Modeling the Heroin Epidemic

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Blue font: contains questions I have, things to discuss.
Red font: things I am working on/need to do; reminder for me: use present tense, use powerful/direct language.

Abstract

Fill in after write paper.

Introduction

Want to "funnel in": start with general epidemic information and then narrow in on the drugs involved. Re-order to better fit funnel with "all" stats first, then prescription opioids, then heroin, then fentanyl (follows flow of people better, too)

General opioid epidemic
Stats about opioid epidemic at large to begin paragraph:
The misuse of opioids, including prescription pain relievers, synthetic opioids, and the illegal drug heroin, is rampant in today's society [24]. The opioid crisis was declared a public health emergency in October 2017 by the United States Department of Health and Human Sciences [72]. Opioid overdoses are problematic; out of all drug overdose deaths in 2016, opioids were involved in 66% of them [74]. Between 2014 and 2015, there was an 11% increase in the number of overdose deaths involving opioids, and 21% increase in the following year. There were more opioid overdose deaths in 2016 (rate of 13.1 people per 100,000) than motor vehicle deaths (rate of 12 people per 100,000) [20]. It was estimated that the total economic cost of prescription opioid dependence, abuse, and overdoses in 2013 alone was $78.5 billion [30]. Due to the health risks of the addicted individuals, public health concerns, the number of overdose deaths, and the economic burden, this is an issue worth paying attention to.

Prescription opioid information
About prescription opioids and why we should care:
A large portion of opioids consist of prescription pain relievers which are either natural (morphine and codeine), semi-synthetic (oxycodone, hydrocodone, oxymorphone), or synthetic, (fentanyl, tramadol) [14, 68]. From 1991 to 2011, there was a near tripling of prescriptions that pharmacies distributed [51]. This was in part due to a number of new opioids that were approved by the FDA for use, such as OxyContin, Actiq, Fentora, and Onsolis (fentanyl), in addition to other unapproved opioid products for pain management [75]. Moreover, in the early 2000s, drug manufacturers funded publications and physicians to support opioid use for pain control [43]. A national survey estimated there were 11.5 million individuals of 12 years of age or older in the United States that experienced pain

reliever misuse in the past year, referring to the year 2016 [65]. In this survey, misuse was defined as taking the prescription at a higher dose, more frequently or longer than prescribed, taking someone else's medication, or any other way not directed by a doctor [66]. Misuse of prescription pain relievers occurs for a variety of reasons and the same survey asked individuals who reported prescription pain reliever misuse to give the reason and the source for their most recent misuse. The most prominent responses for reasons of misuse were to relieve physical pain, to feel good or get high, and to relax or relieve tension. The largest source was from friends/relatives or from a healthcare provider, followed by given a prescription or stolen from a health care provider [65]. Options for treatment of opioid addiction involve medications such as buprenorphine, methadone, and naltrexone, in combination with counseling and behavioral therapies [62]. In addition, pregnant women who take prescription opioids also put their babies at risk of neonatal abstinence syndrome, similar to heroin [15].

Connection between opioid and heroin abuse

Transitioning from prescription opioids to heroin:

The misuse of prescription pain relievers leads some individuals to start heroin. According to the National Survey of Drug Use and Health (NSDUH) survey information from 2002-2011, nearly 80% of heroin users reported non-medical prescription pain reliever use prior to their heroin use. Here, non-medical prescription use is defined as taking prescriptions that were not prescribed to the user directly or used only for the feelings it causes. In fact, those who had prior non-medical prescription pain reliever use were 19 times more likely to initiate heroin use than those without prior use [46]. This could in part be due to the higher availability of heroin in recent years at a lower cost than alternative opioids [51]. Moreover, approximately 3.6 percent of non-medical prescription pain reliever users began using heroin within 5 years of their first opioid; although a small percentage, this is a significant number of individuals given the magnitude of opioid addiction [46]. In 2010, an abuse-deterrent formulation of the commonly abused prescription opioid OxyContin was released that made abuse through injection and inhalation more challenging. Although done with the intent of reducing opioid abuse, studies showed that many individuals switched to heroin use instead [21, 22]. One study of young adults ages 18-25 concluded that among many factors including race, education status, martial status, other drug use, as well as many others, the use of non-prescribed opioid pain relievers in the past year was the biggest indicator of an individual using heroin in the past month, past year, or in their lifetime [39]. Comparing NSDUH data from 2002-2004 and 2008-2010, the average yearly rates of past year heroin use increased among non-medical opioid users, but heroin use stayed static for those who reported no non-medical use of opioids; the highest rate of heroin use was among individuals with past year non-medical use of opioids ranging between 100 and 365 days of use [40]. In the 1960's, heroin users were composed mainly of younger, nonwhite men in urban areas with their initial opioid being heroin, but in recent decades, this trend has shifted to older, white, rural and suburban men and women with their initial opioid being a prescription [23]. Opioids are of no shortage in society today and since opioid addiction is driven largely by legal prescription medication availability, this has made a significant proportion of society susceptible to misuse and addiction to opioids, including heroin.

Heroin information

About the drug

Heroin is an illicit drug classified as an opioid and comes in the form of a white or brown powder or as a black substance resembling roofing tar. The drug is injected, sniffed, snorted or smoked and quickly enters the brain to bind to opioid receptors. It provides the user with feelings of euphoria, in addition to physical effects such as heavy feelings in the arms and legs, dry mouth, and sometimes nausea and vomiting [48, 49]. There are short and long term negative effects on the body for using the drug, and consequently, it is currently considered a schedule I drug, meaning that there is no approved medical use of heroin and there is a high likelihood for abuse. [70, 48]. Addicted individuals have withdrawal symptoms such as restlessness, diarrhea, vomiting, and cold flashes, along with cravings for the drug which makes stopping use of the drug very difficult [48]. Treatment options for heroin use are the same as for prescription opioids [62, 48]. Heroin users build up a tolerance to the drug with repeated use and can overdose on the drug, in which their heart rate and breathing is slowed to a dangerous level without medical assistance [49, 48]. Due to built-up tolerance, the risk of overdose is high when individuals stop their use of the drug for a period of time (i.e. while in recovery or hospitalized) and return to use. This is because they may return to the previous amount they were taking before, without knowing what their body can currently tolerate [24].

The effects of heroin, however, extend further than just the specific individual using the drug. Due to the sharing of needles and other equipment involved in the injection of heroin, the human immunodeficiency virus (HIV) and the hepatitis C virus (HCV) are more easily contracted as transmittance occurs through bodily fluids. In addition, risky sexual behavior is heightened under the influence, so addicts have an increased risk of transmitting and contracting these viruses. Women who use heroin during pregnancy put their babies at risk for neonatal abstinence syndrome in which the drug is passed along to the baby, resulting in dependency and thus, withdrawal symptoms upon birth [49].

Statistics regarding heroin/fentanyl and why we should care:

A national survey estimated that out of the United States national population of individuals of 12 years of ago or older, 948,000 were heroin users in 2016, although this number may include under-reporting [65]. There were an estimated 13,219 heroin deaths in 2016, a more than six-fold increase from the year 2002, despite there being roughly half as many heroin users in 2002 [64]. There was a drastic increase in the number of opioid overdose deaths involving heroin around 2010 [13].

In recent years, there has been a trend of lacing heroin with fentanyl, a surgical-grade opioid that is up to 50 times more potent than heroin alone, and therefore, users are unaware of the purity of the heroin they obtain [12, 24, 77]. There was a sharp increase in the number of opioid overdose deaths involving synthetic opioids, which includes fentanyl, around 2013, although death certificate data does not distinguish between prescription and illicitly manufactured fentanyl [13]. In addition, there was a drastic increase in fentanyl reports nationwide from 2014-2017 and reports suggest that the increase in overdoses involving fentanyl in this time period can mostly be attributed to illicitly manufactured fentanyl [74, 18, 53, 13, 3, 11].

Fentanyl information

About the drug

Fentanyl is a synthetic opioid that is made both pharmaceutically mainly for the treatment of advanced cancer pain (comes in the form of oral lozenges, tablets, sprays or patches) and illicitly (comes in the form of powder or counterfeit tablets) [18, 3]. It is 50 times stronger than heroin and up to 100 times stronger than morphine, and has similar effects such as relaxation, euphoria, pain relief, and nausea, among others [73]. The drug is found often mixed with heroin to increase the effects of heroin, and the user may or may not be aware of this mixing. In 2013, there were 942 fentanyl submissions to the DEA nationwide, and in 2014 there were 3,344; in this same time frame, there was a drastic spike in the number of synthetic opioid overdoses, including fentanyl, which leads to the belief that the fentanyl-involved overdose deaths increased due to illicitly-manufactured fentanyl rather than that prescribed [13, 3, 11]. Other reports hypothesize this, as well [18, 53].

Other models

Previous models involving heroin

Look for fentanyl use/addiction models, if any

There have been several models formulated focusing on heroin addiction. Most of them were motivated by the White and Comiskey ordinary differential equation model with three compartments each representing a different stage as a drug-user: the susceptible class including individuals aged 15-64, the drug user class composed of individuals not in treatment, and finally, the drug users in treatment. In this model, individuals in treatment for drug use were only able to die, relapse to drug use, or complete treatment and be immune to drug use for the remainder of the modeling time period. The basic reproduction number, $\mathscr{R}_0$, was calculated and deemed most sensitive to the rate of individuals in the susceptible class becoming drug users; therefore, prevention is more important than treatment for reducing drug use [82]. Extensions to this model have various assumptions including a non-constant population, non-constant time to relapse, age-dependence, time-delays, recovered individuals being unable to return to the susceptible class, and a saturation treatment function with a fourth class [79, 41, 28, 29, 57, 2, 42, 80].

Of interest is a model consisting of 84 ODE's that captured the dynamics between prescription opioid users with acute pain, those with chronic pain, illicit opioid users, heroin users and those who overdose. Results showed that increasing addiction treatment and reducing prescriptions for individuals with chronic pain seemed to have a greater impact on reducing both heroin overdose deaths and the number of opioid abusers compared to reducing prescriptions for acute pain without treatment increases [1]. This was from a conference preceding...in future, look for published model from Benneyan. Approaches for this issue also include agent-based modeling [1, 4]. Put in brief explanation of "Reducing the complexity of an agent-based local heroin market model" paper by Heard.

Summary of Christopher's opioid paper and why formulating another model:

The motivation for our heroin/fentanyl model comes from a prescription opioid ordinary differential equation model consisting of four classes of the national population: susceptibles, prescribed users, addicts, and individiuals in treatment [7]. Model parameters were estimated from literature and simulations were run with these parameters/parameter ranges to compare simulated opioid overdose deaths to actual opioid overdose deaths, thus giving reason to believe this model is realistic. The existence of an addiction-free equilibrium requires that prescribed users cannot become addicted to their own prescriptions and that there are no secondary addictions that come from the accessibility to excess prescription drugs. In this case, $R_0 < 1$, which strongly suggests that the epidemic could not be sustained without primary and secondary addiction through prescriptions. Sobol sensitivity analysis was performed to investigate the sensitivity of the population classes at 10 years to each of the parameters individually and with higher-order interactions among the parameters. The addicted class at this time was most sensitive to the prescription completion rate and treatment entrance rate; high values for these rates were deemed essential in reducing the addicted population fraction when considering a range of values for several other parameters, as well. Among this set of other parameters that were varied, the rate that prescribed users move to addiction and the prescription rate are both important to focus on in reducing addiction, the latter of which is easier to control than the former. Investigating four parameters that are somewhat feasible for control efforts, results showed that given our current prescription rate, in 10 years the addicted population can be decreased given certain rates of completing prescriptions, entering treatment, and completing treatment. Overall, attention should be given primarily to prescription completion and treatment entrance rates, then prescription rates, and finally, treatment completion rates.

The prescription opioid model has given motivation to formulate a separate model with the goal of understanding the more complicated dynamics that arise among opioid addiction with the addition of heroin/fentanyl use. As exemplified previously, heroin and fentanyl play a significant role in the process of opioid addiction and recovery and so it's inclusion provides a more accurate overall picture of the epidemic. In 2016, synthetic opioids, which includes fentanyl, became the number one drug involved in overdose deaths in the country and thus is vital to include [40]. It is crucial to take a more detailed look at the increasing problem of overdose deaths discussed above [13].

How our model is different than previous models:
Previous models have not incorporated the connection between prescription opioid misuse and heroin or fentanyl use at all unless Benneyan publishes/others, instead focusing solely on heroin addiction and recovery. Although there are many factors that play a role in population size, susceptibility to drug use, relapse time and other parts of the drug-using process, we consider individuals in each of the classes to be homogeneous, for simplicity of a starting model. Include more details on how my model different than previous ones. Although there have been theoretical heroin models formulated in the past, we offer a data-driven model due to the enormity of the problem and data that is now available that explicitly shows drastic increases in overdoses in recent years and an overall increase in heroin use and illicit fentanyl presence.

Discussion of how our model differs from the prescription opioid model: best to differ-

entiate throughout the paper; include: We alter how the recovery process is viewed, by thinking about those in recovery still as addicts, and not having the ability to become a susceptible individual again.

Goal paragraph

Goals for our model/questions trying to answer:
To address this apparent problem in today's society, we model the prescription opioid/heroin/fentanyl epidemic in order to understand the dynamics behind the epidemic and predict the trajectory of the epidemic. This model analyzes the epidemic since the time it has been established which we believe was around 2013; after this point, the number of prescriptions have dropped each year, resulting in fewer pills lying around, but leading to the use of other drugs such as heroin and fentanyl due to their lower cost and availability. This contrasts the prescription opioid-only model in [7] in which the focus was on the dynamics of the epidemic as it was ramping up; we instead care about the sustained dynamics and investigate what do we do now that the epidemic is established. We identify important conditions relating to the reduction of prescription opioid/heroin/fentanyl addiction. To do that, we have formulated a population level system of ordinary differential equations model consisting of classes of individuals taking prescription opioids, addicted to prescription opioids, addicted to heroin and/or fentanyl, and stably recovered from addiction to any opioid, and analyzed it. Our overall goal is to explore how different management strategies may alter the epidemic trajectory; specifically, we investigate management strategies for optimally treating pain with prescriptions while reducing prescription opioid, heroin, and fentanyl addiction.

Model Formulation

To the extent of our knowledge, there have been no mathematical models incorporating both prescription opioid addiction and heroin/fentanyl addiction. Although terminology is not always clearly defined in the literature, such as opioid misuse, abuse, dependency, addiction and use disorder, we aim to focus on addiction only, where addiction to opioids is defined as having a pattern of continued non-medical use that is already, or could be, harmful [78]. We take opioid use disorder to fall in this categorization of addiction, due to the definition presented in [63] which includes sustained use regardless of interference with life obligations. Our model consists of five subgroups of a population, in which they are all proportions of the entire population:

1. Susceptibles S: This portion of the population consists of individuals who are not taking prescription opioids of any kind, nor using heroin or fentanyl.

2. Prescription opioid users P: This class of individuals consists of individuals who are prescribed opioids by a health care provider and take the opioids at a level that is not considered addicted. We note that individuals in this class could be misusing prescription opioids, but not at the level of addiction.

3. Opioid addicts A: This group of individuals are addicted to opioids, but not using

heroin or fentanyl, or are actively in treatment for opioid addiction. For individuals who go to treatment for opioid addiction, they remain in this class for at least 4 weeks *after* being discharged from treatment; if they relapse within 4 weeks after treatment, they are again considered addicted and can remain in this class for longer. (Although the opioid class of drug includes heroin and fentanyl, here we take opioids to mean non-heroin and non-fentanyl.)

4. Heroin/fentanyl users H: This class is composed of individuals who are addicted to heroin or fentanyl, or are actively in treatment for heroin/fentanyl addiction. For individuals who go to treatment for heroin/fentanyl addiction, they remain in this class for at least 4 weeks *after* being discharged from treatment; if they relapse within 4 weeks after treatment, they are again considered addicted and can remain in this class for longer. (We note that individuals in this class could be using other drugs or are addicted to opioids in addition to heroin or fentanyl, but they are at least addicted to one of these drugs).

5. Recovered individuals R: This class consists of individuals who completed treatment for opioid or heroin/fentanyl addiction and did not relapse within 4 weeks after treatment, and therefore are considered in a "stable" recovery state.

Clarifications on definitions: We include illicit fentanyl users in the class of heroin users, because of the potency of the drug, which is what those addicted to prescription opioids seek–lower cost and a better high. In addition, a portion of those who overdose from the very powerful drug fentanyl are individuals who are using heroin that is laced with it; therefore, the use of fentanyl is oftentimes intertwined with the use of heroin. There is much variability in the purity of heroin due to the lacing of the drug with fentanyl, and 1 in 5 overdose deaths have multiple drugs present so it is difficult to know the actual cause of death [13]. We believe it is difficult to separate the use of heroin and fentanyl, so putting them in the same class is the most natural choice. Finally, we remark that use of heroin is implicitly understood to be addictive due to the highly addictive nature of the drug, and we assume no casual use of the drug [48]. If an individual uses heroin at a level that it would be easy to stop using, they are better classified as a susceptible individual rather than a heroin addict, based on the definition of addiction we are using. Similarly, we assume that individuals who use fentanyl outside of short-term, carefully monitored settings or prescribed for cancer pain under the supervision of a health provider is assumed to be addicted. We try to take into account these complexities as best as possible with the information in literature.

We denote the initial conditions as $S(0) = S_0$, $P(0) = P_0$, $A(0) = A_0$, $H(0) = H_0$, and $R(0) = R_0$, and we assume all of these values are positive. The initial values for each of the classes are proportions of the entire population.

Here, we present our ordinary differential equation model:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\alpha S - \beta_A SA - \beta_P SP - \theta_1 SH + \varepsilon P + \mu(S+P+A+H+R) + \mu_A A + \mu_H H - \mu S \quad (1)$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \alpha S - \varepsilon P - \gamma P - \theta_2 PH - \mu P \quad (2)$$

$$\frac{\mathrm{d}A}{\mathrm{d}t} = \gamma P + \sigma R\frac{A}{A+H+\omega} + \beta_A SA + \beta_P SP - \zeta A - \theta_3 AH - (\mu+\mu_A)A \quad (3)$$

$$\frac{\mathrm{d}H}{\mathrm{d}t} = \theta_1 SH + \theta_2 PH + \theta_3 AH + \sigma R\frac{H}{A+H+\omega} - \nu H - (\mu+\mu_H)H \quad (4)$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \zeta A + \nu H - \sigma R\frac{A}{A+H+\omega} - \sigma R\frac{H}{A+H+\omega} - \mu R \quad (5)$$

$$S + P + A + H + R = 1 \quad (6).$$

We assume that these five compartments sum to one, so that the population is of constant size, i.e. the total death rate is equal to the incoming rate for the susceptible class since we believe overdose deaths will not significantly alter our population. We impose this since we are working with a short time frame and believe the population will not change very much over this time period. Since the birth and death rate of the susceptible class, μS, is the same, equation (1) simplifies to:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\alpha S - \beta_A SA - \beta_P SP - \theta_1 SH + \varepsilon P + \mu(P+R) + (\mu+\mu_A)A + (\mu+\mu_H)H \quad (1)$$

The parameters involved in this model represent transition rates from one class to another and are per capita yearly rates:

- αS: rate at which susceptible individuals are prescribed opioids (1/year) May change to be clearer in each of these parameters about the units (i.e. per prescription user year or whatever it is) or may just leave that for the parameter table where units are listed
- $\beta_A SA$: rate at which susceptible individuals become addicted to opioids by black market drugs or interaction with other addicts (1/year)
- $\beta_P SP$: rate at which susceptible population obtains extra prescription opioids and becomes addicted per year
- $\theta_1 SH$: rate at which susceptible population becomes addicted to heroin or fentanyl by black market availability or interaction with other heroin or fentanyl users (1/year)
- εP: rate at which individuals return to the susceptible class after being prescribed opioids and did not develop an addiction (1/year)
- $\mu S, \mu P, \mu A, \mu H, \mu R$: natural death rates (1/year)
- $\mu_A A$: enhanced death rate for opioid addicts; overdose rate which results in death (1/year)

- $\mu_H H$: enhanced death rate for heroin or fentanyl addicts; overdose rate which results in death (1/year)
- γP: rate at which prescribed opioid users become addicted to opioids (1/year)
- $\theta_2 PH$: rate at which prescribed opioid users become addicted to heroin or fentanyl (1/year)
- $\sigma R\frac{A}{A+H+\omega}$: rate at which individuals transition from the recovered class into the opioid addicted class which is proportional to the approximate proportion of individuals in the recovered class that came from A that are relapsing back to that class. We include a perturbation term ω here in the case that A and H are both 0, such as in the addiction-free case. (note: even though we do not know where individuals came from originally, we make the assumption that individuals go back to their primary drug of choice/the reason they entered treatment, so relapse back approximately proportional to where they came from Source/explanation below..also, fix wording when take care of this depending on what we go with. Also mention that this is an approximation because it's based on the "current time" class proportions (not the time step when they went to R). We are doing this because the percentages/stats we are using are "relapse rates" so that means individuals are going back where they started.) (1/year)
- ζA: rate at which addicted opioid users enter treatment/rehabilitation (1/year)
- $\theta_3 AH$: rate at which the opioid addicted population becomes addicted to heroin or fentanyl (1/year)
- $\sigma R\frac{H}{A+H+\omega}$: rate at which individuals transition from the recovered class into the heroin/fentanyl addicted class which is proportional to the approximate proportion of individuals in the recovered class that came from A that are relapsing back to that class. We include a perturbation term ω here in the case that A and H are both 0, such as in the addiction-free case. (note: even though we do not know where individuals came from originally, we make the assumption that individuals go back to their primary drug of choice/the reason they entered treatment, so relapse back approximately proportional to where they came from Source below..also, fix wording when take care of this.) (1/year)
- νH: rate at which heroin or fentanyl users enter treatment/rehabilitation

Clarification of some aspects of the model:
We note that although sellers are not directly involved in the model nor have to be addicts themselves, addicted individuals act as a proxy for sellers of the drug and general availability of the drug, whether it is opioids or heroin. This is because the higher number of addicted individuals there are, the more sellers there needs to be which results in an increased exposure to the drug and therefore, increased chance of addiction. Although treatments for addictions are an enormous problem in and of themselves since there is limited success as shown by the parameter values for the recovery rates, we are acknowledging treatments as a part of recovery in our model, but do not go into specifics for this first model. We are classifying overdoses to mean opioid overdose-related deaths (i.e.

not from secondary factors or long term effects). Although overdose death data includes both accidental and non-accidental deaths (i.e. suicide, assault), we assume here that if an individual died from an overdose-related death, they were addicted (i.e. the number of intentional deaths is negligible). This is CDC definition (from data packet) is for prescription opioids and fentanyl; see if also same for heroin. We also note the fact that Naloxone, an overdose-reversing medication, has saved individuals from overdoses, but [49] make some argument that the number saved is negligible compared to the number of overdoses, so we assume results in death most of the time.

