Closed-Form Equilibria

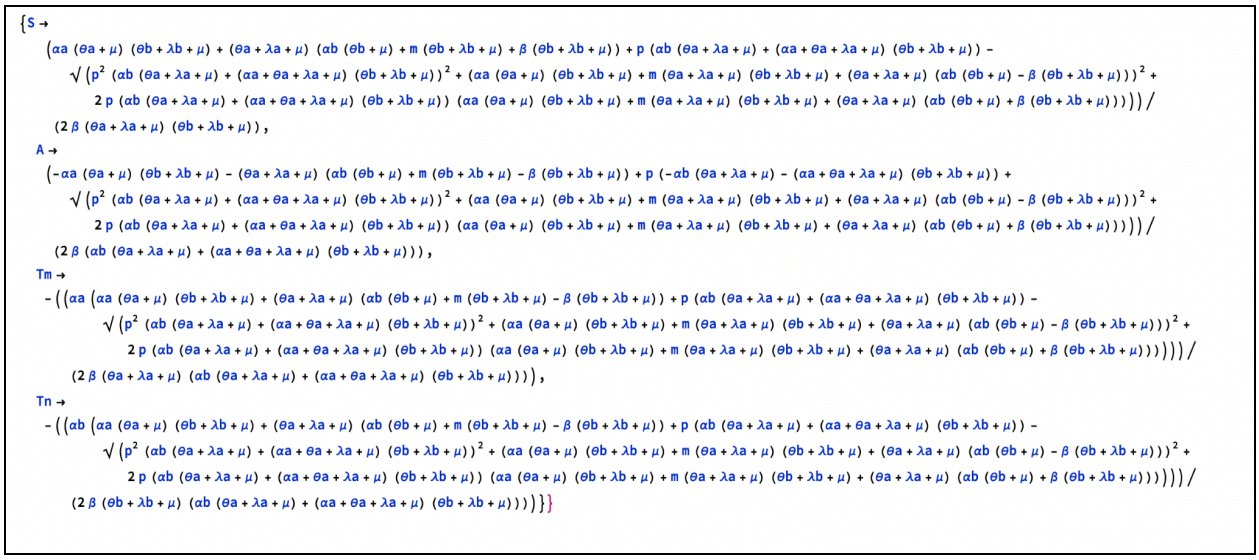

Fig. 12: Positive closed-form equilibria. Variables ‘a’ and ‘b’ correspond to parameter subscripts ‘1’ and ‘2’.

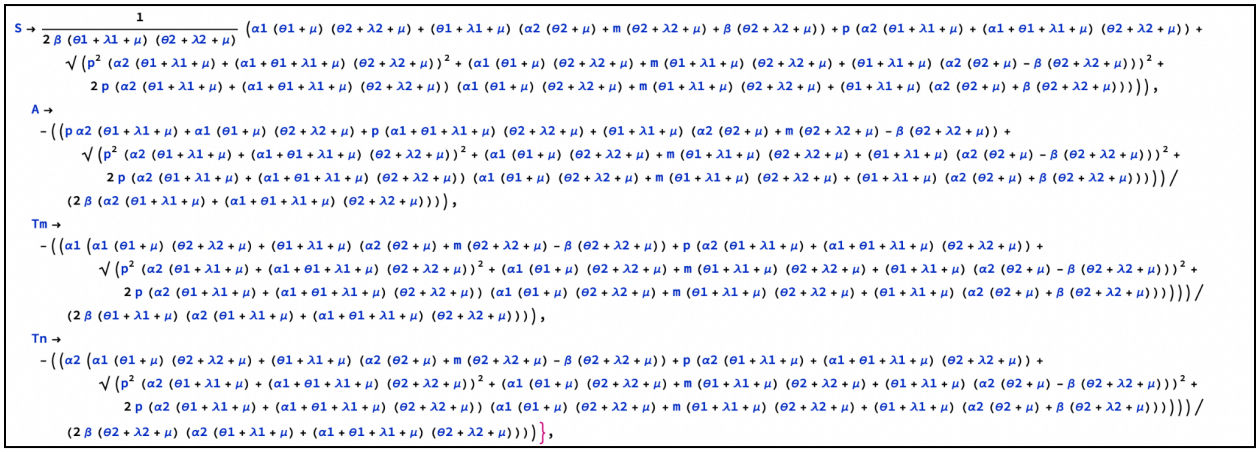

Fig. 13: Closed-form equilibria containing at least one negative population.

