"Modeling the Heroin Epidemic"
Tricia Phillips
July 31, 2018

Background

Heroin information

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 [23, 24]. 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. [34, 23]. 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 drop very difficult [23]. Options for treatment for heroin use involve medications such as buprenorphine, methadone, and naltrexone, in combination with counseling and behavioral therapies [29, 23]. 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 [24, 23]. 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 [13].

A national survey estimated that out of the United States national population of individuals 12 years of ago or older, 948,000 were heroin users in 2016, although this number may include under-reporting [32]. There was 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 [31]. This, in part, is due to the recent trend of lacing heroin with fentanyl, a surgical-grade opioid that is up to fifty times more potent than heroin alone, and therefore, users are unaware of the purity of the heroin they obtain [6, 13, 38]. The effects of heroin, however, extend further than just the using individual. 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. Moreover, risky sexual behavior is more likely under the influence, so for those whose method of use is via smoking or snorting, there is also 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 [24].

Opioid information
Another large portion of opioids consist of prescription pain relievers which include oxycodone, hydrocodone, and morphine products, among others [8]. From 1991 to 2011,

there was a near tripling of prescriptions that pharmacies distributed [26]. 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 [36]. Moreover, in the early 2000s, drug manufacturers funded publications and physicians to support opioid use for pain control [21]. A national survey estimated there were 11.5 million individuals 12 years of age or older in the United States that experienced pain reliever misuse in the past year, referring to the year 2016 [32]. 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 [33]. This subset of the opioid drug class is misused 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 [32]. Treatment options for opioid addiction are the same as heroin [29]. In addition, pregnant women who take prescription opioids also put their babies at risk of neonatal abstinence syndrome, similar to heroin [9].

Question: Maybe leave out since so prescription focused?: In 1995, the American Pain Society stated that pain was being under-treated in doctor offices and hospitals, and consequently, created guidelines for the improvement for pain assessment for acute and cancer cases. This included the recording of pain levels such as on a vital signs sheet [21, 4]. In 2000, the Joint Commission required physicians to accept and respect the self-reporting of pain by patients. By the early 2000s, drug manufacturers funded publications and physicians to support opioid use for pain control [21].

Connection between opioid and heroin abuse

The misuse of prescription pain relievers leads some individuals to start heroin. According to the National Survey of Drug Use and Health 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 [22]. This could in part be due to the higher availability of heroin in recent years at a lower cost than alternative opioids [26]. 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 [22]. 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 [10, 11]. 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 [18].

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 [12]. 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.

Goal paragraph

The misuse of opioids, including prescription pain relievers, synthetic opioids and the illegal drug heroin, is rampant in today's society [13]. The opioid crisis was declared a public health emergency in October 2017 by the United States Department of Health and Human Sciences [35]. It was estimated that the total economic cost of prescription opioid dependence, abuse and overdoses in 2013 alone was $78.5 billion [16]. 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. To address this apparent problem in today's society, we wish to investigate the dynamics behind the opioid and heroin epidemic and identify important conditions relating to the reduction of opioid and heroin addicted individuals. 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 opioids, using heroin and recovering from opioid addiction, including heroin, and analyzed it. Our overall goal is to explore management strategies for optimally treating pain with prescriptions while reducing opioid addiction and heroin use.

Other models

There have been several models formulated focusing on heroin addiction. Most of them were motivated by and extensions of 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. Question: How can the model assume the three compartments make up the entire population, but then have the option for immunity to drug addiction for the remainder of the modeling 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 [42]. Wang, Yang and Li did analysis of this model, changing the assumption that the population was not constant [40].

The White and Comiskey model was modified later on by Liu and Zhang in order to incorporate a relapse distribution in which there was a non-constant time to relapse. They formulated a delay-differential equation, and also took away the assumption that the population was constant. Their conclusions about the sensitivity of $\mathscr{R}_0$ to certain parameters were in line with those from White and Comiskey [19]. Using the same three compartments, another model was formulated with the idea of the relapse rate relying

on the length of time the individual has been undergoing treatment. This coupled ODE-PDE model assumed that susceptibles could only become addicted via interaction with heroin users not undergoing treatment. Prevention was deemed more important than treatment, yet again [14]. Fang, Li, Martcheva and Caialso (2015) also modeled the heroin epidemic allowing susceptibility of becoming a drug user to depend on age, again resulting in a coupled ODE-PDE model [15]. A non-autonomous version of the White and Comiskey model included a distributed time delay for becoming a drug user along with both the parameters and the total high-risk population size being time-dependent [27]. From this, an autonomous model was developed incorporating the distributed time delay, which was converted into a discrete model with the time step-size being one [2]. Finally, a three compartment model consisting of susceptibles, users not in treatment, and those in treatment, assumed that those not in treatment could not recover and return to being susceptible, and that it took two contacts with a drug user to become addicted, resulting in a nonlinear incidence rate; results showed that perhaps the heroin prevalence undergoes periodic changes depending on conditions [20]. Question: Should I go through each paper specifically, like I have above, or moreso "group them" by stating some ways that the White and Comiskey model was modified and then reference them all together?