Explanation of different R class, how different from Christopher's opioid paper:
Fix: don't want to use "negative" language such as "we did something to *avoid* someting else," etc. Reword so saying something like "Other choices for dealing with recovery include..., two recovery classes, etc...
We note that the terms $\sigma R\frac{A}{A+H+\omega}$ and $\sigma R\frac{H}{A+H+\omega}$ were included in order to avoid having two recovered classes, which would prevent the transition of individuals who recovered from one drug to initiate use of the other (or if we included those pathways, would become too complicated for a first model). One study suggested that 10% of the prescription opioid addicts they followed up with post-treatment had used heroin at least five times in the previous year, which demonstrates the importance of keeping these transitions as possibilities [81]. We decided to define a recovered class instead of a recovery class as the model presented in [7] did, because the recovery class would have consisted of two very different groups of individuals: those with a high chance of relapse (e.g. recently finished treatment) and those with a much lower chance of relapse (e.g. successfully finished treatment in the past and has remained free of addiction for a significant amount of time). This definition of the recovered class creates a compartment to place individuals who have been addicted in the past and have finished treatment but are not considered actively addicted anymore and should be dealt with differently than susceptible individuals, those in treatment, and those recently out of treatment. We emphasize here that we do not consider the stably recovered class to contain addicts.

We note here that the recovered class and relapse from that class is one of the key features that distinguishes our model from that of [7]. In the opioid-only model, as the focus was on the dynamics of the epidemic as it was ramping up, at beginning of the epidemic, relapse did not depend on the number that were addicted. In contrast, since the epidemic has been established, there are high numbers of opioid and heroin/fentanyl addicts; the proportion in each category affects where people relapse to. Be clearer with words here, depending on if interaction term or not; may need to alter argument about primary drug/source-driven?

Support/data/arguments for why choosing 4 weeks/acute withdrawal period
Summarize these multiple supporting sources into a few sentences and only go into this much detail in disseration? We choose to use 4 weeks after treatment with no relapse as the mark of when people are "successfully recovered" and can move to R. We chose this time frame due to several studies exhibiting a high level of relapse within weeks of discharge from treatment, which suggests individuals are not stably recovered. One study following up with opiate dependent individuals (of which 88% of the study population were heroin

users) showed that 59% of the individuals discharged from treatment relapsed within 1 week and 71% within 4 weeks [58]. Moreover, 80% of individuals who relapsed after treatment did so within 4 weeks and that 92% of individuals who relapsed after discharge had gone back to treatment prior to their follow-up interview (which was between 18-42 months). These statistics convey the unstable nature of an addicts' recovery, particularly within a few weeks of post-treatment (since that's when a majority of them relapsed). In another opiate dependent group study evaluating their relapse risk, 27% had relapsed on the discharge day of their most recent treatment program, 41% had relapsed within 1 week and 65% within 4 weeks [6]. The only study found specifically for prescription opioid addicts suggested that 91% of them who completed a two-phase treatment program relapsed back into addiction within 8 weeks post-treatment [81]. On the lower side, in another study an estimated 32% of the 68 opiate addicts interviewed returned to addiction within 4 weeks and 65% lapsed, which we note has potential to lead to dependence in time; at the 6 month follow-up, 50% of the 60 individuals interviewed were dependent [10]. An older study following up with opiate users post-treatment for 6 months showed that 32% had lapsed within 1 week post-discharge when interviewed; 71% had lapsed by the 6th week; and 44% had returned to the daily use of opiates (considered addicted) at the 2 month mark [31]. Furthermore, the study stated that several individuals who completed the withdrawal portion of the program lapsed while in the second, in-patient part of treatment (although not necessarily equating to a full relapse back into addiction) which supports our claim that those who entered treatment addicted should be still be considered addicted while in treatment. Later analysis of this study regarding relapse factors stated that 25% of those who lapsed mentioned withdrawal symptoms as playing a role in their lapses [9]. These statistics suggest that opiate-abstinence can be difficult to achieve in this initial time period post-treatment: "...the period immediately after leaving a residential treatment is of massively high risk: the great majority of lapses occurred with the first few weeks after discharge...after the first four weeks, there were few additional lapses...first few weeks after discharge as a *critical period* in the process of recovery" [31]. This suggests four weeks can be viewed as an important marker in recovery, and that individuals who bounce back to addiction/frequently relapse in this time frame should simply remain in their respective addicted classes. Other studies suggest significant lapse and relapse rates within weeks and months for heroin addicts and opiate addicts, as well [38, 32].

Therefore, since 71% of heroin addicts relapse within 4 weeks post-treatment and an estimated 91% of prescription opioid addicts in recovery relapse back to addiction within 8 weeks post-treatment (the majority most likely within four weeks based on these other studies), we keep these individuals in the addiction class up for 4 weeks post-treatment since they have not stably "recovered," i.e. at a point where they are less likely to fall back into addiction [58, 81].

Information on relapse coming from primary drug and not source-driven, argument for form of our transition terms being proportional to number in each addicted class

In one study, 63% of initial lapses occurred around other opioid users, 48% in another addicts' home, and 31% in ones own home [31]. This may lead one to believe that interactions with other addicts would play a large role with an initial lapse/relapse; however, following this study, the authors explored the circumstances that led to the lapses of these study subjects and results proved differently. The top factors that led to these

initial lapses were cognitive factors (planned to use), mood states (angry, sad, lonely, etc.), and external influences (situations unrelated to drug use that led to use). This was taking into consideration the number of people who mentioned the factors, the total number of times the factors were mentioned, the number of individuals who deemed the factor most important, and finally, the number of individuals that indicated the factor was the initiator of a sequence of other factors, as lapse often is a result of multiple factors occurring simultaneously. These were also the factors that were primarily contributed to the continued use of opiates. It seems clear that source-driven factors, specifically social pressure (offered drugs), drug availability (in another users' home or in the area), drug-related clues (objects used for drug-taking/observing others under the influence), and interpersonal influences (seeing or thinking about certain people) had relatively little importance compared to the others mentioned above [9]. It is because of this that we argue individuals return to their primary drug of choice compared to what is simply available; although we are interested specifically in a return to addiction, that is umbrellaed under the broader category of lapses.

We mention that another study specifically on heroin users enabled the study subjects to choose categories they deemed as most important in their relapse according to a phrase attached to the category and this was compared to the results of independent judges selecting the categories based on individuals' responses. The highest mean ratings for the categories that the subjects chose were for the giving into temptations/urges in the presence of substance cues and direct social pressure, whereas the judges deemed negative emotional states and indirect social pressure as the most frequent reasons. However, given that subjects were provided a phrase that correlated with a certain category, one could argue that if an individual did not agree with the exact phrase, they may have chosen an alternative option that they related to more (e.g. "I felt bored" represented the entire category of "negative emotional states other than frustration and/or anger.). Moreover, the previous study applies both to opioid addicts and heroin addicts, rather than just heroin addicts [34].

Explanation of pathways omitted:

We omitted an interaction term between prescribed users and addicted individuals moving into the addicted class under the assumption that their own prescription is the primary source of their addiction, and that an illicit source or interaction with addicts would be secondary. Moreover, we did not include an interaction term RA to go from the recovered class to the opioid addicted class because we assume that individuals who are in a stable recovery state are not influenced by addicts or by the general availability of the drug to fall back into addiction themselves; similarly for RH. If keep this, can refer to opioid paper. Currently working on these terms/ideas, so will most likely be updated. We do not have a pathway from R to P; although individuals have the potential of obtaining a legal prescription from a doctor since doctors are not necessarily informed that their patient was in recovery in the past find resource that talks about doctors being "case-history blind", we believe it is not realistic that an individual who has recovered from an opioid or heroin addiction would be able to successfully take prescription opioids in a non-addictive manner, and therefore would be in the addicted class almost immediately. Although there may be a few exceptions to this, we make this simplifying assumption for a first model.

We omitted the pathway from R to S since individuals who have been to treatment and recovered are much more likely to fall into addiction than a susceptible individual, and therefore, must be treated differently than a susceptible individual who has not been to recovery (i.e. cannot be homogeneously mixed in S). We think of individuals in the recovered class as in a permanent state of recovery for the rest of their lives, although they are not undergoing active recovery, and we think of this class as an absorbing state. Find source talking about addicted individuals who underwent recovery much more likely to fall back into addiction than susceptible individual...addiction being a disease. This is a change from the opioid model; discuss dynamical difference. Along these same lines, there is no pathway from A or H to S because we are under the assumption that an addicted individual either remains addicted or goes to recovery to help their addiction and will never be characterized as a susceptible individual again. We recognize that there may be additional pathways among the classes, but the ones we have chosen to include in this first model are a result of balancing simplicity and robustness.

This compartmental model can be represented by the following flow diagram with each arrow representing either the transition rate between one class to another or birth/death:

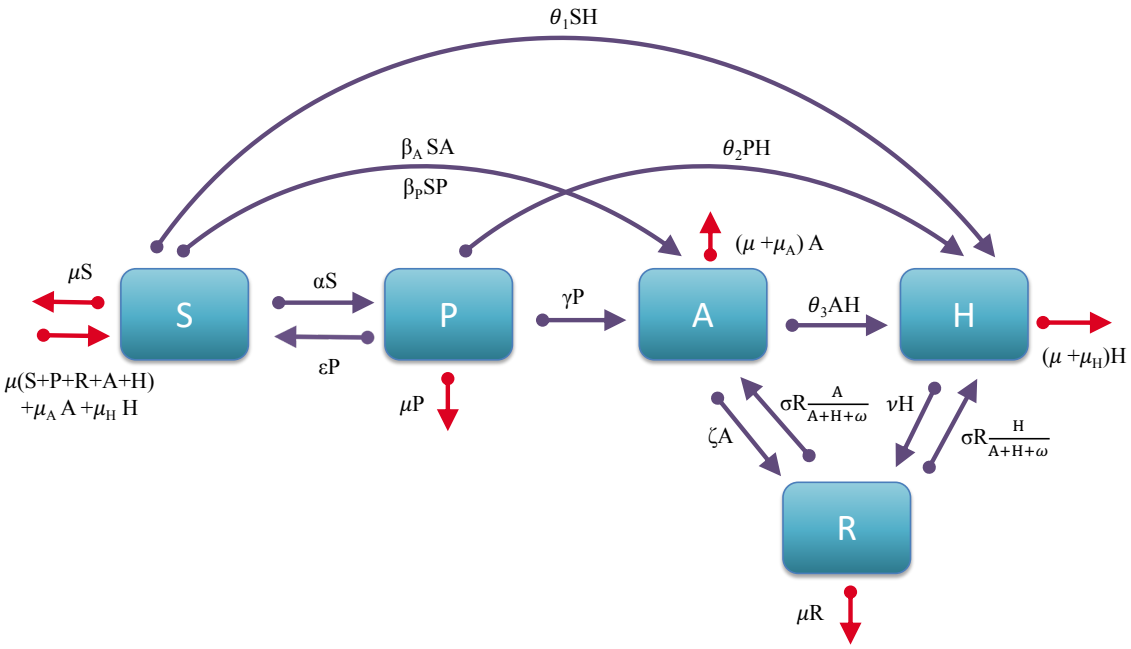


Figure 1: Schematic diagram for heroin model

Analysis of the Model

Addiction-Free Equilibrium

To find the addiction-free equilibrium, we set equations (1)-(5) equal to zero and require that $A = H = 0$ since these two compartments consist of individuals who are addicted to

opioids or heroin. We are left with the system:

$$0 = -\alpha S^* - \beta_P S^* P^* + \varepsilon P^* + \mu(P^* + R^*) \quad (7)$$

$$0 = \alpha S^* - \varepsilon P^* - \gamma P^* - \mu P^* \quad (8)$$

$$0 = \gamma P^* + \beta_P S^* P^* \quad (9)$$

$$0 = \mu R^* \quad (10)$$

$$1 = S^* + P^* + A^* + H^* + R^* \quad (11)$$

Equation (10) forces either $\mu = 0$ or $R^* = 0$; however, $\mu > 0$ since this is the natural death rate, so we require $R^* = 0$. If $P^* \neq 0$, this forces $\gamma + \beta_P S^* = 0$ from equation (9), and since all of our parameters and variables are non-negative, then it must be $\gamma = 0$ and $\beta_P = 0$. We note that $\gamma = 0$ means that individuals who are prescribed opioids cannot become addicted to opioids, and $\beta_P = 0$ means that only black market opioids are available for susceptibles to become addicted to opioids and there are no excess prescription drugs available. Under the assumption that $\gamma = 0 = \beta_P$ to ensure the existence of our addiction-free equilibrium, we calculate the addiction-free equilibrium to be:

$$S^* = \frac{\varepsilon + \mu}{\alpha + \varepsilon + \mu}$$

$$P^* = \frac{\alpha}{\alpha + \varepsilon + \mu}$$

$$A^* = 0$$

$$H^* = 0$$

$$R^* = 0$$

If $P^* = 0$, then equation (8) forces either $S^* = 0$ or $\alpha = 0$. If $S^* = 0$, then the solution $S^* = P^* = A^* = H^* = R^* = 0$ contradicts equation (11). If $\alpha = 0$, then we use equation (11) to solve for the addiction-free equilibrium of (1,0,0,0,0); this solution is included in the addiction-free equilibrium above when $\alpha = 0$, as well.

Basic Reproduction Number, $\mathscr{R}_0$

The basic reproduction number, denoted $\mathscr{R}_0$, is a term used in epidemiological models that gives the expected number of secondary disease cases that result from the introduction of a disease to a susceptible population. The value of $\mathscr{R}_0$ represents how successful the spread of the disease is expected to be; if $\mathscr{R}_0 < 1$, then the disease is expected to die out and the disease-free equilibrium will be locally stable; conversely, if $\mathscr{R}_0 > 1$, then the disease is expected to spread and the disease-free equilibrium will be unstable [76].

This idea may be applied to the context of our model since for the addiction-free equilibrium to occur, γ and β_P must both be equal to 0, which means individuals can become

addicted only with interactions with opioid addicted individuals or heroin users so this takes the form of an infectious disease. Thus, in this case in which the prescription part is essentially taken out of the model so that it is a black-market-only driven model, $\mathscr{R}_0$ can be calculated. This value will be the ratio of the number of new addictions in the next year compared to the current year. At the addiction-free equilibrium, the population is completely susceptible, as needed for $\mathscr{R}_0$ to be an accurate measurement of addiction potential. We note that our goal in this section is to explore the structure of the model and not obtain a result for the full model. The disease compartments are those that contain infected individuals, or in our case, addicts [76]. Our model incorporates two addiction compartments, A and H, since these both consist of opioid or heroin/fentanyl addicted individuals. We will utilize the Next Generation Matrix Method in order to calculate $\mathscr{R}_0$.

For the purposes of calculating $\mathscr{R}_0$, we will assume $\gamma = 0$ and $\beta_P = 0$ in order to ensure the existence of the addiction-free equilibrium. This results in the following system:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= -\alpha S - \beta_A SA - \theta_1 SH + \varepsilon P + \mu(P+R) + (\mu+\mu_A)A + (\mu+\mu_H)H \\
\frac{\mathrm{d}P}{\mathrm{d}t} &= \alpha S - \varepsilon P - \theta_2 PH - \mu P \\
\frac{\mathrm{d}A}{\mathrm{d}t} &= \sigma R\frac{A}{A+H+\omega} + \beta_A SA - \zeta A - \theta_3 AH - (\mu+\mu_A)A \\
\frac{\mathrm{d}H}{\mathrm{d}t} &= \theta_1 SH + \theta_2 PH + \theta_3 AH + \sigma R\frac{H}{A+H+\omega} - \nu H - (\mu+\mu_H)H \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \zeta A + \nu H - \sigma R\frac{A}{A+H+\omega} - \sigma R\frac{H}{A+H+\omega} - \mu R.
\end{aligned}$$

In general, the differential equations of the n disease compartments, x_i', may be written as:

$$x_i' = \mathscr{F}_i(x,y) - \mathscr{V}_i(x,y), \quad i = 1, ..., n$$

where x is a vector with the disease compartments as components, y a vector with the non-disease compartments as components, $\mathscr{F}_i$ represents the rate that secondary infections contribute to disease compartment i and $\mathscr{V}_i$ represents the rate of transitions, i.e. rate at which the disease compartment i is decreased by means of death, recovery and progression of the disease for $i = 1, 2$ [76].

Thus, for our two addicted compartments, we may write:

$$\begin{aligned}
\frac{dA}{dt} &= \mathscr{F}_1(x,y) - \mathscr{V}_1(x,y) \\
\frac{dH}{dt} &= \mathscr{F}_2(x,y) - \mathscr{V}_2(x,y)
\end{aligned}$$

where $x = [A \quad H]^T$ and $y = [S \quad P \quad R]^T$.

Thus, under the assumption that A and H are the addicted compartments and abiding by the parameter restrictions stated above, the assumptions of the Next Generation Method are satisfied for matrices $\mathscr{F}$ and $\mathscr{V}$ formulated here:

$$\mathscr{F} = \begin{pmatrix} \sigma R\frac{A}{A+H+\omega} + \beta_A SA \\ \theta_1 SH + \theta_2 PH + \sigma R\frac{H}{A+H+\omega} \end{pmatrix}$$

$$\mathscr{V} = \begin{pmatrix} \zeta A + \theta_3 AH + (\mu + \mu_A)A \\ -\theta_3 AH + \nu H + (\mu + \mu_H)H \end{pmatrix}.$$

These assumptions include the following:

- $\mathscr{F}_i(0, y) = 0$ and $\mathscr{V}_i(0, y) = 0$, $\forall y \geq 0$, $i = 1, 2$, which ensures that new addictions arise only from interacting with those currently addicted, and there is no immigration into the addicted compartments; these guarantee that the population free of addiction remains that way.
- $\mathscr{F}_i(x, y) \geq 0$, $\forall x, y \geq 0$, $i = 1, 2$ since these represent new addictions.
- $\mathscr{V}_i(x, y) \leq 0$ whenever $x_i = 0, i = 1, 2$ since there must be inflow only when the respective compartment is empty.
- $\sum_{i=1}^{2} \mathscr{V}_i(x, y) \geq 0$, $\forall x, y \geq 0$ since this represents the total outflow from all addicted compartments.
- The addiction-free system, $\frac{\mathrm{d}S}{\mathrm{d}t}\Big|_{A,H=0}$, $\frac{\mathrm{d}P}{\mathrm{d}t}\Big|_{A,H=0}$, and $\frac{\mathrm{d}R}{\mathrm{d}t}\Big|_{A,H=0}$ has a unique equilibrium, $(\frac{\varepsilon+\mu}{\alpha+\varepsilon+\mu}, \frac{\alpha}{\alpha+\varepsilon+\mu}, 0)$ that is asymptotically stable.

Taking $F = \frac{\partial \mathscr{F}_i}{\partial x_j}(0, y_0)$ and $V = \frac{\partial \mathscr{V}_i}{\partial x_j}(0, y_0)$, $i, j = 1, 2$, where $(0, y_0) = (\frac{\varepsilon+\mu}{\alpha+\varepsilon+\mu}, \frac{\alpha}{\alpha+\varepsilon+\mu}, 0, 0, 0)$ is the addiction-free equilibrium, we calculated the following [76]:

$$F = \begin{pmatrix} \beta_A\frac{\varepsilon+\mu}{\alpha+\varepsilon+\mu} & 0 \\ 0 & \theta_1\frac{\varepsilon+\mu}{\alpha+\varepsilon+\mu} + \theta_2\frac{\alpha}{\alpha+\varepsilon+\mu} \end{pmatrix}$$

$$V = \begin{pmatrix} \zeta + \mu + \mu_A & 0 \\ 0 & \nu + \mu + \mu_H \end{pmatrix}.$$

The eigenvalues of FV^{-1} are calculated to be:

$$\sigma(FV^{-1}) = \{\frac{\beta_A(\varepsilon+\mu)}{(\alpha+\varepsilon+\mu)(\zeta+\mu+\mu_A)}, \frac{\theta_1(\varepsilon+\mu)+\theta_2\alpha}{(\alpha+\varepsilon+\mu)(\nu+\mu+\mu_H)}\}$$

$\mathscr{R}_0$ may then be determined as the spectral radius of FV^{-1}, in which the (i, j) entry is the expected number of secondary addictions in compartment i produced by individuals initially in compartment j :

$$\mathscr{R}_0 = \text{WHICHEVER IS LARGEST WHEN KNOW VALUES!}$$

Include proof of non-negative IC implies non-negative solutions?
Cannot solve explicitly for endemic equilibrium
What other analysis should be done?

Numerical Results (literature information and parameter estimation)

Tennessee background/why this state specifically
Tennessee specific information/start to talk about Tennessee
The U.S. opioid prescription rate per capita from 2006-2017 was at its peak in 2012 with a rate of 81.3 prescriptions per 100 individuals [19]. Tennessee has been consistently above that number for this entire time period with the following rates for years 2006-2017: 124.8, 128.8, 132.9, 138.4, 140.0, 138.5, 136.1, 127.1, 121.3, 114.9, 107.5, and 94.4, respectively [16]. From it's peak in Quarter 3 of 2014 to Quarter 4 of 2018, the number of opioid prescribed individuals in the state decreased by 28% [53]. There was a 300% increase from 2013 to 2016 of heroin overdose deaths, and in the same time period over a 450% increase in deaths involving fentanyl, mostly from illicitly manufactured fentanyl. From 2013-2017, there was over an 800% increase in overdose deaths involving fentanyl [54]. Overall, opioid overdose deaths increased from 11.0 to 18.1 per 100,00 individuals from 2012 to 2016. In 2016, 80% of opioid overdose deaths involved multiple drugs, up from 63% in 2012. We note again that 1 in 5 overdose deaths have multiple drugs present; therefore it can be difficult to know the actual cause of death [13]. Given this information, we note that the increase in heroin deaths could partly be attributed to the lacing of the drug with fentanyl, but given that there is a separate category for fentanyl as the cause of death, it seems it is not the only reason. Due to these alarming statistics within the state of Tennessee, we apply our model specifically to this state, as we believe facing this problem on a smaller scale with less heterogeneity than at the national level could be informative.

Data used within code
Applying model to Tennessee population We apply our model to the Tennessee population specifically in order to analyze the opioid epidemic on a smaller scale than the national level. Although there is still heterogeneity across Tennessee, it is lower than the amount one would find on a national scale.

Leave data table/information here or put in appendix?
Below we present a data table consisting of estimates of the number of individuals in Tennessee in various categories for the years 2013-2018 found either in literature or that we estimated; explanations of each of the categories follows.