9.2. Proof of Positive Compartments in Chosen Equilibrium

9.2.1. Theorem: The equilibrium from the equations seen in Fig. 12 is positive for all parameter sets.

Proof:

For S: Let

$$X = p(\alpha_2(\theta_1 + \lambda_1 + \mu) + (\alpha_1 + \theta_1 + \lambda_1 + \mu)(\theta_2 + \lambda_2 + \mu)),$$

$$Y = \alpha_1(\theta_1 + \mu)(\theta_2 + \lambda_2 + \mu) + (\theta_1 + \lambda_1 + \mu)(\alpha_2(\theta_2 + \mu)$$

$$+\mu^*(\theta_2 + \lambda_2 + \mu) + \beta(\theta_2 + \lambda_2 + \mu)),$$

$$W = \frac{1}{2\beta(\theta_1+\lambda_1+\mu)(\theta_2+\lambda_2+\mu)},$$

$$Z = 2(\beta(\theta_2 + \lambda_2 + \mu))^2.$$

Consequently, $S = W(X + Y - \sqrt{(X + Y)^2 - Z})$. Moreover, since we assume that all parameters are positive, it is true that

$(X + Y)^2 > (X + Y)^2 - Z$, so

$$X + Y > \sqrt{(X + Y)^2 - Z}.$$

Therefore, S will always be positive.

For T_m: Let redefine $X, Y, Z,$ and W as follows:

$$X = p(\alpha_2(\theta_1 + \lambda_1 + \mu) + (\alpha_1 + \theta_1 + \lambda_1 + \mu)(\theta_2 + \lambda_2 + \mu)),$$

$$Y = \alpha_1(\theta_1 + \mu)(\theta_2 + \lambda_2 + \mu) + (\theta_1 + \lambda_1 + \mu)(\alpha_2(\theta_2 + \mu)$$

$$+\mu^*(\theta_2 + \lambda_2 + \mu) - \beta(\theta_2 + \lambda_2 + \mu),$$

$$Z = 4\beta(\theta_2 + \lambda_2 + \mu),$$

$$W = \frac{\alpha_1}{(2\beta(\theta_1+\lambda_1+\mu)(\alpha_2(\theta_1+\lambda_1+\mu)+(\alpha_1+\theta_1+\lambda_1+\mu)(\theta_2+\lambda_2+\mu)))}.$$

Then

$$T_m = -W((X + Y) - \sqrt{(X + Y)^2 + Z}).$$

Consequently, we have that

$$(X+Y)^2 < (X+Y)^2 + Z, \text{ so}$$

$$X + Y < \sqrt{(X+Y)^2 + Z}.$$

Since $X + Y < \sqrt{(X+Y)^2 + Z},\ (X+Y) - \sqrt{(X+Y)^2 + Z}$ will be negative. It then follows that $-W((X+Y) - \sqrt{(X+Y)^2 + Z})$ will be positive. As a result, T_m will be positive.

For A: Next, we move on to A and break its formula into several parts.

$$X = -(-\alpha_1(\theta_1+\mu)(\theta_2+\lambda_2+\mu) - (\theta_1+\lambda_1+\mu)(\alpha_2(\theta_2+\mu)$$

$$+\mu^*(\theta_2+\lambda_2+\mu) - \beta(\theta_2+\lambda)2+\mu)),$$

$$Y = -p(-\alpha_2(\theta_1+\lambda_1+\mu) - (\alpha_1+\theta_1+\lambda_1+\mu)(\theta_2+\lambda_2+\mu)),$$

$$U = (p^2(\alpha_2(\theta_1+\lambda_1+\mu) + (\alpha 1+\theta_1+\lambda_1+\mu)(\theta_2+\lambda_2+\mu))^2$$

$$+(\alpha 1(\theta_1+\mu)(\theta_2+\lambda_2+\mu) + \mu^*(\theta_1+\lambda_1+\mu)(\theta_2+\lambda_2+\mu)$$

$$+(\theta_1+\lambda_1+\mu)(\alpha_2(\theta_2+\mu) - \beta(\theta_2+\lambda_2+\mu)))^2 + 2p(\alpha_2(\theta_1+\lambda_1+\mu)$$

$$+(\alpha 1+\theta_1+\lambda_1+\mu)(\theta_2+\lambda_2+\mu))(\alpha 1(\theta_1+\mu)(\theta_2+\lambda_2+\mu)$$