A deviation from the three compartmental model was done that included a fourth compartment which consisted of individuals who successfully recovered from their heroin use, whether through deciding to stop use by themselves or via treatment measures. The treatment of heroin users is limited by the availability of treatment facilities and resources and therefore, a saturated treatment function is incorporated; the saturation parameter was concluded as having the most vital role in the persistence of the epidemic. This implies that intervention is important early on before heroin addicts accumulate in the community and thus, prompt treatment is necessary [41]. Question: Should only include population level models, correct...not something like a heroin market model (agent-based) with drug users, sellers, homeless & police? Question: this is a "conference proceeding"; is that okay? Another model consisting of 84 ODE's 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]. Question: could I email an author to see the full model?

Others have taken a completely different approach, specifically using agent-based modeling. In addition to their ODE model, Benneyan, Garrahan, Ilieș, and Duan (2017) formulated two agent-based models: the first being a cellular automata model consisting of a grid with neighboring cells updated depending on state variables adjacent to the cells; the second being a network model with nodes that represent individuals/subpopulations and weighted pathways dependent on relational strength and nearness. Question: similarly, not all variables are defined, such as P(x,y) so could get full model? The former was to better understand regional spread and the latter to investigate spread among individuals; their results suggested that with various regulation practices for opioids, heroin death rates would decrease, but the authors recognize the reality of unintended consequences of these legislations [1] Agar (2001) created an agent-based model, consisting of a world

with 2,500 patches and 100 agents each assigned an experimentation value which defines how likely that individual is to experiment with heroin, depending on their interest in trying something new, their attitude toward illicit drug use, and their desire to follow societal rules. The model was able to track the number of heroin experimenting individuals over time with the agent moving randomly, one patch selected at random to contain heroin in the beginning, and the ability for individuals to obtain heroin from their original patch, from others who have experimented, or from another patch where the transferring of heroin between agents occurred [3].

The motivation for our heroin model came from a previous model focusing on opioid addicts through prescriptions or via the black market [5]. In order for the model to have an addiction-free equilibrium, both addictions that come from prescriptions and addictions from accessibility to excess prescription drugs must be eliminated, which equates to the need for close administration and monitoring of those prescribed. Furthermore, near the addiction-free state, the prevention of prescription opioid users becoming addicted is more important for staying near the addiction-free equilibrium than reducing the number of prescriptions getting into the hands of non-prescribed users. Question: any endemic equilibrium explicitly calculated or showing have forward bifurcation is enough for existence + endemic equilibrium connection or no to the AFE analysis? However, away from the addiction-free state, a realistic situation, the most important factors in reducing the number of addicted individuals include increasing the prescription completion rate, increasing entry into treatment (even among low success rates), and decreasing the prescription rate. The purpose of formulating a separate model from this prescription opioid model is to be able to understand the more complicated dynamics that arise among opioid addiction with the addition of heroin use. As exemplified previously, heroin plays 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 addition, since heroin users overdose almost as much as prescription opioid users and in recent years, a sharp increase of heroin overdoses has occurred, it is crucial to take a more detailed look at this increasing problem [7].

Currently working on details on how my model different than the previous ones. For the most part, models have not incorporated the connection between prescription opioid misuse and heroin use at all, 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 take

Future models to look for when published:
"Sub-epidemics within the opioid epidemic" by Hawre Jalal, Jeanine Buchanich, Lauren Balmert, Mark S. Roberts, and Donald Burke (see notes in binder from 7/2018);
"Leveraging Geospatial Methods to Accurately Identify Clusters of Opioid Drug Abuse and Target Interventions" by Zan Dodson, Eun-hye Yoo, and Jeanine Buchanich;
"A Dynamic Disease Transmission Model of the Opioid Epidemic" by David Sinclair, Hawre Jalal, Mark S. Roberts, and Donald Burke;
"A Multi-Cohort Simulation Model of the Opioid Epidemic" by Hawre Jalal, Mark S. Roberts, and Don Burke
"Heroin math: the good, the bad and the ugly" by Nicholas Battista;

Extensions

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 [24]. 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 [25]. 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 [9]. Incorporating these ideas into the model and parameter information would be possible future extensions.