Table 1: Number of individuals in each category, 2013-2018

	2013	2014	2015	2016	2017	2018
Total population	6,493,432	6,540,826	6,590,808	6,645,011	6,708,794	6,770,010
Population 12 and older	*5,519,417*	*5,559,702*	*5,602,187*	*5,648,259*	*5,702,475*	**5,754,509**
Heroin users	-	14,000	14,000	19,000	-	-
Heroin addicts	-	**7,560**	**7,560**	**10,260**	-	-
Rx opioid addicts (includes heroin addicts)	-	-	48,000	42,000	-	-
Rx opioid addicts (excludes heroin addicts)	*43,418*	*42,928*	**42,816**	**37,464**	*34,805*	-
Prescribed opioid users (includes Rx addicts)	1,845,144	1,824,342	1,819,581	1,761,363	1,636,374	-
Prescribed opioid users (excludes Rx addicts)	*1,825,910*	*1,805,325*	**1,800,614**	**1,744,766**	*1,620,955*	-
Prescription opioid overdose deaths	-	-	679	-	-	-
Heroin/fentanyl overdose deaths	-	-	374	-	-	-
Prescription opioid treatment admissions	4,485	4,530	4,326	-	-	-
Heroin treatment admissions	555	743	1,083	-	-	-

Explanations of the estimates/where they come from in literature/assumptions made

We note that *italicized* values are numbers that we estimated by extrapolating from a different year, whereas **bolded** values are numbers that we estimated by information within the same year. All other numbers are actual reported data and numbers in blue are data used directly in parameter estimation. Some values are used in Appendix A for parameter calculations rather than directly in the parameter estimation process–may change depending on if use those calculations at all/otherwise, may get rid of treatment admission data, for example.

The first row provides the **total population estimates in Tennessee** each year as of July 1 of the corresponding year [69]. However, since the remainder of the data we use is specific to individuals 12 and older, we estimate the number in this age group. There were an estimated 1,073,214 individuals in Tennessee in 2018 aged 12 and under. (Note: we could not find the estimate for this age group for the years 2013-2017, so this is the best estimate we have for this age group). To figure out those who are exactly 12 years old, we take 1/8th of the individuals that are in the age group 5-12 (an estimated 665,401 individuals), which is approximately 83,175 individuals [25]. Thus, an estimated (1073214-83175=) 990,039 individuals are *under* the age of 12 in Tennessee. Given the total population estimate for 2018 being 6,770,010 from row 1, this means that approximately 15% of the population is under the age of 12. Since we do not see a reason for this percentage to be significantly different from year to year, we assume that this percentage is constant throughout the time period we are looking at. Then, we are able to consider the **Tennessee population estimates for individuals 12 and older** in order to align with the rest of the data that is in this age range by taking off 15% of the total population estimates for each year; this is shown in the second row.

The 2014/2015 average number of individuals 12 and older with "Past Year Heroin Use" (**heroin/fentanyl addicts**) was 14,000, the 2015/2016 average number was 14,000, and the 2016/2017 average number was 19,000 as show in row 3 of the table [59, 60, 61]. This number includes those who may have used heroin once or twice in the past year (i.e. tried it but did not become a habit of any sort); however, it is estimated that 54% of heroin users are dependent on the drug, which gives the resulting **bold** estimates in row 4 of the table [47]. In addition, the number of heroin users does not include

fentanyl users explicitly, but we are under the assumption that those who take fentanyl are a subset of those who use heroin, and therefore, would mostly be included in these numbers. We admit the values may be slightly too low, for the cases of individuals who do fentanyl and not heroin, but data has not been found for fentanyl addicts only, and fentanyl is very often found mixed with heroin, as mentioned before. Therefore, we are working under the assumption that it would be a negligible population that is addicted to fentanyl without using heroin. Again, for these estimates, we choose the lower of the two years to place the data points; for example, 10,260 is placed in the year 2016. The values **bolded** in Table 1 are because numbers were based on the data of individuals from the same year, and did not rely on any extrapolated data from a different year.

The **total number of individuals taking prescription opioids for pain (prescribed)** is given in row 5 [52]. Although this number does not explicitly state it is for individuals 12 and older, we assume it is since it comes from the Tennessee Department of Health; if it does include individuals under 12, we assume that number is negligible.

The 2015/2016 average number of individuals 12 and older with "Pain Reliever Use Disorder" (**prescription opioid addicts**) is 48,000 and the 2016/2017 average number was 42,000 [60, 61]. For these estimates, we choose the lower of the two years to place the data points; for example, for the 2015/2016 average, 48,000 is placed in the year 2015. May need to fill in more details about specific data such as collection process, self-reported probably equates to underreported, etc. We note that their definition of pain reliever use disorder includes those who meet the American Psychiatric Association criteria for dependence or abuse. Here, opioid dependence is classified as having "signs and symptoms that reflect compulsive, prolonged self-administration of opioid substances that are used for no legitimate medical purpose or...are used in doses that are greatly in excess of the amount needed for pain relief...regular patterns of compulsive drug use that daily activities are typically planned around obtaining and administering opioids." This definition falls under our definition of opioid addiction. Opioid abuse, on the other hand, they consider to be less severe than dependence, and would not lead to the development of withdrawal symptoms. This latter definition does not fall under our characterization of addiction, but we make a note of this to say that this estimate for those with a pain reliever use disorder may be overestimated for what we are concerned with, but is an acceptable approximation [5]. In addition, we assume very few, if any, individuals are addicted to opioids outside of prescription opioids, but even if they are, we assume they are taking prescription opioids in some capacity, so we take pain reliever use disorder to include those with other non-prescription opioid addiction. We also remind the reader that these numbers include both individuals who are personally prescribed opioids or may obtain them illicitly. Finally, we note that those who are addicted to opioids are considered strictly in the A class, as individuals in R are not considered addicted in our model.

In 2010, on the national level it was estimated that 14% of individuals who abused or were dependent on pain medications also *used* heroin [47]. It was right around this year that the number of overdose deaths due to heroin increased and continued to increase until 2016 [52, 13]. Although fentanyl began being laced with heroin in this time frame, the overdose deaths due to fentanyl were recorded separately and heroin overdose deaths were still increasing despite that; therefore, it seems likely that an increase in

overdose deaths would equate to a larger number of heroin addicts in each of those years. Therefore, we assume a higher percentage that 20% of prescription opioid addicts *used* heroin each of the years 2013-2017. (Although this may not be exact or accurate for all of these years, it is a reasonable starting point to be able to work with the data we do have). However, only 54% of heroin users are *addicts*, which means that 10.8% of prescription opioid addicts are also heroin addicts (.54*.2=.108) [47]. We subtract these heroin addicts from the prescription opioid addict category each year; this results in the non-heroin addicted prescription opioid addicts for years 2015 and 2016. From 2013 to 2017, the number of prescribed opioid users was decreasing, likely due to more awareness of the problem as suggested in [17] which resulted in a decreasing prescribing rate [53]; thus, we expect the number of addicts to also be decreasing in that time period, especially due to the movement of individuals to heroin use. For 2015, we see there were 42,816 (non-heroin addicted) prescription opioid addicts compared to 1,819,581 prescribed opioid users, which is an approximate ratio of 1:42.5; thus, we use the exact ratio of addicts to prescribed opioids users for 2013 and 2014, as well, to estimate the number of opioid addicts (these values are in *italics* in Table 1 since they are extrapolated from a different year). Although the numbers are most likely higher than this, this is an estimate. We apply a similar idea for the year 2017, utilizing data from 2016 that there are 37,464 (non-heroin addicted) prescription opioid addicts out of 1,761,363 prescription users, which is an approximate ratio of 1:47 (also *italicized* in Table 1), but we use the exact ratio to calculate.

The total number of prescribed opioid users each year, however, includes individuals addicted to their prescriptions. In a 2015 study done among adults with prescription opioid use disorder, 44.3% of them had obtained prescription opioids for their most recent episode of misuse from 1 or more physicians [33]. We make the assumptions that individuals who are addicted to heroin are not using *prescribed* opioids, since they are more expensive and provide less of a high; although this study consisted of individuals with prescription opioid use disorder, regardless of their heroin addiction status, we will extrapolate this percentage to those who are non-heroin addicted [51]. We recognize this percentage may be on the low side (i.e. if heroin addicts were taken out of the study, this percentage may be higher since those non-heroin addicted would possibly obtain more from a physician source), but we take this as our best estimate. Therefore, we assume that 44.3 out of 100 non-heroin addicted prescription opioid addicts are personally prescribed opioids and subtract 44.3% of the number of non-heroin prescription opioid addicts in each year from the prescribed opioid class in the corresponding year to obtain the number of non-addicted prescribed opioid users for 2013-2017.

We use data on the number of prescription opioid overdose deaths which include natural, semi-synthetic, and synthetic opioids; however, we subtract out the number of fentanyl overdoses (fentanyl is classified as a synthetic prescription opioid), since those overdoses are counted for in their own category, listed below. This results in (848-169=) 679 as the **total number of prescription opioid overdose deaths** for 2015 [53]. Although this number does not explicitly state it is for individuals 12 and older, we assume it is since it comes from the Tennessee Department of Health; if it does include individuals under 12, we assume that number is negligible.

We add together the heroin and fentanyl overdoses for the state of Tennessee to obtain the **total number of heroin and fentanyl overdoses** in 2015 to be (205+169=) 374 [53]. We consider all fentanyl overdoses coming from the heroin/fentanyl addicted class (rather than split between the A and H classes) since reports suggest that most fentanyl overdoses come from illicitly manufactured fentanyl as discussed before [18, 53, 13, 3, 11]. Although this number does not explicitly state it is for individuals 12 and older, we assume it is since it comes from the Tennessee Department of Health; if it does include individuals under 12, we assume that number is negligible.

For Tennessee individuals 12 and older, **the number of treatment admissions for non-heroin opiates/synthetics** as the primary substance of abuse to facilities that receive state/public funding (generally referring to funding by the state substance abuse agency) is found in row 11 of Table 1 [26]. Here, we take non-heroin opiates/synthetics to mean prescription opioids. We are under the assumption that if one were addicted to heroin in addition to prescription opioids, their heroin problem would be the primary reason for going to treatment and would be included in the following numbers. Finally, row 12 of Table 1 gives the **number of treatment admissions for heroin** as the primary substance of abuse to facilities that receive state/public funding (generally referring to funding by the state substance abuse agency) for Tennessee individuals 12 and older [26]. Again, these numbers do not include fentanyl users explicitly, but we are under the assumption that those who take fentanyl are a subset of those who use heroin, and therefore, would mostly be included in these numbers. We admit the values may be slightly too low, for the cases of individuals who do go to treatment with the primary substance of abuse being fentanyl, but there is not data available for those numbers currently.

Table 2: Individuals Prescribed Opioids Quarterly, 2013-2018

Quarter	Prescribed opioid users (includes Rx addicts)	Prescribed opioid users (excludes Rx addicts)
2013 Quarter 1	856,000	**847,077**
2013 Quarter 2	870,000	**860,931**
2013 Quarter 3	874,000	**864,889**
2013 Quarter 4	856,000	**847,077**
2014 Quarter 1	842,000	**833,223**
2014 Quarter 2	860,000	**851,035**
2014 Quarter 3	871,000	**861,921**
2014 Quarter 4	850,000	**841,140**
2015 Quarter 1	836,000	**827,285**
2015 Quarter 2	861,000	**852,025**
2015 Quarter 3	865,000	**855,983**
2015 Quarter 4	854,000	**845,098**
2016 Quarter 1	840,000	**832,085**
2016 Quarter 2	829,000	**821,189**
2016 Quarter 3	801,000	**793,453**
2016 Quarter 4	783,000	**775,622**
2017 Quarter 1	783,000	**775,622**
2017 Quarter 2	772,000	**764,726**
2017 Quarter 3	747,000	**739,961**
2017 Quarter 4	713,000	**706,282**
2018 Quarter 1	695,000	**688,502**
2018 Quarter 2	690,000	**683,722**
2018 Quarter 3	648,000	**641,942**
2018 Quarter 4	631,000	**625,162**

The Tennessee Department of Health also has quarterly estimates for the number of patients receiving opioids for pain by quarter from 2013-2018, as shown in the table above [53, 54]. In both reports, a graph is given without specific numbers, so we utilized the online tool Webdigitizer to give best estimates to the values plotted. However, these numbers again include those who are opioid addicted. To be able to calculate an estimate for the number of non-addicted prescribed opioid users, we need an estimate of the number of opioid addicts in each quarter. We calculate the ratio of prescribed opioid users each quarter compared to the entire year, and use this same ratio to calculate the number of prescription opioid addicts per quarter. (Although this may not be exact, it is a reasonable starting point to be able to work with the data we do have). For instance, in 2013 Quarter 1, there were 856,000 prescribed opioid users (includes addicts), which is approximately $1/46^{th}$ of the 1,845,144 prescribed opioid users (includes addicts) over the entire year. Therefore, we assume a similar ratio for (non-heroin addicted) opioid addicts, which gives an estimate of 20,142 prescription opioid addicts in 2013 Quarter 1. However, we care about approximately how many of these are using opioids that they are personally prescribed, which following similar calculations as before, is $.443 * 20142 = 8,923$ individuals; this number must be subtracted from 856,000 resulting in the estimated number of non-addicted prescribed opioid users in 2013 Quarter 1. We do this calculation for all quarters from 2013-2017. However, in 2018, we do not have data on the number of total prescription users for the whole year, so we extrapolate from 2017 information. There is a decreasing trend of (non-heroin addicted) opioid addicted

individuals from 2013-2017, so we assume that trend continues in 2018. Between quarters 1 and 2 of 2017, there is a decrease of 104 (non-heroin addicted) opioid addicted individuals; between quarters 2 and 3 of 2017 there is a decrease of 236; between quarters 3 and 4 there is a decrease of 320. Taking the average of these results in a 220 person decrease each quarter. Thus, taking the most recent number of 6718 (non-heroin addicted) opioid addicted individuals in 2017 Quarter 4, we subtract 220 which results in 6498 (non-heroin addicted) opioid addicted individuals for 2018 Quarter 1, 6278 in 2018 Quarter 2, 6058 in 2018 Quarter 3, and 5838 in 2018 Quarter 4. Therefore, these numbers are subracted from the number of individuals that are prescribed opioids in each 2018 quarter.

We acknowledge that many data points are only estimates since there is a nesting of the classes, but believe they are a good starting point for our purposes here. Appendix A contains calculations for μ, μ_A, and μ_H based on data in Table 1, as well as other parameter and initial condition calculations.

Parameter estimation process
Edit from/update from /combine with information from data_using_parameter_estimation file in heroin model multistart folder
How many details to give for paper? Put in anything needed for paper from MatLab_descriptions.pdf if applicable.

The age-adjusted death rate (μ) and overdose death rates (μ_A and μ_H) are calculated in Appendix A, and the results are shown here:

Parameter (rate)	Value Assumed	Units
μ	0.00868	$\frac{1}{\text{year}}$
μ_A	0.00870	$\frac{1}{\text{year}}$
μ_H	0.0507	$\frac{1}{\text{year}}$
ω	10^{-10}	dimensionless

In order to estimate the remaining parameters for our model, we utilized the ordinary least squares method and formulated an objective function to minimize, which consists of the squared differences between data and model simulations. The data utilized (shown in blue in Table 1) are the proportion of non-addicted prescription users (years 2013-2017), opioid addicts (years 2013-2017), and heroin/fentanyl addicts (years 2014-2016) out of the entire population in a given year. These represent the proportion of individuals in P at some point during each of the years 2013-2017, the proportion of individuals in A at some point during each of the years 2014-2015, and the proportion of individuals in H at some point during each of the years 2014-2016. From Table 2, we have the proportion of the population that is in P each quarter of the years 2013-2018. This results in a total of 37 data points.
Although we have an estimate for the total number of prescription opioid users and opioid addicts in 2013, we do not know these numbers at the start of 2013; similarly, we do not know this information for the other states. Therefore, we estimate the initial conditions using this process, as well. Thus, we estimate 17 inputs total (parameters and initial conditions combined, where m and b are both estimated for $\alpha = m \cdot t + b$).

Include these next couple of descriptions in paper or only in dissertation?
We simulate the proportions in each of these classes throughout the year in the following way. In order to count the proportion of individuals in P, A, or H at some point throughout a certain year, we need to count those who are in each of the classes AT ALL during the year, even if they leave or come back at some point. We note that we neglect higher order terms, i.e. people who go into the P class multiple times, since we can't keep track of individuals in model; the data we use is about total proportion of people who are in the class at some point throughout the year but they are kept track of and only counted once.

To get the output from the model of the proportion of non-addicted prescription opioid users in each year, we take the proportion of non-addicted prescription opioid users at the beginning of each of the years and add on the proportion of individuals that enter the P class at any point during the year. This latter part comes from integrating over those who enter the P class: $\int_0^t X'(t)dt = \int_0^t \alpha S(t)dt$ which is equal to $X(t) - X(0)$; here, we take $X(0) = 0$. For every year except 2013, a subtraction must be done since integrating gives the proportion from time 0 to time t, but we only want the proportion from time $t-1$ to time t (i.e. the new cases in a given year). Thus, the calculation is as follows for each year, with the last equation in each line what was calculated in the code (noting that our time step is years, but our linspace is broken into quarters of a year, so each entry represents the beginning of a quarter of a year):

2013: $P_0 + \int_0^1 \alpha S dt = y(1,2) + y(5,6) - y(1,6)$
2014: $y(5,2) + \int_1^2 \alpha S dt = y(5,2) + \int_0^2 \alpha S dt - \int_0^1 \alpha S dt = y(5,2) + y(9,6) - y(5,6)$
2015: $y(9,2) + \int_2^3 \alpha S dt = y(9,2) + \int_0^3 \alpha S dt - \int_0^2 \alpha S dt = y(9,2) + y(13,6) - y(9,6)$
2016: $y(13,2) + \int_3^4 \alpha S dt = y(13,2) + \int_0^4 \alpha S dt - \int_0^3 \alpha S dt = y(13,2) + y(17,6) - y(13,6)$
2017: $y(17,2) + \int_4^5 \alpha S dt = y(17,2) + \int_0^5 \alpha S dt - \int_0^4 \alpha S dt = y(17,2) + y(21,6) - y(17,6)$

We denote Data1= [1825910./5519417; 1805325./5559702; 1800614./5602187; 1744766./5648259; 1620955./5
as the vector of values that represents the total proportion of the population that enters the P class at some point during the years 2013-2017 and Estim1=

$y(1,2)+y(5,6)-y(1,6); y(5,2)+y(9,6)-y(5,6); y(9,2)+y(13,6)-y(9,6); ...y(13,2)+y(17,6)-y(13,6); y(17,$

represents the total proportion that the model simulates as entering the P class at some point during the years 2013-2017, as described above. The vector Diff1=Estim1-Data1 represents the difference in these values each of the years. In order to find the relative error we calculate

$$\sqrt{\sum_{i=1}^{5} \text{Diff1(i)}^2} / \sqrt{\sum_{i=1}^{5} \text{Data1(i)}^2}.$$

To get the output from the model of the proportion of (non-heroin addicted) opioid addicts in each of the years 2013-2017, we take the initial proportion of opioid addicts in each of these years and add the proportion of individuals that enter the A class at any point during the year 2014 or 2015. This latter part comes from integrating over those who enter the A class: $\int_0^t L'(t)dt = \int_0^t (\gamma P + \sigma R \frac{A}{A+H+\omega} + \beta_A SA + \beta_P SP)dt$ which is equal to $L(t) - L(0)$; here, we take $L(0) = 0$. Similar to above with the subtraction of integrals

to calculate for a specific year, we have:
2013: $y(1,3)+\int_0^1(\gamma P+\sigma R\frac{A}{A+H+\omega}+\beta_A SA+\beta_P SP)dt=y(1,3)+y(5,7)-y(1,7)$
2014: $y(5,3)+\int_1^2(\gamma P+\sigma R\frac{A}{A+H+\omega}+\beta_A SA+\beta_P SP)dt=y(5,3)+y(9,7)-y(5,7)$
2015: $y(9,3)+\int_2^3(\gamma P+\sigma R\frac{A}{A+H+\omega}+\beta_A SA+\beta_P SP)dt=y(9,3)+y(13,7)-y(9,7)$
2016: $y(13,3)+\int_3^4(\gamma P+\sigma R\frac{A}{A+H+\omega}+\beta_A SA+\beta_P SP)dt=y(13,3)+y(17,7)-y(13,7)$
2017: $y(17,3)+\int_4^5(\gamma P+\sigma R\frac{A}{A+H+\omega}+\beta_A SA+\beta_P SP)dt=y(17,3)+y(21,7)-y(17,7)$

Similar to above, Data2=[43418./5519417; 42928./5559702; 42816./5602187; 37464./5648259; 34805./5702475] and Estim2=

$$y(1,3)+y(5,7)-y(1,7); y(5,3)+y(9,7)-y(5,7); y(9,3)+y(13,7)-y(9,7); ...y(13,3)+y(17,7)-y(13,7); y(17,$$

represent the actual and simulated total proportion of individuals in A at some point during the years 2013-2017. Again, we have Diff2=Estim2-Data2 being the vector of differences in these values each of the years and the relative error is calculated by

$$\sqrt{\sum_{i=1}^{5}\text{Diff2(i)}^2}/\sqrt{\sum_{i=1}^{5}\text{Data2(i)}^2}.$$

To obtain the output from the model of the proportion of heroin/fentanyl addicts for each year 2014-2016, we take the initial proportion of heroin/fentanyl addicts in each of these years and add the proportion of individuals that enter the H class at any point during the year. This latter part comes from integrating over those who enter the H class: $\int_0^t M'(t)dt=\int_0^t(\theta_1 SH+\theta_2 PH+\theta_3 AH+\sigma R\frac{H}{A+H+\omega})dt$ which is equal to $M(t)-M(0)$; here, we take $M(0)=0$. Similar to above with the subtraction of integrals to calculate for a specific year, we have:
2014: $y(5,4)+\int_1^2(\theta_1 SH+\theta_2 PH+\theta_3 AH+\sigma R\frac{H}{A+H+\omega})dt=y(5,4)+y(9,8)-y(5,8)$
2015: $y(9,4)+\int_2^3(\theta_1 SH+\theta_2 PH+\theta_3 AH+\sigma R\frac{H}{A+H+\omega})dt=y(9,4)+y(13,8)-y(9,8)$
2016: $y(13,4)+\int_3^4(\theta_1 SH+\theta_2 PH+\theta_3 AH+\sigma R\frac{H}{A+H+\omega})dt=y(13,4)+y(17,8)-y(13,8)$

Data3=[7560./5559702; 7560./5602187; 10260./5648259] and Estim3=

$$y(5,4)+y(9,8)-y(5,8); y(9,4)+y(13,8)-y(9,8); y(13,4)+y(17,8)-y(13,8)$$

represent the actual and simulated total proportion of individuals in H at some point during the years 2014-2016, with Diff3=Estim3-Data3 being the vector representing the difference in these values each year. The relative error is calculated as

$$\sqrt{\sum_{i=1}^{3}\text{Diff3(i)}^2}/\sqrt{\sum_{i=1}^{3}\text{Data3(i)}^2}.$$

Finally, to obtain the output from the model of the proportion of prescription opioid addicts for each year 2014-2016, we take the initial proportion of prescription opioid users addicts in each quarter and add the proportion of individuals that enter the P class at any point during the quarter. Since we do not know the exact population in each quarter for Tennessee (only have yearly estimates), we keep the yearly population

as constant for each quarter, although we are aware that is not exact. This latter part comes from integrating over those who enter the P class: $\int_0^t X'(t)dt = \int_0^t \alpha S(t)dt$ which is equal to $X(t) - X(0)$; here, we take $X(0) = 0$. Similar to above, we will use subtraction of integrals to calculate for a specific quarter:
2013 Quarter 1: $y(1,2) + \int_0^{0.25} \alpha S dt = y(1,2) + y(2,6) - y(1,6)$
2013 Quarter 2: $y(2,2) + \int_{0.25}^{0.5} \alpha S dt = y(2,2) + \int_0^{.5} \alpha S dt - \int_0^{0.25} = y(2,2) + y(3,6) - y(2,6)$
2013 Quarter 3: $y(3,2) + \int_{0.5}^{0.75} \alpha S dt = y(3,2) + \int_0^{.75} \alpha S dt - \int_0^{0.5} \alpha S dt = y(3,2) + y(4,6) - y(3,6)$
2013 Quarter 4: $y(4,2) + \int_{0.75}^{1} \alpha S dt = y(4,2) + \int_0^{1} \alpha S dt - \int_0^{0.75} \alpha S dt = y(4,2) + y(5,6) - y(4,6)$
$\vdots$
2018 Quarter 4: $y(24,2) + \int_{5.75}^{6} \alpha S dt = y(24,2) + \int_0^{6} \alpha S dt - \int_0^{5.75} \alpha S dt = y(24,2) + y(25,6) - y(24,6)$

Data4=[847077./5519417; 860931./5519417; 864889./5519417; 847077./5519417;... 833223./5559702; 851035./5559702; 861921./5559702; 841140./5559702;... 827285./5602187; 852025./5602187; 855983./5602187; 845098./5602187;... 832085./5648259; 821189./5648259; 793453./5648259; 775622./5648259;... 775622./5702475; 764726./5702475; 739961./5702475; 706282./5702475;... 688502./5754509; 683722./5754509; 641942./5754509; 625162./5754509] and Estim4=y(1:24,2)+y(2:25,6)-y(1:24,6); represent the actual and simulated total proportion of individuals in P at some point during a quarter in the years 2013-2018, with Diff4=Estim4-Data4 being the vector representing the difference in these values each year. The relative error is calculated as

$$\sqrt{\sum_{i=1}^{24} \text{Diff4(i)}^2} / \sqrt{\sum_{i=1}^{24} \text{Data4(i)}^2}.$$

Since we wish to minimize the difference in all three of these data sets with the values that our model simulates, we add together their relative norms and set this as our objective function value to minimize. Thus our

$$\text{objective function value} =$$

$$\sqrt{\sum_{i=1}^{5} \text{Diff1(i)}^2} / \sqrt{\sum_{i=1}^{5} \text{Data1(i)}^2} + \sqrt{\sum_{i=1}^{5} \text{Diff2(i)}^2} / \sqrt{\sum_{i=1}^{5} \text{Data2(i)}^2} + \sqrt{\sum_{i=1}^{3} \text{Diff3(i)}^2} / \sqrt{\sum_{i=1}^{3} \text{Data3(i)}^2} + \sqrt{\sum_{i=1}^{24}$$

Note that we take the relative error in each of these due to the differences in magnitude of the data.
We use the Global Optimization Toolbox in MATLAB, specifically utilizing the MultiStart algorithm and fmincon local solver. Since the global minimum is of interest, we use fill in number starting points as this is a local solver. We give lower bounds of 0.00001 for all of the parameters and an upper bound of 2 for all of the parameters except ε with an upper bound of 4 since this parameter can easily be greater than 1 (i.e. in a given year, a prescription user may end prescription use more than once). We run our model from 2013-2018, keeping a short time frame so that dynamics are relatively the same in the time period with the time step in years.