$$+\mu^*(\theta_1+\lambda_1+\mu)(\theta_2+\lambda_2+\mu)+(\theta_1+\lambda_1+\mu)(\alpha_2(\theta_2+\mu)+\beta(\theta_2+\lambda_2+\mu)))),$$

$$D = \sqrt{U}.$$

Then $A = -X - Y + D$. For A to be positive, we must ensure that $D > X + Y$. To do this, we observe the first component of D, $\sqrt{(X+Y)^2}$. We also observe the addition of several

positive parameters, which we will wrap in the expression Z. Then $D = \sqrt{(X+Y)^2 + Z}$, and because $X + Y = \sqrt{(X+Y)^2}$, we know that $X + Y < \sqrt{(X+Y)^2 + Z}$ because $Z > 0$. Therefore, $A = -X - Y + D > 0$ and A is positive.

For T_n: Finally, we prove that T_n is positive. Let us define the following expressions:

$$X = p(\alpha_2(\theta_1 + \lambda_1 + \mu) + (\alpha_1 + \theta_1 + \lambda_1 + \mu)(\theta_2 + \lambda_2 + \mu)),$$

$$Y = (\alpha_1(\theta_1 + \mu)(\theta_2 + \lambda_2 + \mu) + (\theta_1 + \lambda_1 + \mu)(\alpha_2(\theta_2 + \mu)$$

$$+\mu^*(\theta_2 + \lambda_2 + \mu) - \beta(\theta_2 + \lambda_2 + \mu)),$$

$$Z = 4\beta(\theta_2 + \lambda_2 + \mu).$$

Next, let

$W = \frac{\alpha_2}{(2\beta(\theta_2+\lambda_2+\mu)(\alpha_2(\theta_1+\lambda_1+\mu)+(\alpha_1+\theta_1+\lambda_1+\mu)(\theta_2+\lambda_2+\mu)))}$. Then

$$T_n = -W((X+Y) - \sqrt{(X+Y)^2 + Z}),$$

$$(X+Y)^2 < (X+Y)^2 + Z,$$

$$X + Y < \sqrt{(X+Y)^2 + Z}.$$

Consequently, as $X + Y < \sqrt{(X+Y)^2 + Z}$, $(X+Y) - \sqrt{(X+Y)^2 + Z}$ will be negative. It then follows that $-W((X+Y) - \sqrt{(X+Y)^2 + Z})$ will be positive. Hence T_n will be positive.

Now, as we have proven that $S, A, T_m, T_n \geq 0$, we conclude that $S + A + T_m + T_n \geq 0$.

9.3. Proof of Negative Compartment in Second Equilibrium

9.2.1. Theorem: The equilibrium equation for A seen in Fig. 13 is negative when parameter values are positive.

Proof:

In the second equilibrium, we have a negative sign ahead of the equation for A. Additionally, all terms in the equation are positive except for $-\beta(\theta_2 + \lambda_2 + \mu)$. Let us define the following expressions:

$$X = (p(\alpha_2 + \theta_1 + \lambda_1 + \mu) + (\alpha_1(\theta_1 + \mu)(\theta_2 + \lambda_2 + \mu))),$$

$$Y = (\alpha 1(\theta_1 + \mu)(\theta_2 + \lambda_2 + \mu) + \mu^*(\theta_1$$

$$+\lambda_1 + \mu)(\theta_2 + \lambda_2 + \mu) + (\theta_1 + \lambda_1 + \mu)(\alpha_2(\theta_2 + \mu))),$$

$$W = \frac{1}{2\beta(\alpha_2(\theta_1+\lambda_1+\mu))+(\alpha_1+\theta_1+\lambda_1+\mu)(\theta_2+\lambda_2+\mu))},$$

$$Z = \beta(\theta_2 + \lambda_2 + \mu).$$

Then we have

$$A = -W(X + (Y - Z) + \sqrt{X^2 + (Y - Z)^2 + 2XY + 2XZ}),$$

so

$$\sqrt{X^2 + (Y - Z)^2 + 2XY + 2XZ} > \sqrt{(X + (Y - Z))^2},$$

which means that

$$\sqrt{X^2 + (Y - Z)^2 + 2XY + 2XZ} > X + (Y - Z).$$

This will result in a positive term being multiplied by the negative at the beginning of the equilibrium equation for A. Consequently, any A-population produced by this closed-form solution will be negative, and so the solution may be discarded.

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