Model Formulation

To our extent of our knowledge, there have been no mathematical models incorporating both prescription opioid use and heroin use. Write up differences within my model compared to other models. Our model consists of five subgroups of the (national) 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 are using heroin.

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 opioids, but not at the level of addiction.

3. Opioid addicts (A): This group of individuals are addicted to opioids or are dependent on opioids. Although the opioid class of drug includes heroin, here we will take opioids to mean non-heroin.

4. Heroin users (H): This class is composed of individuals who use heroin, which is implicitly understood to be addictive due to the drug being highly addictive [23]. We note that individuals in this class could be using other drugs or are addiction to opioids

6

in addition to heroin, but they are at least using heroin.

5. Individuals in treatment/rehabilitation (R): This class consists of individuals undergoing treatment for their addiction to opioids and/or heroin.

We assume that our 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. 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 [39]. We take opioid use disorder to fall in this categorization of addiction, due to the definition presented in [30] which includes sustained use regardless of interference with life obligations. We also recognize there is difficultly in modeling to the the variability of the purity of heroin, as overdose deaths could come from the opioid fentanyl rather than the actual heroin itself, and in fact, 1 in 5 overdose deaths have multiple drugs present so it is difficult to know the actual cause of death [7]. We try to take into account this complexity as best as possible with the information in literature. overdoses could include suicides as well...look into

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. From data, the initial values for each of the classes are the following proportions of the entire population, and therefore are dimension-less: EDIT for local data in Knox County/Tennessee.

Here, we present our ordinary differential equation model:

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

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

$$\frac{\mathrm{d}A}{\mathrm{d}t} = \gamma P + \sigma_A R + \beta(1-\xi)SA + \beta\xi SP - \zeta A - \theta_3 AH - (\mu+\mu_A)A \quad (3)$$

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

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \zeta A + \nu H - \delta R - \sigma_A R - \sigma_H R - \mu R \quad (5).$$

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

- αS: rate at which susceptible individuals are prescribed opioids (1/year)

- β : rate at which susceptible individuals become addicted to opioids by some means other than by prescription (1/year)

- $\beta(1-\xi)SA$: rate at which susceptible individuals become addicted to opioids by black market drugs or interaction with other addicts (1/year, dimension-less)

7

- $\beta\xi SP$: rate at which susceptible population obtains extra prescription opioids and becomes addicted (1/year, dimension-less)

- $\theta_1 SH$: rate at which susceptible population becomes addicted to heroin by black market availability or interaction with other heroin 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)

- δR: rate at which both opioid and heroin addicts enter back into the susceptible class after successfully finishing treatment (note: successfully finishing treatment does not protect individuals from future addiction, as there is no recovery) (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 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 (1/year)

- $\sigma_A R$: rate at which individuals transition from treatment into the opioid addicted class (note: not considered relapse because do not know where individuals came from originally) (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 (1/year)

- $\sigma_H H$: rate at which individuals transition from treatment into the heroin addicted class (note: not considered relapse because do not know where individuals came from originally) (1/year)

- νH: rate at which heroin users enter treatment/rehabilitation

Since susceptible individuals die and give birth at the same rate, μS, those terms do not appear in the differential equation for susceptibles. Also, 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 incorporating treatments at a shallow level as a part of our model. As noted before, we are classifying overdose as deaths that have

occurred from the drug, although we note the fact that Naloxone, an overdose-reversing medication, has saved individuals from overdoses [24].

We omitted an interaction term between prescribed users and addicted individuals moving into the addicted class, under the assumption that since prescribed users have access to their own prescriptions to get addicted, they do not need an illicit source or interaction with addicts to become addicted themselves. Moreover, we did not include an interaction term RA to go from the recovery to addicted class because we assume that individuals in recovery already know the feeling of addiction and do not need the influence of addicts or general availability of the drug to fall into addiction themselves. Previous work that focused on opioids (excluding heroin) concluded that the model was relatively insensitive to this path, and therefore, we have omitted it [5]. Find specific info for this. Similarly, we did not include an RH term from the recovery to heroin class for a very similar reason. We do not have a pathway from R to P, since it does not seem realistic that an individual recovering from opioid or heroin addiction would be able to either get a prescription at all or take it in a non-addictive manner.