Although we do not know any other exact rate values from literature, we use data from Table 1 to calculate rough estimates for β_A, β_P, ν, ζ, and the initial conditions, P_0, A_0, H_0, and R_0 (found in Appendix A) in order to guide our knowledge of the range of values the true values of these parameters may lie. May change, depending on if use info for all of these parameters/IC or not; include relationships of theta values here or in both places?.

Thus, we have the following ranges for our parameters:

parameters estimating:	$[m$	β_A	β_P	θ_1	ε	γ	θ_2	$\sigma]$
lower bounds:	$[-0.1$	0.00001	0.000001	0.00001	0.8	0.001	0.0001	0.0001]
upper bounds:	$[\ 0.1$	0.01	0.01	0.001	8	0.1	2	1],

parameters estimating:	$[\zeta$	θ_3	ν	b	P_0	A_0	H_0	$R_0]$
lower bounds:	[0.0001	0.001	0.0001	0.1	0.0001	0.00001	0.00001	0.00001]
upper bounds:	$[\ 0.5$	4	0.1	0.8	0.5	0.1	0.1	0.1].

We choose these realistic bounds for the following reasons:
-0.1≤m≤ 0.1: we assume that since α will be a value less than 1 based on estimate in [7], so it's slope will not be very large in absolute value
$0.00001 \leq \beta_A \leq 0.01$: based on preliminary calculations in Appendix A
$0.000001 \leq \beta_P \leq 0.01$: based on preliminary calculations in Appendix A
$0.00001 \leq \theta_1 \leq 0.001$: chosen intuitively that a susceptible individual interacting with a heroin user would have less than a 0.1 probability of transitioning to the heroin class
$0.8 \leq \varepsilon \leq 8$: estimate from [7]
$0.001 \leq \gamma \leq 0.1$: estimate based on value in [7]
$0.0001 \leq \theta_2 \leq 2$: chosen intuitively that a prescription opioid user interacting with a heroin user would have a larger probability of transitioning to the heroin class than that of a susceptible individual (see *) [46]
$0.0001 \leq \sigma \leq 1$: unknown, chosen intuitively for relapses that could occur from a stably recovered state
$0.0001 \leq \zeta \leq 0.5$: unknown, wide bounds
$0.001 \leq \theta_3 \leq 4$: chosen intuitively that an opioid addict interacting with a heroin user would have a much larger probability of transitioning to the heroin class than that of a susceptible individual (see *) [46]
$0.0001 \leq \nu \leq 0.1$: unknown, wide bounds
$0.01 \leq b \leq 0.8$: estimated based on value of α in [7]
$0.0001 \leq P_0 \leq 0.5$: assume small but no greater than 50% of the population
$0.00001 \leq A_0 \leq 0.1$: assume small but no greater than 10% of the population
$0.00001 \leq H_0 \leq 0.1$: assume small but no greater than 10% of the population
$0.00001 \leq R_0 \leq 0.1$: assume small but no greater than 10% of the population

*We consider a national study of individuals 12 and older to establish a general relationship among these three rates. For a national study consisting of 609,000 participants, "the recent heroin incidence rate was 19 times higher among those who reported prior nonmedical pain reliever (NMPR) use (0.39%) than among those who did not report NMPR use (0.02%) [46]. NMPR use can occur within the prescription class (i.e. from misuse that's not considered addiction), or in the addiction class. Thus, we will extrapolate this information to say that the rate that prescription opioid users and opioid addicts move to

heroin use is at least 19 times greater than the rate at which susceptibles move to heroin use (i.e. $\theta_2 + \theta_3 > 19\theta_1$), where both θ_2 and θ_3 are greater than θ_1.
The following table displays the 17 inputs that were estimated with this process, along with their resulting estimated values. The objective function value was equal to 0.1609.

Table 3: Parameter Estimation Results (alpha linear)

Input	Estimated Value	Units
m	-0.0156	$\frac{1}{\text{year}}$
b	0.303	$\frac{1}{\text{year}}$
α	[0.303, 0.287, 0.272, 0.256, 0.240, 0.225, 0.209]	$\frac{1}{\text{year}}$
β_A	0.00235	$\frac{1}{\text{year}}$
β_P	0.000141	$\frac{1}{\text{year}}$
θ_1	0.000507	$\frac{1}{\text{year}}$
ε	2.54	$\frac{1}{\text{year}}$
γ	0.00115	$\frac{1}{\text{year}}$
θ_2	0.0370	$\frac{1}{\text{year}}$
σ	0.0284	$\frac{1}{\text{year}}$
ζ	0.265	$\frac{1}{\text{year}}$
θ_3	3.51	$\frac{1}{\text{year}}$
ν	0.00657	$\frac{1}{\text{year}}$
P_0	0.0835	dimensionless
A_0	0.00671	dimensionless
H_0	0.000874	dimensionless
R_0	0.0509	dimensionless
S_0	0.858016	dimensionless

Below are the fits of our model simulations to data.

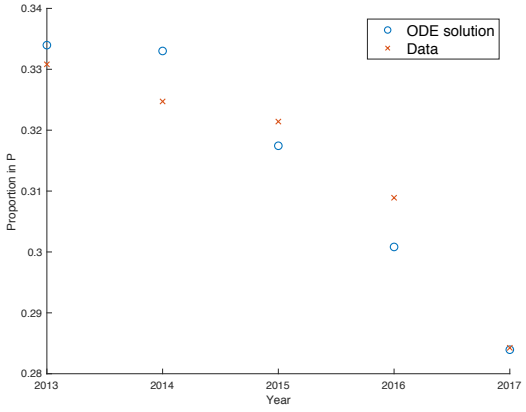


Figure 2: Model simulation fit to yearly prescription opioid user data

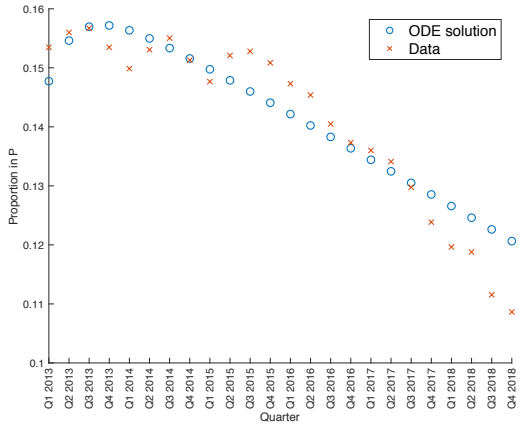


Figure 3: Model simulation fit to quarterly prescription opioid user data

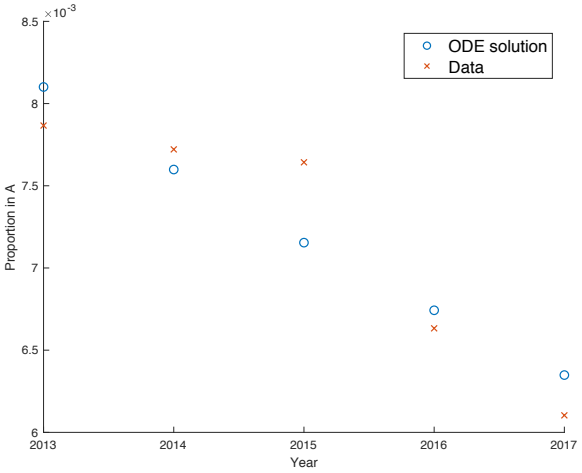


Figure 4: Model simulation fit to yearly prescription opioid addict data

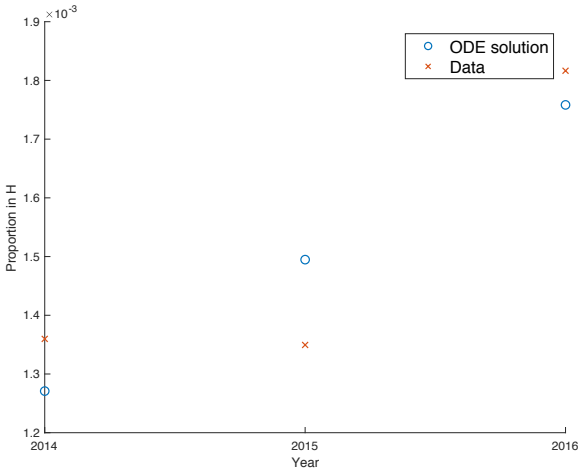


Figure 5: Model simulation fit to yearly heroin/fentanyl addict data

The parameters from Table 3 result in the following solution curves of each of the classes from 2013 through the end of 2018:

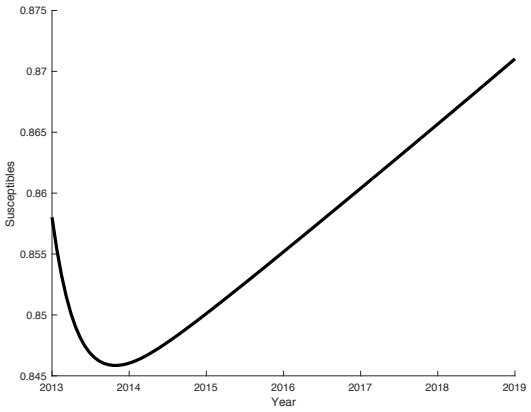


Figure 6: Numerical simulation for susceptible class

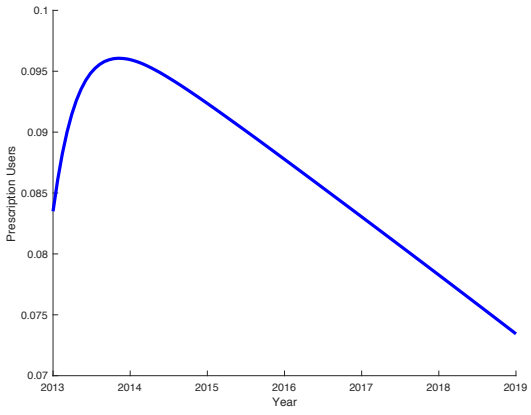


Figure 7: Numerical simulation for prescription opioid user class

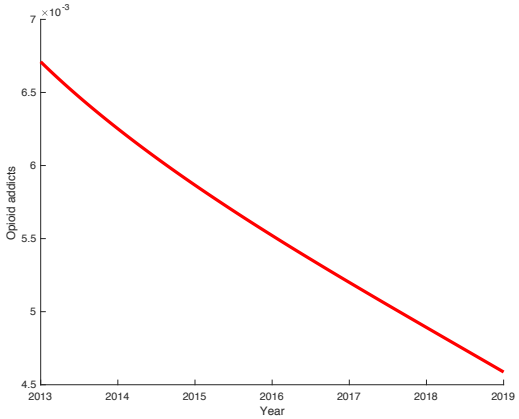


Figure 8: Numerical simulation for prescription opioid addict class

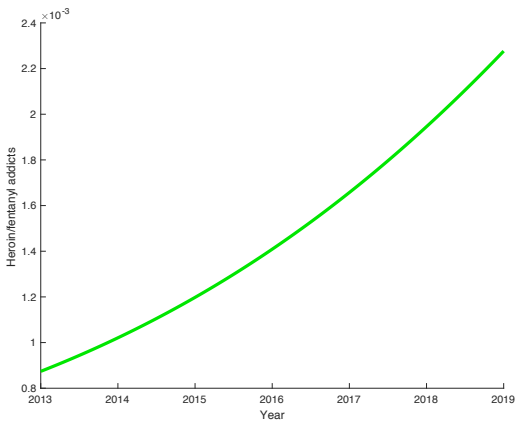


Figure 9: Numerical simulation for heroin addict class

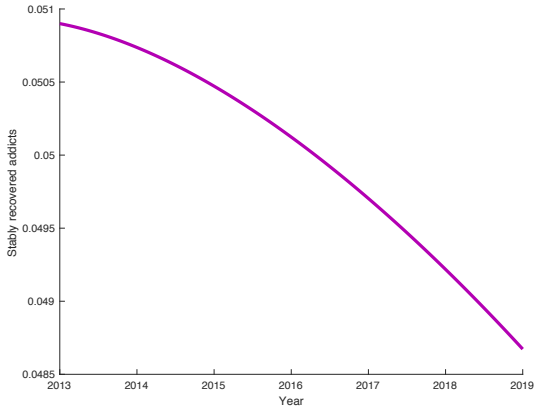


Figure 10: Numerical simulation for stably recovered class

In order to better capture the dynamics observed in the prescription opioid user data in which there is an apparent change in prescribing behavior at the end of 2015/beginning of 2016, we make alpha piecewise linear. We chose the switching point to be Quarter 2 of 2016, as the "Tennessee Prescription Safety Act of 2016" was made effective on April 27, 2016 in which the highlights can be summarized in this way: fill in from [67]
Making alpha continuous adds only one more parameter to be estimated. The ranges on parameters are the same as before with the only addition being the slope c of α after Quarter 2 of 2016 ranging between -0.1 and 0.1, where

$$\alpha(x) = \begin{cases} m \cdot t + b \text{ before Quarter 2 2016 } (t \leq 3.25) \\ m(3.25) + b + c(t - 3.25) \text{ after Quarter 2 2016 } (t > 3.25) \end{cases}$$

Figure out why works in that form
The results are given here:
The following table displays the 18 inputs that were estimated with this process, along with their resulting estimated values. The objective function value (using rounded parameters found in Table 4) is fval=0.1279.

Table 4: Parameter Estimation Results (alpha piecewise linear)

Input	Estimated Value	Units
m	-0.00483	$\frac{1}{\text{year}}$
b	0.283	$\frac{1}{\text{year}}$
c	-0.0313	$\frac{1}{\text{year}}$
α	[0.283, 0.278, 0.273, 0.269, 0.244, 0.213, 0.181]	$\frac{1}{\text{year}}$
β_A	0.0044	$\frac{1}{\text{year}}$
β_P	0.000469	$\frac{1}{\text{year}}$
θ_1	0.000502	$\frac{1}{\text{year}}$
ε	2.49	$\frac{1}{\text{year}}$
γ	0.00146	$\frac{1}{\text{year}}$
θ_2	0.148	$\frac{1}{\text{year}}$
σ	0.0283	$\frac{1}{\text{year}}$
ζ	0.318	$\frac{1}{\text{year}}$
θ_3	2.38	$\frac{1}{\text{year}}$
ν	0.0482	$\frac{1}{\text{year}}$
P_0	0.095	dimensionless
A_0	0.00647	dimensionless
H_0	0.000843	dimensionless
R_0	0.0584	dimensionless
S_0	0.8393	dimensionless

Below are the fits of our model simulations to data.

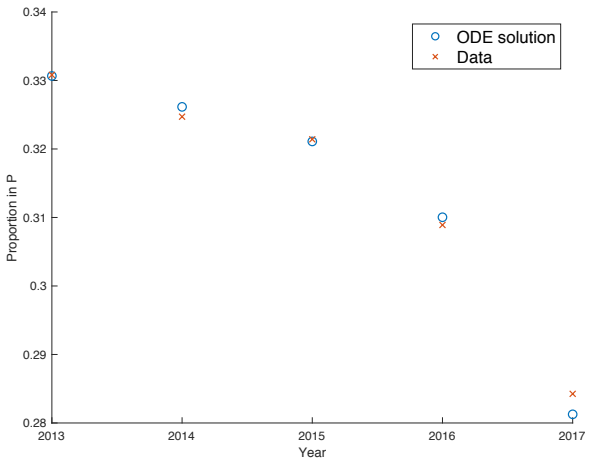


Figure 11: Model simulation fit to yearly prescription opioid user data

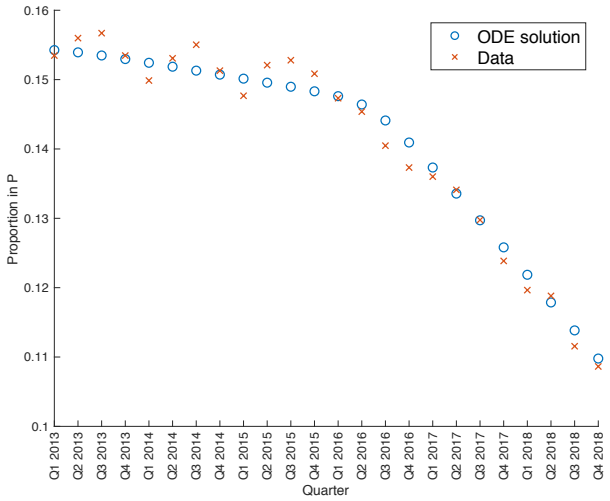


Figure 12: Model simulation fit to quarterly prescription opioid user data

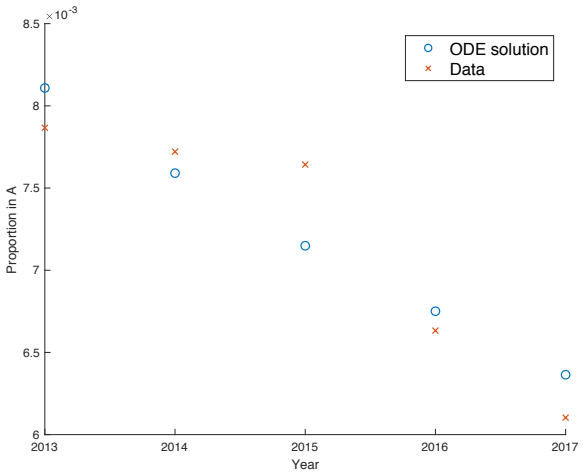


Figure 13: Model simulation fit to yearly prescription opioid addict data

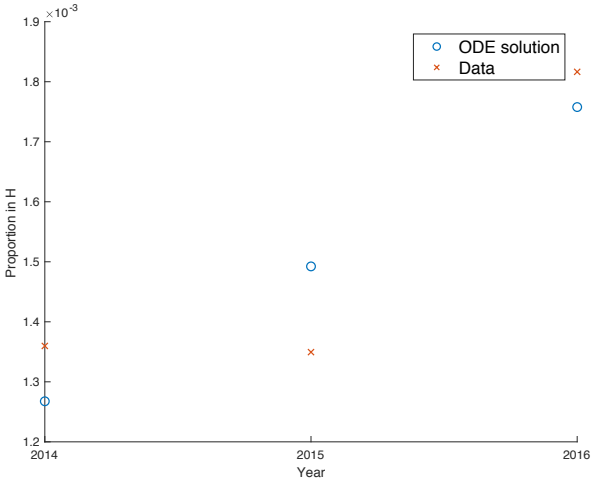


Figure 14: Model simulation fit to yearly heroin/fentanyl addict data

The parameters from Table 4 result in the following solution curves of each class from 2013 through the end of 2018:

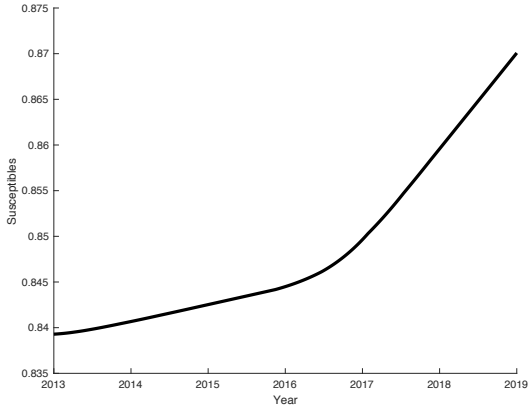


Figure 15: Numerical simulation for susceptible class

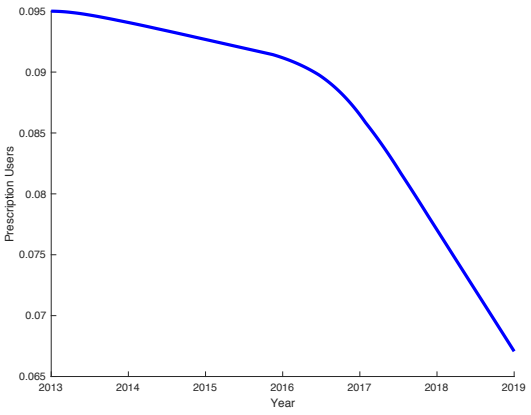


Figure 16: Numerical simulation for prescription opioid user class

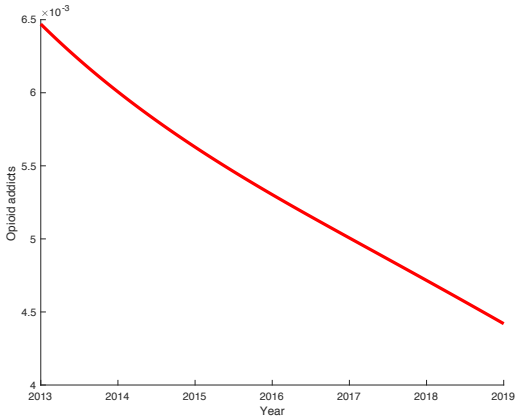


Figure 17: Numerical simulation for prescription opioid addict class

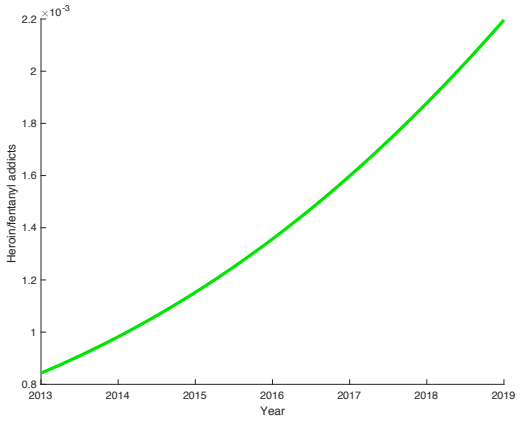


Figure 18: Numerical simulation for heroin addict class

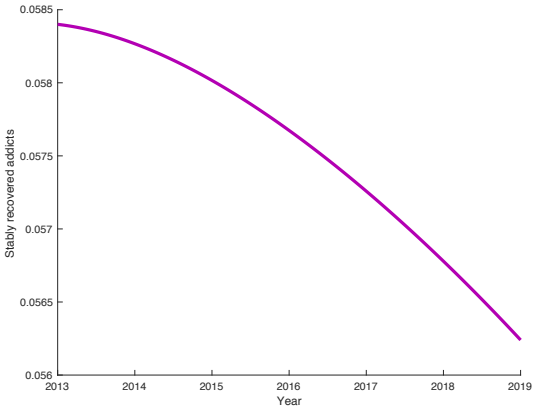


Figure 19: Numerical simulation for stably recovered class

We use AIC (Akaike's Information Criterion) in order to compare the fit of our model to data in both the alpha linear case and alpha piecewise linear case [45]. The AIC score balances the change in the fit of the model to data with the change in the number of parameters being estimated. The idea is to determine whether the model fits the data better because of the addition of one more parameter or because it actually is a better fit, i.e. is it a better fit considering we add one more parameter to estimate? The score is meaningless by itself and must be used in the context of comparing two scores. The AIC score is the sum of the lack of fit and the complexity of the model and is given by:

$$\text{AIC} = N \ln\left(\frac{SS}{N}\right) + 2K$$

where N is the number of data points the model is fitting to, SS is the sum of squares of the differences between model simulated points and data points, and K is the number of parameters we estimate (with non-linear least squares in our case) plus one since the value of SS is also being estimated. In our case,

$$SS = \sum_{i=1}^{5} \text{Diff1(i)}^2 + \sum_{i=1}^{5} \text{Diff2(i)}^2 + \sum_{i=1}^{3} \text{Diff3(i)}^2 + \sum_{i=1}^{24} \text{Diff4(i)}^2.$$

In our model, we have N=37 data points; for the alpha linear case, $K = 17 + 1 = 18$ and for the alpha piecewise linear case, $K = 18 + 1 = 19$. Since our sample size N=37 is not very large in general and in particular, since K is either 49% of 51% of this value (significantly smaller), it is recommended to use the corrected AIC scores for small sample sizes (denoted AIC_c). Here,

$$\text{AIC}_c = N \ln\left(\frac{SS}{N}\right) + 2K + \frac{2K(K+1)}{N-K-1}.$$

Note that if N were large, the denominator in this last fraction would be much larger than the numerator and therefore, the corrective term would be very small and therefore not necessary.
In the alpha linear case,

$$\text{AIC}_c = 37 \ln\left(\frac{8.0617e-04}{37}\right) + 2(18) + \frac{2(18)(18+1)}{37-18-1} = -323.1629$$

and in the alpha piecewise linear case,

$$\text{AIC}_c = 37\ln\left(\frac{1.2961e-04}{37}\right) + 2(18) + \frac{2(18)(18+1)}{37-18-1} = -382.0855.$$

The lower the AIC score, the better the model fits to the data. We see here that the alpha piecewise linear case is a better fit since it is the lower of the two AIC numbers. Another way to see this is to subtract the two values, letting AIC_{cP} represent the the alpha piecewise linear case and AIC_{cL} represent the alpha linear case:

$$\begin{aligned}
\Delta\text{AIC}_c &= \text{AIC}_{cP} - \text{AIC}_{cL} \\
&= N(\ln(SS_P) - \ln(SS_L)) + 2(K_P - K_L) + \frac{2K_P(K_P+1)}{N-K_P-1} - \frac{2K_L(K_L+1)}{N-K_L-1} \\
&= 37((\ln(1.2961e-04) - \ln(8.0617e-04)) + 2(1) + \frac{2(19)(19+1)}{37-19-1} - \frac{2(18)(18+1)}{37-18-1} \\
&\approx -58.92
\end{aligned}$$

We observe that $\ln(1.2961e-04) - \ln(8.0617e-04)$ will always be negative (adding an additional parameter will reduce the sum of squares value and rewritten as $\ln\left(\frac{1.2961e-04}{8.0617e-04}\right)$, the argument will always be less than 1) and the remaining terms deal with the difference of adding one more parameter, which will always be positive. In this case, however, these positive terms added on is not enough to compensate for the first negative term, and the net result is negative; this means that the difference of the sum of squares values is better than expected from the addition of one estimated parameter.

Since the AIC scores are relatively far apart, the alpha piecewise linear model seems to be the better choice out of the two. To support this choice, the probability that the alpha piecewise linear model is the better of the two can be given by the following calculation:

$$\begin{aligned}
\text{probability} &= \frac{e^{-0.5(\text{AIC}_{cP}-\text{AIC}_{cL})}}{1+e^{-0.5(\text{AIC}_{cP}-\text{AIC}_{cL})}} \\
&= \frac{e^{-0.5(-58.92)}}{1+e^{-0.5(-58.92)}} \\
&\approx 1.0.
\end{aligned}$$

This means there is a 100% chance that the alpha piecewise linear model is a better choice than the alpha linear model regarding fit to the data with the additional parameter being estimated. (Note that when using $\text{AIC}_{cL} - \text{AIC}_{cP} = 58.92$, the probability that alpha linear is better than alpha piecewise is 1.6057745e-13, which rounds to 0).

The evidence ratio gives information on how many more times likely the alpha piecewise linear model is correct compared to the alpha linear model. Since our probability is 1 above, we expect this ratio to be large. It is defined as:

$$\begin{aligned}
\text{evidence ratio} &= \frac{\text{probability alpha piecewise linear model is correct}}{\text{probability alpha linear model is correct}} \\
&= \frac{\frac{e^{-0.5(-58.92)}}{1+e^{-0.5(-58.92)}}}{\frac{e^{-0.5(58.92)}}{1+e^{-0.5(58.92)}}}
\end{aligned}$$

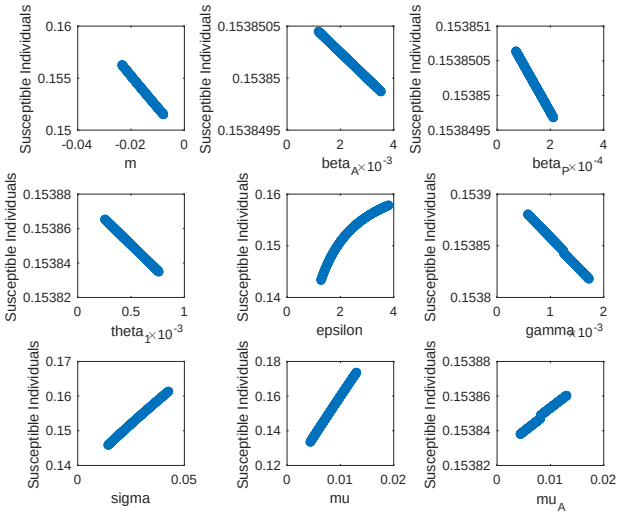
$$= \frac{1}{e^{-.5(58.92)}}$$
$$= 6.22e + 12,$$

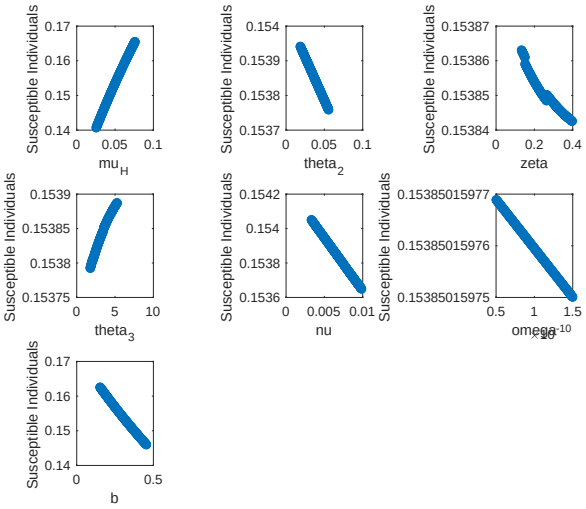
which provides additional justification that the alpha piecewise linear model is more accurate than the alpha linear model.

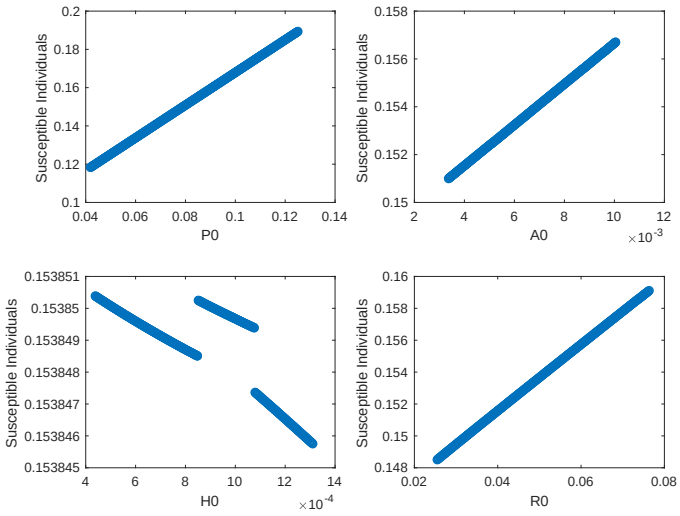
Later: throw out everything 2016 and on since there seems to be a change right at 2016? Maybe make alpha piecewise where it's constant until 2018 and then slope downward? Great overall result if can say inflection point at 2016, where Rx's really decrease at that point bc prescribing too much and individuals turning to heroin instead(...but need to be careful, bc some data points I use are an average between 2 years and I select the lower of the 2 years to place the data point).
May investigate other functions of alpha that may not be linear. Consider a more general function for alpha(t) to capture P data. Could do a piecewise fit (linear or non-linear) at end of 2015/beginning of 2016, or even have the point fitted where it switches the piecewise function; goal would be to analyze data by looking at time-varying parameters. Looks like there is transience at from 2013-2016 and then linearity after quarter 3 of 2015 or beginning of 2016
Policy information in 2016: Requirements with the force of law: Tenn. Code Ann. § 53-10-310 (2016) Since 2013, providers in Tennessee are required to check the state?s controlled substance database or have a healthcare practitioner delegate check the database before prescribing or dispensing a controlled substance if the healthcare practitioner is aware or reasonably certain that a person is attempting to obtain a Schedule II-V controlled substance, which includes, among other, opioids and benzodiazepines.
In 2013: Requirements with the force of law: Tenn. Code Ann. § 53-11-308 (2013) In 2013, the Tennessee Legislature amended its controlled substances statute to add limitations to the prescribing of opioids. The amended statute prohibits dispensing of prescriptions for any opioids or benzodiazepines in quantities greater than a 30-day supply. The statute also requires prescribers of opioids, benzodiazepines, barbiturates, or carisoprodol to patients who are in chronic, long-term drug therapy for 90 days or longer to consider mandatory urine testing.

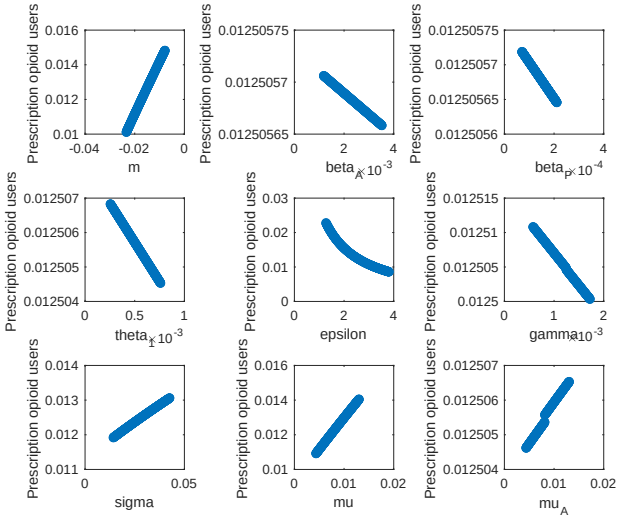
Sensitivity Analysis Here we use two sensitivity analysis techniques to analyze how the uncertainty of our model inputs (parameters and initial conditions) affect the uncertainty in our model outputs. We identity which parameters are important to which population class proportions at the final time and how the uncertainty in each output can be apportioned to the uncertainty in each of the inputs [44**?**].
Latin Hypercube Sampling/PRCC

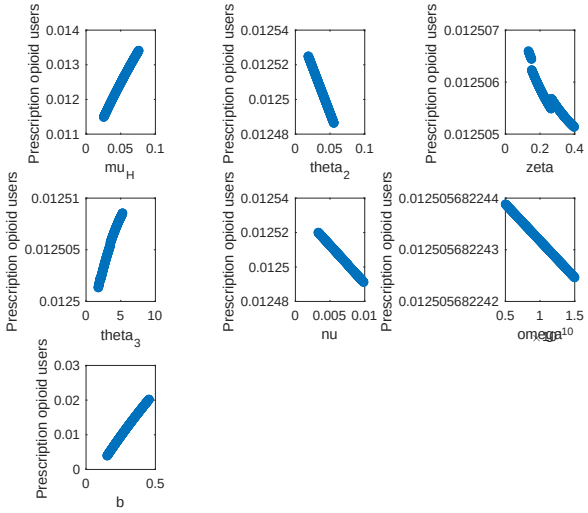
We implement Latin Hypercube Sampling, a type of uncertainty analysis, which examines the uncertainty in the output of a model based on the uncertainty in the inputs [44]. Each of our inputs is sampled from a uniform distribution; the parameter range is divided into N intervals of equal probability, and each interval is randomly sampled once for each parameter. Here, $N > p+1$, where p is the number of inputs, is the minimum requirement. If input ranges do not span across several orders of magnitude, a linear scale is used for sampling; if this is not the case, in order to prevent under-sampling in the outer ranges of the intervals, a log scale would be used. This sampling technique ensures the entire range for the parameter is considered. This results in the $N \times p$ LHS matrix; the model is evaluated from the set of inputs in each row of this matrix. One can study the outputs to gain information on the differences observed in the output from the variation in the parameter combinations in order to quantify the certainty one has with parameters. Do anything with this specifically?
Moreover, sensitivity analysis provides a way to quantify how much the uncertainty in specific model inputs affect specific model outputs. Inputs in biological models often have much uncertainty. Therefore, the information gained from local sensitivity analysis is limited since partial derivatives of the outputs are calculated multiple times based on a small variation in a single input; instead, global sensitivity analysis is advantagoues in that inputs are varied simultaneously. Certain criteria are best for utilizing PRCC (a sampling-based method in which the effect of increasing/decreasing a particular input on a certain output is measured, after taking out the linear effects of all other inputs): nonlinear, monotonic relationships between inputs and outputs; criteria most suitable for Sobol sensitivity analysis (a variance-based method in which the variability in the output can be apportioned to the uncertainty in an input or combination of inputs) is the following: non-linear, non-monotonic relationships. Unable to find specifically how PRCC's are calculated, not in Marino paper or elsewhere. Is that okay?
Although a minimum of $N = 17 + 1 = 18$ sample points for the alpha linear case is required, the sample size must be big enough for which a similar set of parameters are deemed important for a certain output with consecutive runs. We use this standard for each of the results shown below, with the number of samples specifically stated for each. Below are the monotonicity plots for alpha linear for $N = 400$ samples; we note that although some plots may seem non-monotonic, they are actually flat due to the scale on the values.

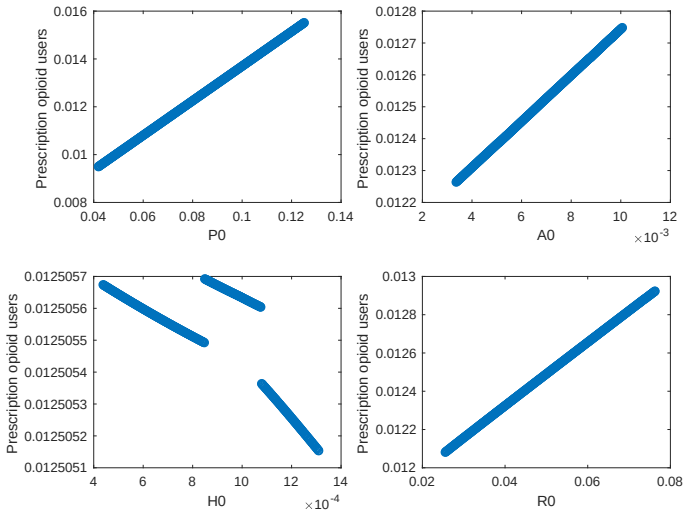

Susceptible Individuals
0.16
0.155
0.15
-0.04
-0.02
0
m
Susceptible Individuals
0.1538505
0.15385
0.1538495
0
2
4
beta$_A$×10^{-3}
Susceptible Individuals
0.153851
0.1538505
0.15385
0.1538495
0
2
4
beta$_P$×10^{-4}
Susceptible Individuals
0.15388
0.15386
0.15384
0.15382
0
0.5
1
theta$_1$×10^{-3}
Susceptible Individuals
0.16
0.15
0.14
0
2
4
epsilon
Susceptible Individuals
0.1539
0.15385
0.1538
0
1
2
gamma$_1$×10^{-3}
Susceptible Individuals
0.17
0.16
0.15
0.14
0
0.05
sigma
Susceptible Individuals
0.18
0.16
0.14
0.12
0
0.01
0.02
mu
Susceptible Individuals
0.15388
0.15386
0.15384
0.15382
0
0.01
0.02
mu$_A$

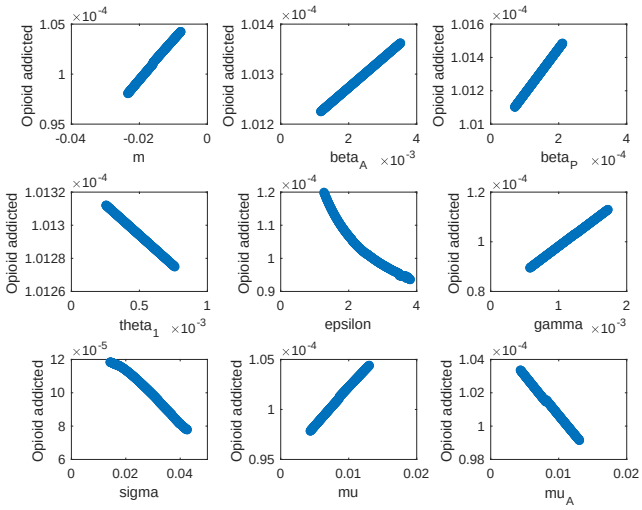

Susceptible Individuals
0.17
0.16
0.15
0.14
0
0.05
0.1
mu_H
Susceptible Individuals
0.154
0.1539
0.1538
0.1537
0
0.05
0.1
theta_2
Susceptible Individuals
0.15387
0.15386
0.15385
0.15384
0
0.2
0.4
zeta
Susceptible Individuals
0.1539
0.15385
0.1538
0.15375
0
5
10
theta_3
Susceptible Individuals
0.1542
0.154
0.1538
0.1536
0
0.005
0.01
nu
Susceptible Individuals
0.15385015977
0.15385015976
0.15385015975
0.5
1
1.5
x 10^-10
omega
Susceptible Individuals
0.17
0.16
0.15
0.14
0
0.5
b

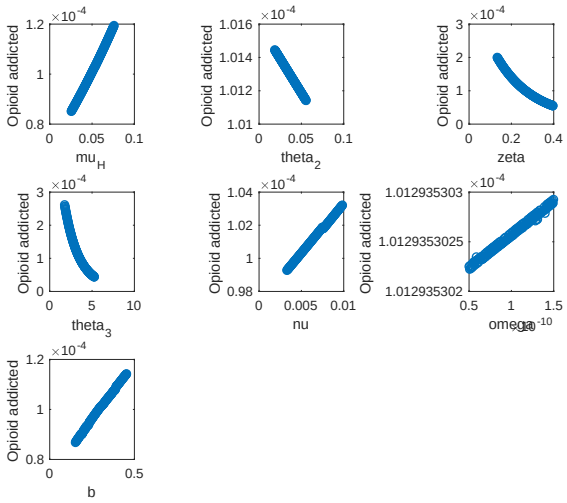

Susceptible Individuals
P0
A0
H0
R0
×10^-3
×10^-4

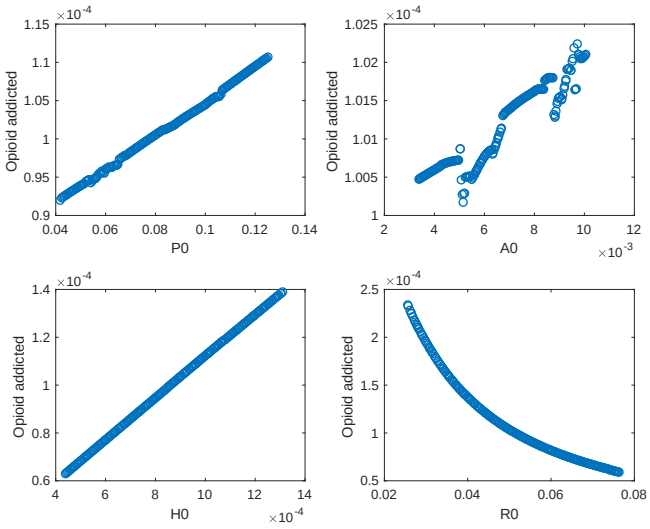

Prescription opioid users
m
beta_A
beta_P
theta_1
epsilon
gamma_1
sigma
mu
mu_A

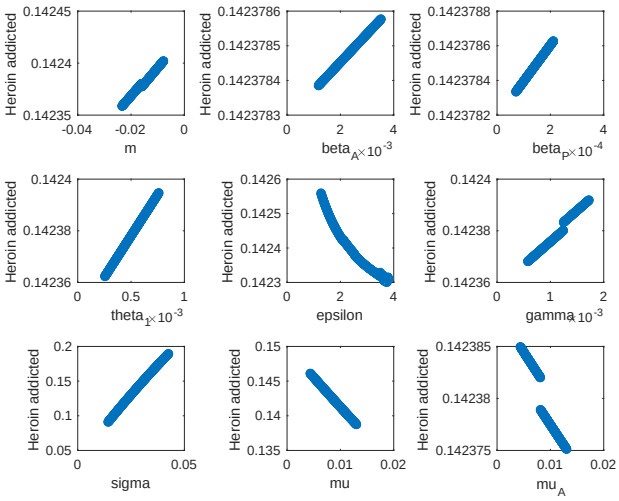

Prescription opioid users
0.014
0.013
0.012
0.011
0
0.05
0.1
mu_H
Prescription opioid users
0.01254
0.01252
0.0125
0.01248
0
0.05
0.1
theta_2
Prescription opioid users
0.012507
0.012506
0.012505
0
0.2
0.4
zeta
Prescription opioid users
0.01251
0.012505
0.0125
0
5
10
theta_3
Prescription opioid users
0.01254
0.01252
0.0125
0.01248
0
0.005
0.01
nu
Prescription opioid users
0.012505682244
0.012505682243
0.012505682242
0.5
1
1.5
omega
x 10^10
Prescription opioid users
0.03
0.02
0.01
0
0
0.5
b

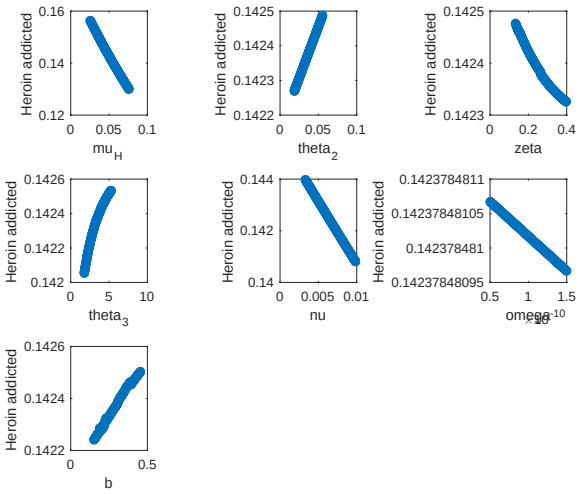

Prescription opioid users
P0
A0
H0
R0
×10^-3
×10^-4

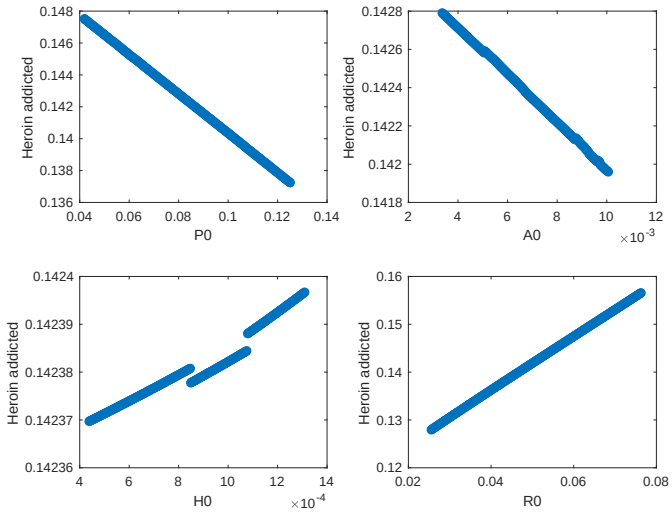

Opioid addicted
m
beta_A
beta_P
theta_1
epsilon
gamma
sigma
mu
mu_A

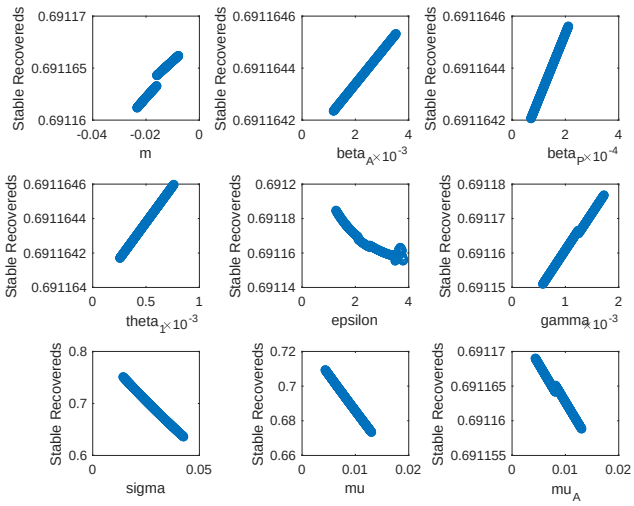

Opioid addicted
×10^-4
1.2
1
0.8
0
0.05
0.1
mu_H
1.016
1.014
1.012
1.01
theta_2
3
2
1
0
0.2
0.4
zeta
theta_3
5
10
1.04
1.02
0.98
0.005
0.01
nu
1.012935303
1.0129353025
1.012935302
0.5
1.5
b

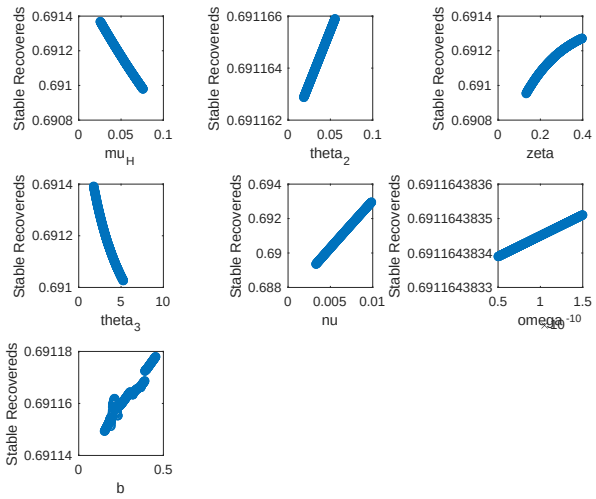

Opioid addicted
P0
A0
H0
R0

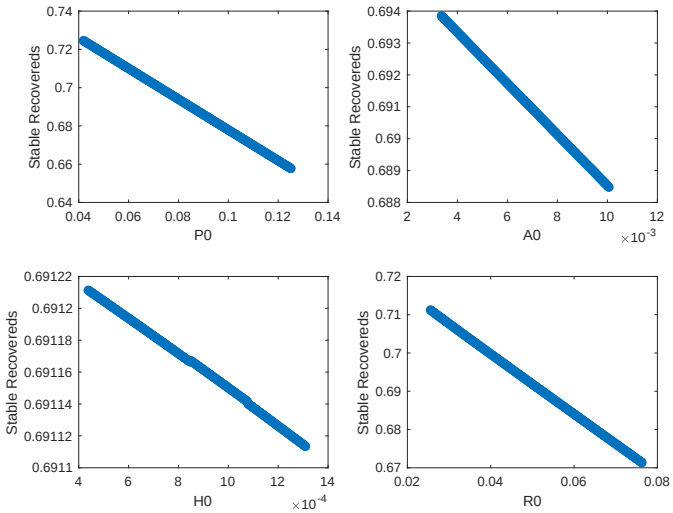

Heroin addicted
0.14245
0.1424
0.14235
-0.04
-0.02
0
m
Heroin addicted
0.1423786
0.1423785
0.1423784
0.1423783
0
2
4
beta_A×10^-3
Heroin addicted
0.1423788
0.1423786
0.1423784
0.1423782
0
2
4
beta_P×10^-4
Heroin addicted
0.1424
0.14238
0.14236
0
0.5
1
theta_1×10^-3
Heroin addicted
0.1426
0.1425
0.1424
0.1423
0
2
4
epsilon
Heroin addicted
0.1424
0.14238
0.14236
0
1
2
gamma_1×10^-3
Heroin addicted
0.2
0.15
0.1
0.05
0
0.05
sigma
Heroin addicted
0.15
0.145
0.14
0.135
0
0.01
0.02
mu
Heroin addicted
0.142385
0.14238
0.142375
0
0.01
0.02
mu_A


Heroin addicted
0.16
0.14
0.12
0
0.05
0.1
mu_H
Heroin addicted
0.1425
0.1424
0.1423
0.1422
0
0.05
0.1
theta_2
Heroin addicted
0.1425
0.1424
0.1423
0
0.2
0.4
zeta
Heroin addicted
0.1426
0.1424
0.1422
0.142
0
5
10
theta_3
Heroin addicted
0.144
0.142
0.14
0
0.005
0.01
nu
Heroin addicted
0.1423784811
0.14237848105
0.142378481
0.14237848095
0.5
1
1.5
x 10^-10
omega
Heroin addicted
0.1426
0.1424
0.1422
0
0.5
b

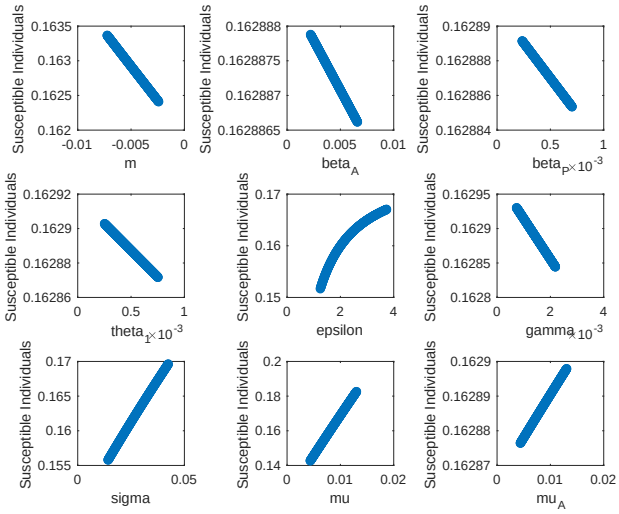

Heroin addicted
P0
A0
H0
R0
×10^-3
×10^-4

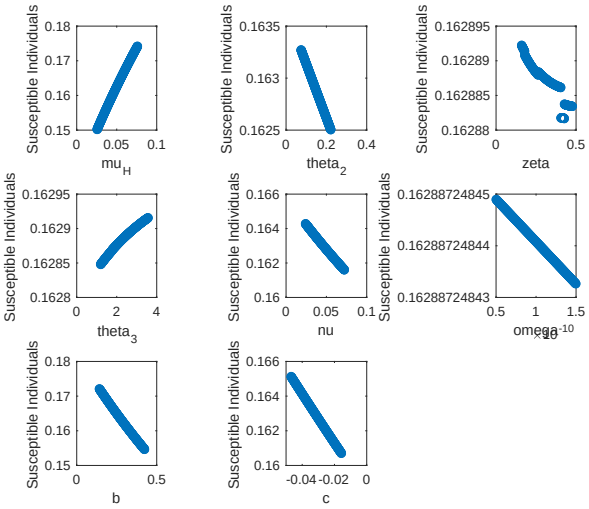

Stable Recovereds
0.69117
0.691165
0.69116
-0.04
-0.02
0
m
0.6911646
0.6911644
0.6911642
0
2
4
beta_A ×10^-3
0.6911646
0.6911644
0.6911642
0
2
4
beta_P ×10^-4
0.6911646
0.6911644
0.6911642
0.691164
0
0.5
1
theta_1 ×10^-3
0.6912
0.69118
0.69116
0.69114
0
2
4
epsilon
0.69118
0.69117
0.69116
0.69115
0
1
2
gamma_1 ×10^-3
0.8
0.7
0.6
0
0.05
sigma
0.72
0.7
0.68
0.66
0
0.01
0.02
mu
0.69117
0.691165
0.69116
0.691155
0
0.01
0.02
mu_A

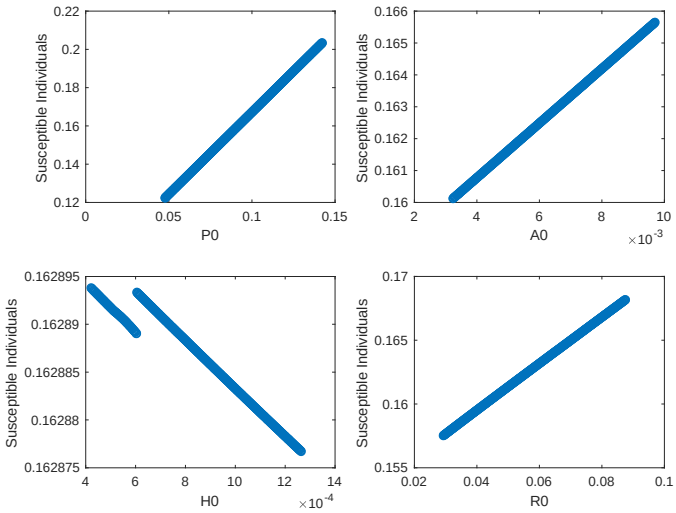

Stable Recovereds
0.6914
0.6912
0.691
0.6908
0
0.05
0.1
mu_H
Stable Recovereds
0.691166
0.691164
0.691162
0
0.05
0.1
theta_2
Stable Recovereds
0.6914
0.6912
0.691
0.6908
0
0.2
0.4
zeta
Stable Recovereds
0.6914
0.6912
0.691
0
5
10
theta_3
Stable Recovereds
0.694
0.692
0.69
0.688
0
0.005
0.01
nu
Stable Recovereds
0.6911643836
0.6911643835
0.6911643834
0.6911643833
0.5
1
1.5
omega
-10
Stable Recovereds
0.69118
0.69116
0.69114
0
0.5
b

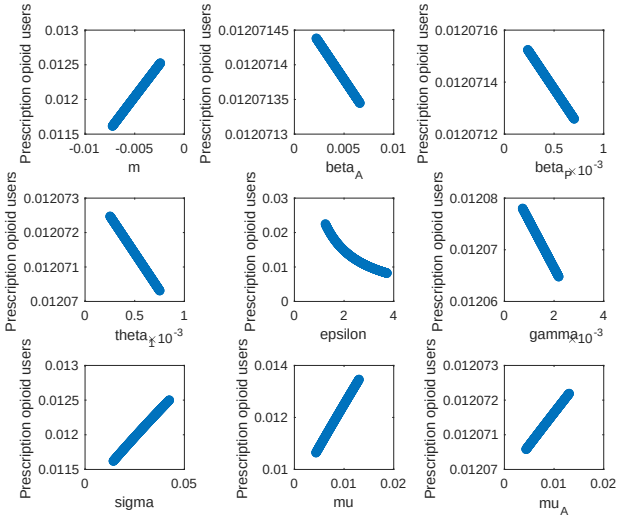


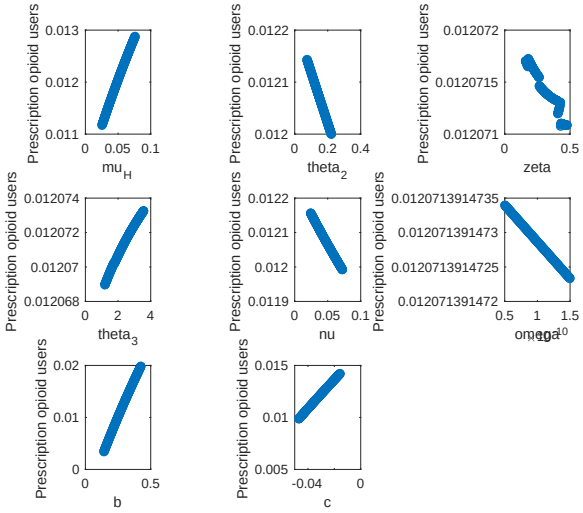
Below are the monotonicity plots for alpha piecewise linear for $N = 400$ samples; we note that although some plots may seem non-monotonic, they are actually flat due to the scale on the values.

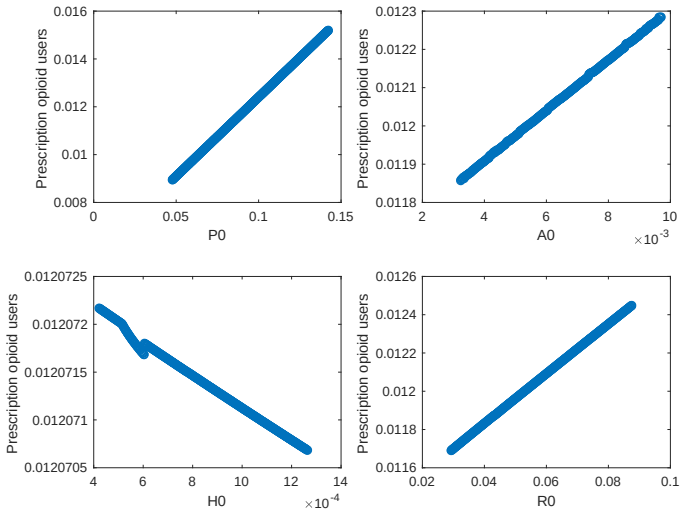

Susceptible Individuals
0.1635
0.163
0.1625
0.162
-0.01
-0.005
0
m
Susceptible Individuals
0.162888
0.1628875
0.162887
0.1628865
0
0.005
0.01
beta_A
Susceptible Individuals
0.16289
0.162888
0.162886
0.162884
0
0.5
1
beta_P ×10^-3
Susceptible Individuals
0.16292
0.1629
0.16288
0.16286
0
0.5
1
theta_1 ×10^-3
Susceptible Individuals
0.17
0.16
0.15
0
2
4
epsilon
Susceptible Individuals
0.16295
0.1629
0.16285
0.1628
0
2
4
gamma_1 ×10^-3
Susceptible Individuals
0.17
0.165
0.16
0.155
0
0.05
sigma
Susceptible Individuals
0.2
0.18
0.16
0.14
0
0.01
0.02
mu
Susceptible Individuals
0.1629
0.16289
0.16288
0.16287
0
0.01
0.02
mu_A

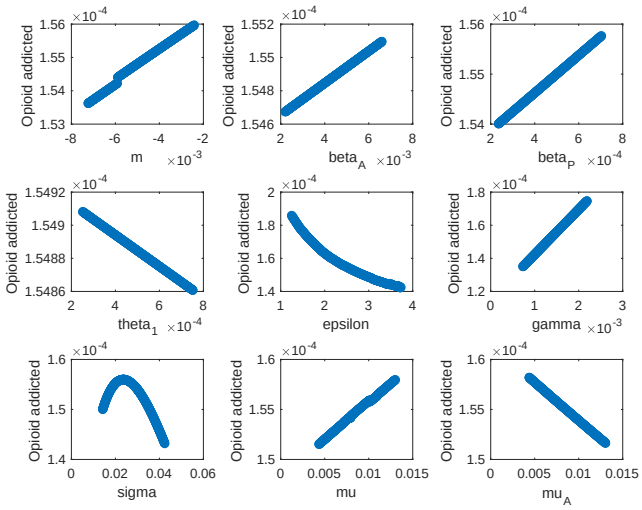

Susceptible Individuals
0.18
0.17
0.16
0.15
0
0.05
0.1
mu_H
0.1635
0.163
0.1625
0.2
0.4
theta_2
0.162895
0.16289
0.162885
0.16288
0.5
zeta
0.16295
0.1629
0.16285
0.1628
2
4
theta_3
0.166
0.164
0.162
0.16
nu
0.16288724845
0.16288724844
0.16288724843
1.5
omega
×10^-10
b
-0.04
-0.02
c

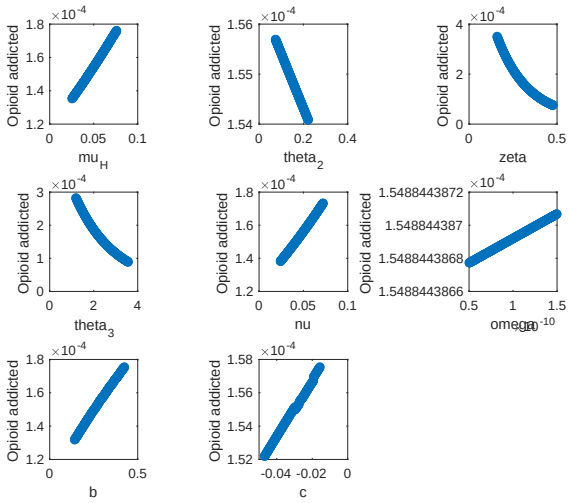

Susceptible Individuals
P0
A0
H0
R0
×10^-3
×10^-4

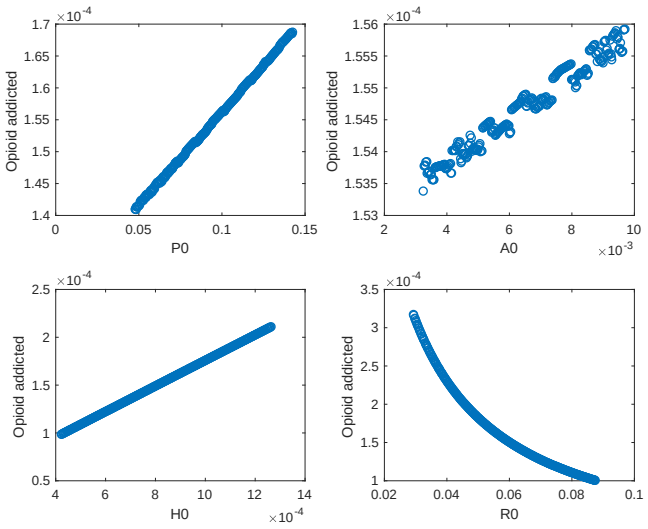

Prescription opioid users
0.013
0.0125
0.012
0.0115
-0.01
-0.005
0
m
0.01207145
0.0120714
0.01207135
0.0120713
0
0.005
0.01
beta_A
0.0120716
0.0120714
0.0120712
0
0.5
1
beta_P
×10^-3
0.012073
0.012072
0.012071
0.01207
theta_I
0.03
0.02
0.01
2
4
epsilon
0.01208
0.01207
0.01206
gamma_A
0.014
0.012
0.01
0.05
sigma
mu
mu_A