In literature, see if PA pathway from P to A significant at all and similarly RA and RP from R to A 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:
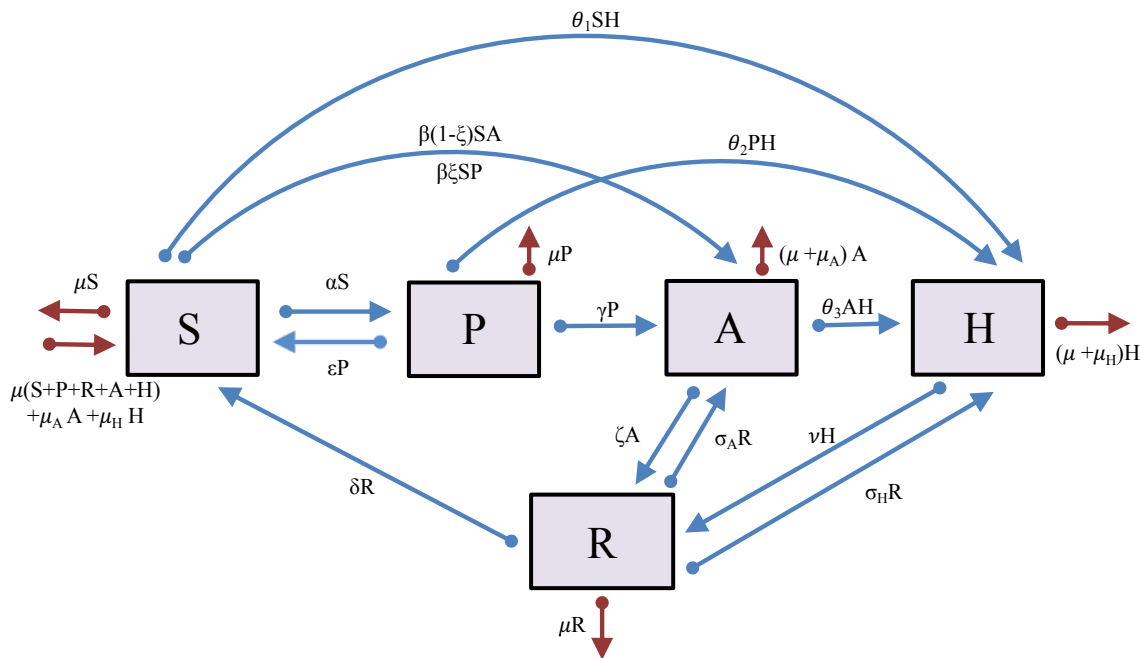

Figure 1: Schematic diagram for heroin model

Parameter Values

EDIT for local data in Knox County/Tennessee: May use ordinary least squares or bay-

We recognize that these estimated parameter values vary based on time and different locations within Knox County or East Tennessee, but are sufficient for analyzing the model.

Proof of existence of solution to ODE system
Will show existence of solution to my ODE system.

Proof of non-negative initial conditions guaranteeing non-negative solutions
We will now show that starting with non-negative initial conditions, solutions for the system (1)-(5) are guaranteed to be non-negative for all time, using the following theorem which is an adaptation of Theorem 2.1 in [28]:

Theorem 1 ([28]: adapted version of Theorem 2.1, Chapter 5) *Assume that when $\phi \in \mathbb{R}^n$ satisfies $\phi \geq 0$ with $\phi_i(0) = 0$ for some i, then $f_i(\phi) \geq 0$. Then, if $\phi \in \mathbb{R}^n$ satisfies $\phi \geq 0$, the solution of $x'(t) = f(x(t)), x(t_0) = \phi$ where $f : \mathbb{C} \to \mathbb{R}^n$ continuous, $\mathbb{C} \subset \mathbb{R}^n$ open and $\phi \in \mathbb{R}^n$, satisfies $x(t) \geq 0$ for all $t \geq t_0$.*

Proof Consider the vector of initial conditions in $\mathbb{R}^5$, $\phi = (S_0, P_0, A_0, H_0, R_0)$. Since each vector component represents a proportion of a population, $\phi \geq 0$.

1) Assume $\phi = (0, P_0, A_0, H_0, R_0) \geq 0$. Then,

$$f_1(\phi) = \epsilon P_0 + \delta R_0 + \mu(P_0 + R_0) + (\mu + \mu_A)A_0 + (\mu + \mu_H)H_0 \geq 0,$$

since all parameters and variables are non-negative.

2) Assume $\phi = (S_0, 0, A_0, H_0, R_0) \geq 0$. Then,

$$f_2(\phi) = \alpha S_0 \geq 0,$$

since α and S_0 are non-negative.

3) Assume $\phi = (S_0, P_0, 0, H_0, R_0) \geq 0$. Then,

$$f_3(\phi) = \gamma P_0 + \sigma_A R_0 + \beta \xi S_0 P_0 \geq 0,$$

since all parameters and variables are non-negative.