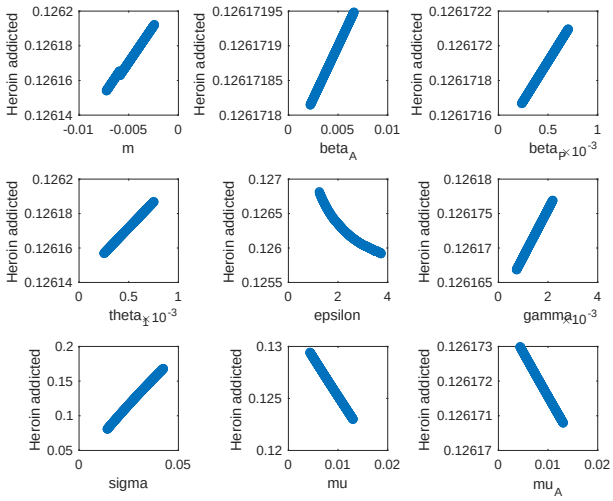

Prescription opioid users
0.013
0.012
0.011
0
0.05
0.1
mu_H
Prescription opioid users
0.0122
0.0121
0.012
0
0.2
0.4
theta_2
Prescription opioid users
0.012072
0.0120715
0.012071
0
0.5
zeta
Prescription opioid users
0.012074
0.012072
0.01207
0.012068
0
2
4
theta_3
Prescription opioid users
0.0122
0.0121
0.012
0.0119
0
0.05
0.1
nu
Prescription opioid users
0.0120713914735
0.012071391473
0.0120713914725
0.012071391472
0.5
1
1.5
omega_10
Prescription opioid users
0.02
0.01
0
0
0.5
b
Prescription opioid users
0.015
0.01
0.005
-0.04
0
c

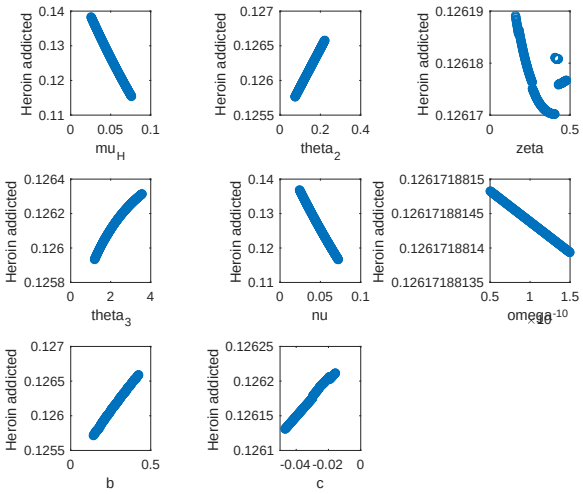

Prescription opioid users
P0
A0
H0
R0
×10^-3
×10^-4

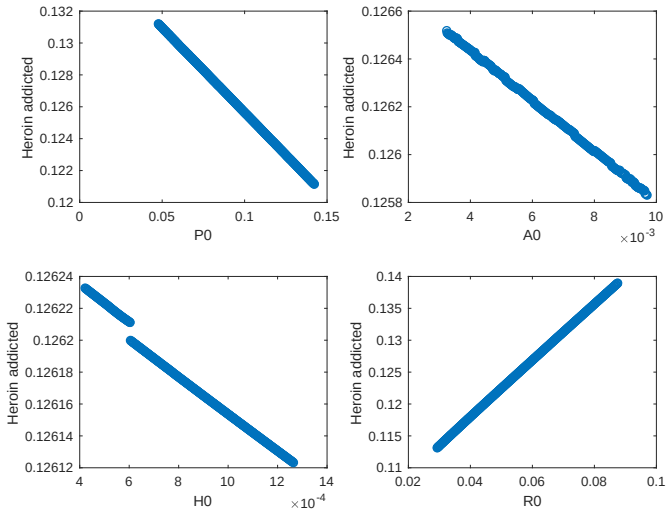

Opioid addicted
m
beta_A
beta_P
theta_1
epsilon
gamma
sigma
mu
mu_A

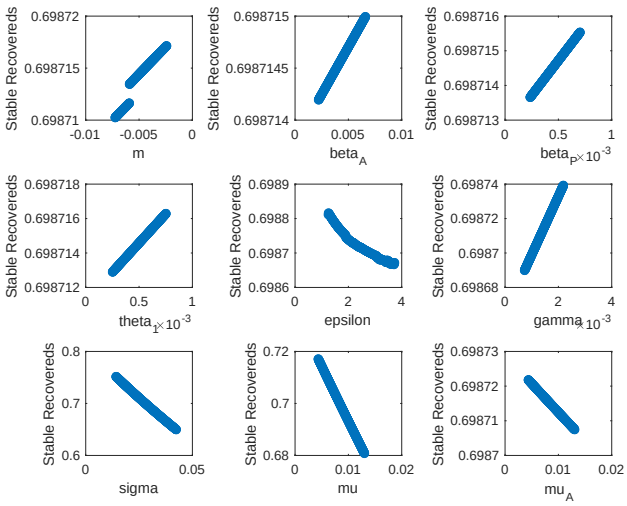

Opioid addicted
×10^-4
1.8
1.6
1.4
1.2
0
0.05
0.1
mu_H
1.56
1.55
1.54
0.2
0.4
theta_2
4
2
0.5
zeta
3
1
theta_3
nu
1.5488443872
1.548844387
1.5488443868
1.5488443866
0.5
1
1.5
omega
×10^-10
1.58
1.52
-0.04
-0.02
b
c

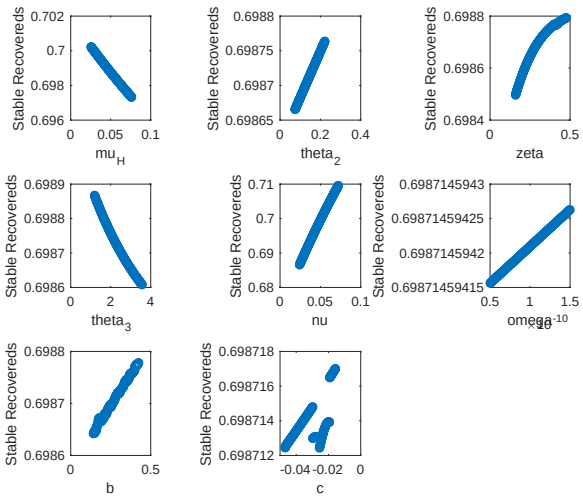

×10^-4
1.7
1.65
1.6
1.55
1.5
1.45
1.4
Opioid addicted
0
0.05
0.1
0.15
P0
×10^-4
1.56
1.555
1.55
1.545
1.54
1.535
1.53
Opioid addicted
2
4
6
8
10
A0
×10^-3
×10^-4
2.5
2
1.5
1
0.5
Opioid addicted
4
6
8
10
12
14
H0
×10^-4
×10^-4
3.5
3
2.5
2
1.5
1
Opioid addicted
0.02
0.04
0.06
0.08
0.1
R0

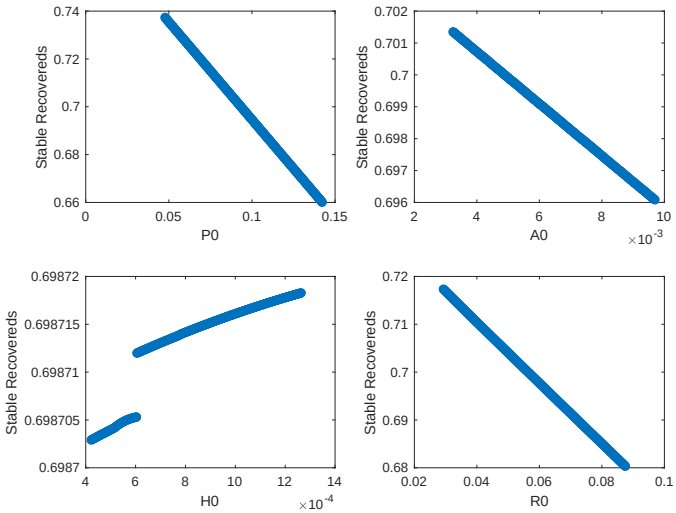

Heroin addicted
0.1262
0.12618
0.12616
0.12614
-0.01
-0.005
0
m
Heroin addicted
0.12617195
0.1261719
0.12617185
0.1261718
0
0.005
0.01
beta_A
Heroin addicted
0.1261722
0.126172
0.1261718
0.1261716
0
0.5
1
beta_P x 10^-3
Heroin addicted
0.1262
0.12618
0.12616
0.12614
0
0.5
1
theta_I x 10^-3
Heroin addicted
0.127
0.1265
0.126
0.1255
0
2
4
epsilon
Heroin addicted
0.12618
0.126175
0.12617
0.126165
0
2
4
gamma_A x 10^-3
Heroin addicted
0.2
0.15
0.1
0.05
0
0.05
sigma
Heroin addicted
0.13
0.125
0.12
0
0.01
0.02
mu
Heroin addicted
0.126173
0.126172
0.126171
0.12617
0
0.01
0.02
mu_A


Heroin addicted
0.14
0.13
0.12
0.11
0
0.05
0.1
mu_H
Heroin addicted
0.127
0.1265
0.126
0.1255
0
0.2
0.4
theta_2
Heroin addicted
0.12619
0.12618
0.12617
0
0.5
zeta
Heroin addicted
0.1264
0.1262
0.126
0.1258
0
2
4
theta_3
Heroin addicted
0.14
0.13
0.12
0.11
0
0.05
0.1
nu
Heroin addicted
0.1261718815
0.12617188145
0.1261718814
0.12617188135
0.5
1
1.5
omega
×10^-10
Heroin addicted
0.127
0.1265
0.126
0.1255
0
0.5
b
Heroin addicted
0.12625
0.1262
0.12615
0.1261
-0.04
-0.02
0
c


Heroin addicted
P0
A0
H0
R0
×10^-3
×10^-4


Stable Recovereds
0.69872
0.698715
0.69871
-0.01
-0.005
0
m
Stable Recovereds
0.698715
0.6987145
0.698714
0
0.005
0.01
beta A
Stable Recovereds
0.698716
0.698715
0.698714
0.698713
0
0.5
1
beta P ×10-3
Stable Recovereds
0.698718
0.698716
0.698714
0.698712
0
0.5
1
theta 1 ×10-3
Stable Recovereds
0.6989
0.6988
0.6987
0.6986
0
2
4
epsilon
Stable Recovereds
0.69874
0.69872
0.6987
0.69868
0
2
4
gamma A ×10-3
Stable Recovereds
0.8
0.7
0.6
0
0.05
sigma
Stable Recovereds
0.72
0.7
0.68
0
0.01
0.02
mu
Stable Recovereds
0.69873
0.69872
0.69871
0.6987
0
0.01
0.02
mu A


Stable Recovereds
0.702
0.7
0.698
0.696
0
0.05
0.1
mu_H
Stable Recovereds
0.6988
0.69875
0.6987
0.69865
0
0.2
0.4
theta_2
Stable Recovereds
0.6988
0.6986
0.6984
0
0.5
zeta
Stable Recovereds
0.6989
0.6988
0.6987
0.6986
0
2
4
theta_3
Stable Recovereds
0.71
0.7
0.69
0.68
0
0.05
0.1
nu
Stable Recovereds
0.6987145943
0.69871459425
0.6987145942
0.69871459415
0.5
1
1.5
x 10^-10
omega
Stable Recovereds
0.6988
0.6987
0.6986
0
0.5
b
Stable Recovereds
0.698718
0.698716
0.698714
0.698712
-0.04
-0.02
0
c



We set the ranges for the parameters to be +/- 50% of the baseline parameter values, which result in these ranges for alpha linear:

Parameter	Range of values
m	[-0.0234,-0.0078]
β_A	[0.00118,0.00353]
β_P	[0.0000705,0.000212]
θ_1	[0.000254,0.000761]
ε	[1.27,3.81]
γ	[0.000575,0.00173]
σ	[0.0142,0.0426]
μ	[0.00434,0.01302]
μ_A	[0.00435,0.0131]
μ_H	[0.0254,0.0761]
θ_2	[0.0185,0.0555]
ζ	[0.133,0.398]
θ_3	[1.755,5.265]
ν	[0.00329,0.00986]
ω	[0.00000000005,0.00000000015]
b	[0.152,0.455]
P_0	[0.0418,0.125]
A_0	[0.00336,0.01]
H_0	[0.000437,0.00131]
R_0	[0.0255,0.0764]

Table 3: LHS/PRCC Sensitivity Analysis Results for alpha linear with 200 samples

Input	PRCC for proportion of A class at final time	p-value for proportion of A class at final time
m	-0.011535	0.8722
β_A	0.099737	0.15997
β_P	-0.0938	0.18646
θ_1	0.10841	0.12651
ε	-0.29203	2.7188e-05
γ	0.34199	7.1776e-07
σ	-0.34694	4.832e-07
μ	-0.11397	0.10808
μ_A	-0.060767	0.39267
μ_H	0.39758	5.5605e-09
θ_2	0.020953	0.76838
ζ	-0.91537	3.6041e-80
θ_3	-0.95001	4.81e-102
ν	0.08866	0.21187
b	0.41521	9.7498e-10
ω	0.023761	0.7384
P_0	0.2641	0.0001576
A_0	-0.045736	0.52017
H_0	0.8625	1.7749e-60
R_0	-0.93392	2.1118e-90

Table 4: LHS/PRCC Sensitivity Analysis Results for alpha linear for 400 samples

Input	PRCC for proportion of H class at final time	p-value for proportion of H class at final time
m	0.0029174	0.95362
β_A	-0.071717	0.15223
β_P	0.076742	0.12545
θ_1	0.043042	0.39059
ε	-0.0061562	0.90231
γ	-0.024102	0.6308
σ	0.99231	0
μ	-0.40926	1.386e-17
μ_A	-0.019459	0.69802
μ_H	-0.87371	1.2531e-126
θ_2	-0.059779	0.2329
ζ	0.0013806	0.97804
θ_3	0.031708	0.52717
ν	-0.22839	3.9385e-06
b	-0.013039	0.79489
ω	0.11267	0.024221
P_0	-0.58071	1.94e-37
A_0	-0.033281	0.50686
H_0	0.0063497	0.89926
R_0	0.9417	2.2302e-190

The parameter ranges utilized for alpha piecewise linear are shown here:

Parameter	Range of values
m	[-0.00725,-0.00242]
β_A	[0.0022,0.0066]
β_P	[0.000235,0.000704]
θ_1	[0.000251,0.000753]
ε	[1.25,3.74]
γ	[0.00073,0.00219]
σ	[0.0142,0.0425]
μ	[0.00434,0.01302]
μ_A	[0.00435,0.0131]
μ_H	[0.0254,0.0761]
θ_2	[0.074,0.222]
ζ	[0.159,0.477]
θ_3	[1.19,3.57]
ν	[0.0241,0.0723]
ω	[0.00000000005,0.00000000015]
b	[0.142,0.423]
c	[-0.0470,-0.0157]
P_0	[0.0475,0.143]
A_0	[0.00324,0.00971]
H_0	[0.000422,0.00126]
R_0	[0.0292,0.0876]

Table 5: LHS/PRCC Sensitivity Analysis Results for alpha piecewise linear with 300 samples

Input	PRCC for proportion of A class at final time	p-value for proportion of A class at final time
m	-0.0098742	0.86476
β_A	0.039135	0.4995
β_P	0.071251	0.2185
θ_1	-0.028338	0.62493
ε	-0.34531	7.9457e-10
γ	0.38344	6.0576e-12
σ	0.17775	0.0019976
μ	0.076348	0.18724
μ_A	-0.080501	0.1643
μ_H	0.3881	3.1914e-12
θ_2	-0.044068	0.44698
ζ	-0.94843	1.0065e-150
θ_3	-0.895	1.7153e-106
ν	0.28789	3.9074e-07
ω	-0.010821	0.85194
b	0.41994	3.0241e-14
c	0.0048736	0.93301
P_0	0.29884	1.3241e-07
A_0	0.051754	0.37171
H_0	0.85937	8.4662e-89
R_0	-0.90818	9.91e-115

Table 6: LHS/PRCC Sensitivity Analysis Results for alpha piecewise linear with 400 samples

Input	PRCC for proportion of H class at final time	p-value for proportion of H class at final time
m	-0.072153	0.14975
β_A	0.094057	0.060188
β_P	-0.038181	0.44635
θ_1	0.023331	0.64178
ε	-0.021226	0.67212
γ	-0.0072294	0.88539
σ	0.99131	0
μ	-0.32236	4.0009e-11
μ_A	0.046263	0.35608
μ_H	-0.84869	3.7468e-112
θ_2	-0.018376	0.71407
ζ	0.00073979	0.98823
θ_3	0.084117	0.092945
ν	-0.8352	2.1231e-105
b	0.03716	0.45861
c	-0.0093803	0.85164
ω	0.044832	0.37117
P_0	-0.64294	4.9687e-48
A_0	-0.032792	0.51314
H_0	0.066229	0.18621
R_0	0.93811	2.2638e-185

It is beneficial to also implement Sobol sensitivity analysis in order to examine if there are any higher-order interactions among parameters that are occurring and also to be able to apportion the output variance to certain inputs.

Sobol sensitivity analysis

In order to explore the sensitivity of each of the population classes to the inputs (parameters and initial conditions), we implemented Sobol sensitivity analysis. First, the Saltelli sampler is utilized to generate N(2D+2) samples where N is the number of sample points and D is the number of inputs in the model [36]. Saltelli are the statistically good points chosen in the parameter space to test and the outputs are the values of S, P, A, H and R at the final time (year 2018) for the different parameter and initial condition samples. Cannot figure out why N(2D+2) when including second order interactions. One method as described in [56] creates an $N \times 2k$ matrix of random numbers, and then splits this into two $N \times k$ matrices containing half of the samples each (call them J and L). From there, a third matrix is created in (M_i) which the i^{th} column is substituted by the i^{th} column of matrix L. The model output is then computed for all parameter samples (all of the rows of J, L, and M_i), which gives a total of N+N+$D \times N$ evaluations, or N(D+2). From here, the first-order sensitivity index is measured as $S_i = \frac{V[E(Y|X_i)]}{V(Y)}$
should these have subscripts for V (subscript X_i) and E (subscript $X_{\ i}$)?
If so, does the mean come from only functions evaluated from M_i matrix? But that wouldn't match what's in [55] because equivalent of M_i there is $B_A^{(i)}$ which is not what they take the mean/variance over, it's X_i. So the first order index utilizes output from matrices A and B that are completely random as well and not focused on only varying

that one parameter X_i? This measures how much the output variance could be reduced on average if the i^{th} input were fixed and the sum of the S_i's is equal to 1 if the model is additive(? a stats thing, so ours is not?) and less than 1 otherwise; the sum of the S_{T_i} values is only equal to 1 for additive models and otherwise greater than 1.
In [55], instead, the matrix $X_{\ i}$ represents the $N \times (k-1)$ matrix of all inputs except input i. While fixing input i to some value, each row of $X_{\ i}$ is used to evaluate the model; this is done for each generated value of the i^{th} input and then the mean of all of the outputs is taken. The variance of this mean is taken for this fixed input i, and then normalized over the variance of all of the outputs resulting in the first-order sensitivity index $S_i = \frac{V_{X_i}[E_{X\ i}(Y|X_i)]}{V(Y)}$ (this is normalized since the numerator can take values all the way from 0 to V(Y) based on the identity $V_{X_i}[E_{X\ i}(Y|X_i)] + E_{X_i}[V_{X\ i}(Y|X_i)] = V(Y)$). The total effect index is given by $S_{Ti} = 1 - \frac{V_{X\ i}[E_{X_i}(Y|X\ i)]}{V(Y)}$. Understand why.
How know which one the sobol analysis is using in SALib package, can't find anywhere how many evaluations it does; does it matter?
Read Saltelli paper and other reference total indices equation 44: term+complement+interaction terms

For first-order indices, only one parameter is varied and the rest are held constant; for second-order indices, two parameters are varied and the rest are held constant; and for total-order indices, every combination of parameters is varied, from a single parameter varying alone to all higher-order interactions between parameters. The length of the colored bars, with each color representing a specific class, measures the contribution of a certain parameter to the variance of each of the classes in the model. The longer the colored bar, the higher the effect the parameter has on that class of individuals; the sum of each color adds to 1, so that for each parameter the relative contribution to each of the classes is represented. We are able to retrieve the confidence intervals on the sensitivity of each of the populations to a respective change in the parameter(s) for first order changes, second order changes and total order changes.

Below are the ranges we chose for each parameter, which are +/-50% of the baseline values found from parameter estimation or calculations of the parameters. We note that α takes on a linear form in this case, and specifically, $\alpha = m \cdot t + b$. In this case, N=100,000 and D=20 for a total of 4,200,000 samples, in which this value of N ensures that results do not change with a slightly higher N value. We ran this for 6 years and the sensitivities of the population classes to each of the parameters were calculated at the final time.

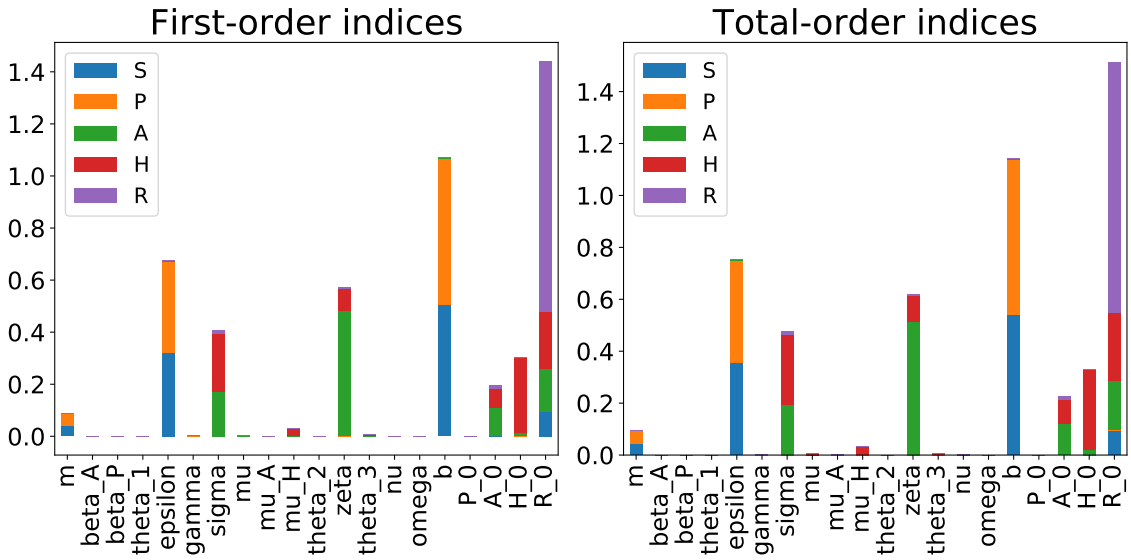


Figure 11: Sobol sensitivity results-classes at the final time (t=6 years representing end of 2018) for alpha linearly dependent on time

Parameter	Range of values
m	[-0.0234,-0.0078]
β_A	[0.00118,0.00353]
β_P	[0.0000705,0.000212]
θ_1	[0.000254,0.000761]
ε	[1.27,3.81]
γ	[0.000575,0.00173]
σ	[0.0142,0.0426]
μ	[0.00434,0.01302]
μ_A	[0.00435,0.0131]
μ_H	[0.0254,0.0761]
θ_2	[0.0185,0.0555]
ζ	[0.133,0.398]
θ_3	[1.755,5.265]
ν	[0.00329,0.00986]
ω	[0.00000000005,0.00000000015]
b	[0.152,0.455]
P_0	[0.0418,0.125]
A_0	[0.00336,0.01]
H_0	[0.000437,0.00131]
R_0	[0.0255,0.0764]

Below are the ranges we chose for each parameter, which are +/-50% of the baseline values found from parameter estimation or calculations of the parameters for the case of α taking on a piecewise linear form. Specifically,

$$\alpha(x) = \begin{cases} m \cdot t + b \text{ before Quarter 2 2016 } (t \leq 3.25) \\ m(3.25) + b + c(t - 3.25) \text{ after Quarter 2 2016 } (t > 3.25) \end{cases}$$

In this case, N=100,000 and D=21 for a total of 4,400,000 samples. We ran this for 6 years and the sensitivities of the population classes to each of the parameters were calculated at the final time.

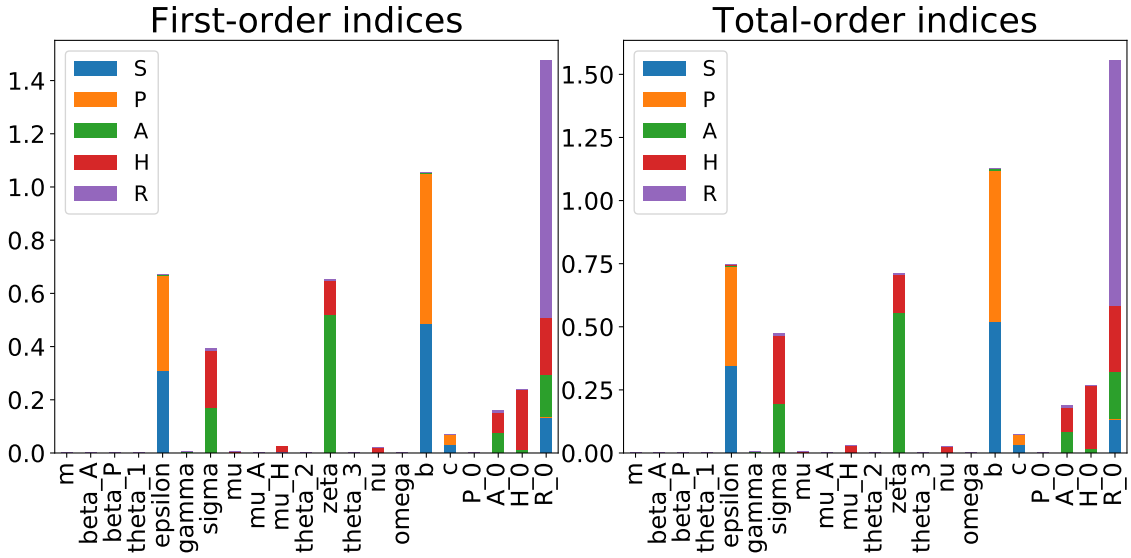


Figure 12: Sobol sensitivity results-classes at the final time (t=6 years representing end of 2018) for alpha linearly piecewise dependent on time

Parameter	Range of values
m	[-0.00725,-0.00242]
β_A	[0.0022,0.0066]
β_P	[0.000235,0.000704]
θ_1	[0.000251,0.000753]
ε	[1.25,3.74]
γ	[0.00073,0.00219]
σ	[0.0142,0.0425]
μ	[0.00434,0.01302]
μ_A	[0.00435,0.0131]
μ_H	[0.0254,0.0761]
θ_2	[0.074,0.222]
ζ	[0.159,0.477]
θ_3	[1.19,3.57]
ν	[0.0241,0.0723]
ω	[0.00000000005,0.00000000015]
b	[0.142,0.423]
c	[-0.0470,-0.0157]
P_0	[0.0475,0.143]
A_0	[0.00324,0.00971]
H_0	[0.000422,0.00126]
R_0	[0.0292,0.0876]

The confidence intervals for each parameter corresponding to a certain population class is shown below:

Edit: Comparing the sensitivity analyses between alpha linear and alpha piecewise linear, the main difference is seen in the parameter m (alpha linear case was more sensitive to this parameter because it was the slope of alpha but in the alpha piecewise linear case, m was one order of magnitude less negative than c, and that took the place of the more sensitive slope parameter). In both cases, the first-order index results are very similar to their respective total-order index results which suggests that there are not higher-order interactions occurring. Other differences to point out is that H is more sensitive to ν in the piecewise linear case, a small difference in the sensitivity of A and H to ζ and finally, slight differences are seen in the initial conditions.

We observe that the P class is most sensitive to ε and b in either case, which is advantageous from a control perspective as controlling how much is prescribed is more manageable than preventing individuals from getting addicted to prescription opioids.

Conclusions

What did we show that we didn't know before?
Think of questions that we can confront the model with regarding heroin and fentanyl deaths and connect to data on deaths; give results that give the reader an answer to these questions; think about analysis can do on model.

Extensions
Need to edit
In our model we assume homogeneous mixing of the individuals in each of the compartments and therefore, each individual has the same probability of transitioning from one stage to another, interacting with individuals from other stages, or leaving the system via death. Although done for the purpose of simplification, this is not an accurate representation of reality since there are factors that affect these probabilities, such as race, gender, geographical location and age. For example, there has been a shift in heroin use from urban areas to some suburban and rural areas and there is an increasing number of individuals ages 18-25 using the drug [49]. West Virginia, New Hampshire and Ohio had the highest rates of opioid-related overdose deaths per 100,000 people in 2016 and Tennessee and Arkansas were among the states with the highest prescription rates per 100 people the same year [50]. Men have a higher likelihood of overdosing on prescription pain relievers compared to women, but since 1999, there has been a steeper increase in the number of women overdoses than men. In addition, women may form a quicker dependence on opioids compared to men, and have a higher probability of being prescribed higher doses and for longer periods of time [15]. Specific to heroin, using data from the 2008-2010 NSDUH studies, past year heroin use was twice as likely for men compared to women, and highest in the 18-25 year old age group [40]. Incorporating these ideas into the model and parameter information would be possible future extensions. Although there is data on the misuse of opioids, we decided to focus specifically on addiction rather than misuse, due to the harmful consequences this behavior can have for an individual. However, the behavior and actions of individuals are not always very clearly defined, and there may be a benefit to expanding the spectrum of classes that individuals can fall into. In Tennessee specifically, the majority of individuals who overdosed either on heroin or fentanyl were white and male [53]. A more detailed look could be given to the individual cases of hepatitis C for opioid users.

Appendix A

Calculations of parameters from literature

The **age-adjusted death rate** for Tennessee in 2016 was calculated to be 886.3 out of 100,000 individuals, or approximately 50,094 people out of a total population 12 and older of 5,651,993 [35]. Subtracting off the number of people who died from a prescription opioid or heroin/fentanyl overdose in 2016 results in 48,825 people who died that year. This implies that (5,651,993-48,825)/5,651,993 ≈ 0.991 is the proportion of the population that remains by the beginning of 2017. If we consider T_0 to be the total population in 2016, we can find the continuous-time rate at which individuals die naturally from the equation $0.991T_0{=}T_0e^{-\mu t}$, which results in the natural death rate $\mu \approx 0.00868$.

We calculate the overdose death rate in the year 2015, since we have a reasonable estimate for the number of (non-heroin) prescription opioid addicted individuals in that year. To find the continuous-time rate at which individuals are dying from the addicted class, we consider the equation $kA_0 = A_0e^{-\mu_A t}$, where A_0 is the number of individuals addicted to prescription opioids in 2015 and k is the proportion of these individuals in the addicted class at the start of 2016 (when $t = 1$). In 2015, there were 679 individuals out of the entire Tennessee population 12 and older that overdosed on prescription opioids [53]. However, it is estimated that only 54.6% of these individuals were actually at an increased risk for an opioid-related overdose death; we assume that if an individual met the criteria for at least one high-risk factor, that they were considered addicted to prescription opioids [8]. Therefore, we assume 54.6% of the 679 individuals that overdosed were addicted. With a total of 42,816 prescription opioid addicts (non-heroin addicted) in 2015, this means that (42,816-0.546·679)/42,816 ≈ 0.991 is the proportion of addicted individuals that remain by the beginning of the next year. This implies $0.991A_0 = A_0e^{-\mu_A(1)}$, and solving results in $\boldsymbol{\mu_A \approx 0.00870}$. We note here that since we want a rate of overdose deaths out of the addicted class, we use the number of non-heroin addicted prescription opioid addicts, although the overdose death data is out of all prescription opioids addicts, whether they are addicted to heroin or not. However, since we do not know the number of overdoses specifically for non-heroin addicted prescription opioid addicts, we use this simplification that all of the opioid overdose deaths are from this group.

Similarly, we may calculate μ_H. There were 7,560 heroin/fentanyl addicts in 2015 and 374 heroin-related overdoses. We make the simplifying assumption that if an individual died of a heroin overdose they were addicted to heroin. This means that (7,560-374)/7,560 $\approx$ 0.951 is the proportion of heroin users that remain at $t = 1$, which implies $0.951H_0 = H_0e^{-\mu_H(1)}$, which results in $\boldsymbol{\mu_H \approx 0.0507}$, the continuous-time rate at which individuals are dying from the heroin class.

We make a note that individuals that do not have an opioid use disorder and die because of an opioid overdose are counted in the "natural mortality rate."

Estimates of parameters from literature

WILL MOST LIKELY DELETE THIS SECTION BECAUSE NOW ESTIMATING PARAMETERS AND IC WITH MULTISTART??–unless use as reasoning for bounds, i.e. to have intuition on order of magnitudes for betaA and betaP, but NOT zeta or nu or any IC

Since there is no information for values of θ_1, θ_2, or θ_3 for Tennessee in the literature, we consider a national study of individuals 12 and older to establish a relationship among these three rates. For a national study consisting of 609,000 participants, "the recent heroin incidence rate was 19 times higher among those who reported prior non-medical pain reliever (NMPR) use (0.39%) than among those who did not report NMPR use (0.02%) [46]. NMPR use can occur within the prescription class (i.e. from misuse that's not considered addiction), or in the addiction class. Thus, we will extrapolate this information to say that the rate that prescription opioid users and opioid addicts move to heroin use is 19 times greater than the rate at which susceptibles move to heroin use (i.e. $\theta_2 + \theta_3 > 19\theta_1$), where both θ_2 and θ_3 are greater than θ_1. We will make an assumption here that $\theta_2 + \theta_3$ is exactly $19\theta_1$, and that there is somewhat of an elevated risk of moving to heroin use from the prescription class versus the susceptible class, taking $\theta_2 = 3\theta_1$. This leaves $\theta_3 = 16\theta_1$.

Okay to use even though opioid model is not a sub-model anymore (since we've changed the recovery class and terms? We argue that β_A is a reasonable parameter to estimate because the opioid-only model was insensitive to this parameter and although less so, β_P was relatively insignificant compared to other parameters explored [7]. We were not able to find values in the literature specific to Tennessee regarding an illicit-induced addiction rate; however, we use information from the national level, as we do not have any evidence that this national average rate is significantly different in Tennessee. Have this work checked/all units okay? In 2015, there were an estimated 2.1 million individuals 12 and older that initiated pain reliever misuse recently. Using this source, we take pain relievers to be equivalent to prescription opioids [37]. To calculate approximately how many of these would end up having a use disorder in 2015, this same study states that 12.5 million people misused prescription opioids in the past year total, and that there were 2.0 million with a prescription opioid disorder; using these number, we make an estimate that

$$\frac{\text{2 million people with pain reliever use disorder in 2015}}{\text{12.5 million people who misused pain relievers in 2015}} = 0.16.$$

We extrapolate this to estimate that 16% of the 2.1 million recent initiates are those who should be counted in the use disorder category (although we do not know the timeline of developing the use disorder and it may not happen within the year, it gives a rough idea). This results in an estimate of 336,000 individuals that were recent initiates of pain reliever misuse that we will consider having a use disorder within the year 2015. In the same year, a study was done regarding the source of the most recent episode of misuse of prescription opioids among adults reporting an prescription opioid use disorder in the past year [33]. (Note: this study was for individuals age 18 and older whereas the study done in [37] was for those 12 and older; we will assume for simplicity that the information for those 18 and older will be similar to those between 12 and 18, as well.) Here, 52.8% of the prescription opioids were from a non-physician source, which included being given to/bought from a friend/relative, or bought from a drug dealer/stranger. For simplicity,

let IPUD indicate individuals with a prescription use disorder. Thus,

$$\frac{336,000 \text{ IPUD}}{320 \text{ million people}} \cdot \frac{0.528 \text{ opioid source for IPUD is illicit}}{\text{opioid sources} \cdot \text{year}}$$
$$= 0.000554 \frac{\text{IPUD obtain opioids illicitly}}{\text{opioid sources} \cdot \text{year}}.$$

From [33], we see that

$$\frac{.138 \text{ opioids obtained from drug dealers/strangers by IPUD}}{.528 \text{ opioids obtained illicitly by IPUD}} = .26$$

relates to individuals obtaining opioids by the black market or interaction with other addicts and

$$\frac{.218 + .141 + .031 \text{ opioids given/bought from a friend/relative or other for IPUD}}{.528 \text{ opioids obtained illicitly by IPUD}} = .74$$

relates to individuals obtaining opioids from extra prescriptions that are available. This means that 74% of illicit opioids come from a friend/relative/other source, whereas 26% of illicit opioids are from the black market for opioid addicts. In our model, we consider two cases in which individuals become addicted (friend/relative versus black market) and we make the assumption that these percentages also apply to the two routes that one would become an addict in the first place via illicit opioids.
Thus,

$$\frac{0.26 \text{ opioids from drug dealers/strangers}}{\text{opioids obtained illicitly}} \cdot \frac{0.000554 \text{ opioids obtained illicitly}}{\text{opioid sources} \cdot \text{year}}$$
$$= \frac{0.000141 \text{ opioids from drug dealers/strangers}}{\text{opioid sources} \cdot \text{year}}$$

is the rate that individuals illicitly obtain their prescription opioids from the black market/other addict interaction and become addicted

$$\implies \beta_A = \frac{0.000141}{\text{year}}.$$

Similarly,

$$\frac{0.74 \text{ opioids from friend/relative or other}}{\text{opioids obtained illicitly}} \cdot \frac{0.000554 \text{ opioids obtained illicitly}}{\text{opioid sources} \cdot \text{year}}$$
$$= \frac{0.000403 \text{ opioids from friend/relative or other}}{\text{opioid sources} \cdot \text{year}}$$

is the rate that individuals illicitly obtain their prescription opioids from extra pills that are available and become addicted

$$\implies \beta_P = \frac{0.000403}{\text{year}}.$$

Although these may be good estimates for rates if they were rates of linear terms(i.e. $\beta_A S$ and $\beta_P * S$, they are rates of non-linear terms, and therefore, can be much better

estimated using ordinary least squares. (Note: this does provide insight on realistic orders of magnitudes, though). As mentioned before, 71% of heroin users relapse within 4 weeks [58]. Although these are on a national level, we will assume the rates do not differ significantly for Tennessee, as we were not able to find any relapse statistics specifically for the state. It is estimated that for every 10 people with substance use disorder, only 1 receives treatment for it [71]. We assume this is an approximation for opioid and heroin/fentanyl addicts, as well, and assume this is the case for a year-long period. In 2015, there were 13,110 discharges total in the state of Tennessee for substance abuse programs in facilities that receive state/public funding (generally referring to funding by the state substance abuse agency); out of those, 7,003 were due to completion of treatment, which is 53.4% of all discharges [27]. Realistically, an individual cannot go to a stably recovered class without going to treatment, completing treatment and remaining clean for 4 weeks post-treatment, since addiction is a disease. Using HA to represent heroin addict, we calculate

$$\frac{1 \text{ HA in treatment}}{10 \text{ HA} \cdot \text{year}} \cdot \frac{53.4 \text{ HA complete treatment}}{100 \text{ HA in treatment}} \cdot \frac{29 \text{ HA do not relapse within 4 weeks post-treatment}}{100 \text{ HA completed treatment}}$$

$$= \frac{0.015486 \text{ HA do not relapse within 4 weeks post-treatment}}{\text{HA} \cdot \text{year}}$$

$$\implies \nu \approx \frac{0.0155}{\text{year}}.$$

Studies done among opiate addicts (not just heroin) in recent years ([6, 10]) suggest lower relapse rates at 4 weeks compared to the study consisting mostly of heroin users in [58] in which 71% of the addicts relapsed within 4 weeks. Thus, we assume the relapse rate for prescription opioids will be slightly lower than that for heroin. We know from a study done in [81] that at the 8 week mark, 91% of prescription opioids users had relapsed, so this is an upper limit, and we know from studies that higher rates of relapse occur in the first few weeks following treatment, as discussed before. Therefore, we make an estimate that 60% of prescription opioids users relapse within 4 weeks after treatment. Letting OA represent opioid addicts, we calculate

$$\frac{1 \text{ OA in treatment}}{10 \text{ OA} \cdot \text{year}} \cdot \frac{53.4 \text{ OA complete treatment}}{100 \text{ OA in treatment}} \cdot \frac{40 \text{ OA do not relapse within 4 weeks post-treatment}}{100 \text{ OA completed treatment}}$$

$$= \frac{0.02136 \text{ OA do not relapse within 4 weeks post-treatment}}{\text{OA} \cdot \text{year}}$$

$$\implies \zeta \approx \frac{0.0214}{\text{year}}.$$

Since the H class is homogeneously mixed with all addicts, whether they have been in treatment or not, the calculation for ν takes that into consideration to produce an average rate among all addicts within the class and therefore, gives a rate at which any individual from that class would transition to the recovered class; similarly for the A class.

Estimates of initial conditions from literature

Not updated!–should just be the 2,000,000/90*16.5/2.34 number for prescribed users any

given day but cannot get the units right. In the first quarter of 2013, there were 856,000 individuals prescribed opioids in Tennessee, and a total of 2,000,000 prescriptions in the same quarter; this is approximately 2.34 prescriptions per prescribed user in this quarter [53]. In addition, the average number of days that prescribed users in Tennessee actively took prescription opioids in 2013 was 66.9 days; extrapolating this to the first quarter gives

$$\frac{x \text{ average prescription days}}{90 \text{ days}} = \frac{66.9 \text{ average prescription days}}{365 \text{ days}}$$
$$\implies x \approx 16.5$$

as the average number of prescription days in the first quarter of 2013 for a prescribed user. Since we do not know the number of individuals using prescription opioids at the beginning of the year, we use

$$\begin{aligned}&\#\text{ of prescribed users at beginning of 2013}\\ &+\frac{2,000,000 \text{ prescriptions}}{90 \text{ prescription days}} \cdot \frac{16.5 \text{ average prescription days}}{2.34 \text{ average number of prescriptions}}\\ &= 856,000 \text{ prescription users in entire first quarter of 2013}\end{aligned}$$

gives an estimate that

$$\#\text{ of prescribed users at beginning of 2013} = 699,304.$$

However, as before, approximately 44.3% of these prescription opioid users are addicted to their prescriptions, which means

$$\#\text{ of non-addicted prescribed users at beginning of 2013} = (1-.443)*699,304 = 389,512.$$

Although we do not know the total population at the beginning of 2013, we will take it to be approximately the total population from 2012 before any births or deaths occur, which was 6,450,632. Adjusting this to the population 12 and older as done in Table 1, we take 15% off of the total population to arrive at 5,483,037 [69].
Thus, we estimate

$$P_0 = \frac{389,512}{5,483,037} = 0.0710$$

of the population was using opioid prescriptions at the beginning of 2013. In 2013, we observe a ratio of approximately 1 non-heroin addicted prescription opioid addict to 42.1 non-addicted prescription opioid user, so we assume this is the ratio at the beginning of the year, as well. This gives

$$A_0 = \frac{P_0}{42.1} = 0.00169.$$

We do not have information on the number of heroin users in 2013, so we extrapolate from information in 2015. We note first that although opioid overdose deaths increase from 2013 to 2015, that does not necessarily equate to more heroin users in 2015, due to the rise in fentanyl contamination during this time period...HOWEVER, IT SEEMS THAT

if heroin were laced with heroin, it would be counted as fentanyl overdose, so the fact that heroin overdoses are also still increasing through 2016 suggests more heroin addicts overall [13]. In order to keep a proportion approximately equivalent to the number of opioid addicts to heroin users in 2015, we assume the same ratio of approximately 1:3.43 heroin users to opioid addicts in 2013, as well. In 2013, addicts make up 0.00148 of the population at the start of 2013, so we assume $H_0 \approx 0.000431$. (Note: the proportion of prescription opioid users to heroin users is also similar, particularly regarding the order of magnitude expected.)

Before, we estimated 48,674 opioid addicts in 2013; this higher number is supported by an overall higher prescribing rate in 2013 compared to the next few years [17]. We will assume the number of heroin users is the same in 2013 as in 2014 and 2015. There were 4,485 prescription opioid treatment admissions and 555 heroin treatment admissions in 2013, which is 0.057 of the opioid addict and heroin user population combined that are in recovery. Only 35% of those in treatment do not relapse within 4 weeks after treatment, and thus have the ability to be in R, which is approximately .0804 of the entire A+H class [6]. Since 90% of individuals relapse within one year post-treatment, that means that an additional 55% relapse after the 4 week mark and move out of R; therefore, we make a simplifying assumption that 10% of those that can be in R actually are at a specific point in time, resulting in a proportion of .00804 of addicted and heroin users total [6]. This equates to approximately 504 individuals, which out of a total population 12 years and older in 2013 of 5,517,716, we conclude $R_0 = 0.000091$.

Unit conversions from data to parameters is only when calculating/estimating them by hand, correct?

Table of parameter values and units of parameters

Parameter	Description	Units
μ	natural mortality rate	$\frac{1}{\text{year}}$
μ_A	opioid addict overdose death rate	$\frac{1}{\text{year}}$
μ_H	heroin addict overdose death rate	$\frac{1}{\text{year}}$
α	prescription rate	$\frac{1}{\text{year}}$
β_A	illicit addiction rate from the black market	$\frac{1}{\text{year}}$
β_P	illicit addiction rate from availability of excess pills	$\frac{1}{\text{year}}$
θ_1	heroin addiction rate for susceptible individuals	$\frac{1}{\text{year}}$
ε	rate of finishing prescription addiction-free	$\frac{1}{\text{year}}$
γ	opioid addiction rate from prescription	$\frac{1}{\text{year}}$
θ_2	heroin addiction rate for prescription opioids users	$\frac{1}{\text{year}}$
σ	relapse to addiction	$\frac{1}{\text{year}}$
ζ	rate of stable recovery for opioid addict	$\frac{1}{\text{year}}$
θ_3	heroin addiction rate for opioid addicts	$\frac{1}{\text{year}}$
ν	rate of stable recovery for heroin addict	$\frac{1}{\text{year}}$
ω	perturbation term	dimensionless
S	proportion of susceptible individuals	dimensionless
P	proportion of susceptible individuals	dimensionless
A	proportion of susceptible individuals	dimensionless
H	proportion of susceptible individuals	dimensionless
R	proportion of susceptible individuals	dimensionless

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