4) Assume $\phi = (S_0, P_0, A_0, 0, R_0) \geq 0$. Then,

$$f_4(\phi) = \sigma_H R_0 \geq 0,$$

since σ_H and R_0 are non-negative.

5) Assume $\phi = (S_0, P_0, A_0, H_0, 0) \geq 0$. Finally,

$$f_5(\phi) = \zeta A_0 + \nu H_0 \geq 0,$$

since all parameters and variables are non-negative.

Addiction-Free Equilibrium Was unable to solve for endemic equilibrium...need to eventually?

To find the addiction-free equilibrium, we set equations (1)-(5) equal to zero and require that $A = H = R = 0$ since these three compartments consist of individuals who are addiction to opioids or heroin. We are left with the system:

$$0 = -\alpha S^* - \beta\xi S^* P^* + \epsilon P^* + \mu P^*$$
$$0 = \alpha S^* - \epsilon P^* - \gamma P^* - \mu P^*$$
$$0 = \gamma P^* + \beta\xi S^* P^*.$$

If $P^* = 0$, then the only solution is $S^* = P^* = H^* = R^* = 0$, but $S^* = P^* = H^* = R^* = 1$ by assumption, so this is not possible. Thus, we will assume $P^* \neq 0$. This forces $\gamma + \beta\xi S^* = 0$ and since all of our parameters and variables are non-negative, then it must be $\gamma = 0$ and either $\beta = 0$ or $\xi = 0$. We have that $\gamma = 0$ means that individuals who are prescribed opioids cannot become addicted to opioids. In addition, $\xi = 0$ means that only black market opioids are available and there are no excess prescription drugs available and $\beta = 0$ means that susceptibles are unable to become addicted to opioids at all. We claim that $\beta = 0$ is less realistic than the former since eliminating two paths to addiction from the susceptible class is less realistic than just eliminating one path. Under the assumption that $\gamma = 0 = \xi$ to ensure the existence of our addiction-free equilibrium and that $1 = S + P + A + H + R$, we calculate the addiction-free equilibrium to be:

$$S^* = \frac{\epsilon + \mu}{\alpha + \epsilon + \mu}$$
$$P^* = \frac{\alpha}{\alpha + \epsilon + \mu}$$
$$A^* = 0$$
$$H^* = 0$$
$$R^* = 0$$

Note that enforcing $P^* \neq 0$ implies that $\alpha \neq 0$, as well, which means that individuals are still able to be prescribed opioids.

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 [37].

This idea may be applied to the context of our model since for the addiction-free equilibrium to occur, $\gamma = 0$ and $\xi = 0$, so that individuals can become addicted only with interactions with opioid addicted individuals or heroin users so 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 [37]. Our model incorporates three addiction compartments, A, H, and R, since these all consist of opioid and/or heroin 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 $\xi = 0$ (thus, $\beta \neq 0$) in order to ensure the existence of the addiction-free equilibrium. This results in the following system:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\alpha S - \beta SA - \theta_1 SH + \epsilon P + \delta R + \mu(P + R) + (\mu + \mu_A)A + (\mu + \mu_H)H$$

$$\frac{\mathrm{d}P}{\mathrm{d}t} = \alpha S - \epsilon P - \theta_2 PH - \mu P$$

$$\frac{\mathrm{d}A}{\mathrm{d}t} = \sigma_A R + \beta SA - \zeta A - \theta_3 AH - (\mu + \mu_A)A$$

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

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \zeta A + \nu H - \delta R - \sigma_A R - \sigma_H R - \mu R.$$

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

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

12

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 $i = 1, 2, 3$ [37].

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

$$\frac{dA}{dt} = \mathscr{F}_1(x, y) - \mathscr{V}_1(x, y)$$

$$\frac{dH}{dt} = \mathscr{F}_2(x, y) - \mathscr{V}_2(x, y)$$

$$\frac{dR}{dt} = \mathscr{F}_3(x, y) - \mathscr{V}_3(x, y),$$

where $x = \begin{bmatrix} A & H & R \end{bmatrix}^T$ and $y = \begin{bmatrix} S & P \end{bmatrix}^T$.

Thus, under the assumption that A, H and R 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:

$$\mathscr{F} = \begin{pmatrix} \beta SA \\ \theta_1 SH + \theta_2 PH \\ 0 \end{pmatrix}$$

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

These assumptions include the following:

- $\mathscr{F}_i(0, y) = 0$ and $\mathscr{V}_1(0, y) = 0$, $\forall y \geq 0$, $i = 1, 2, 3$, 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.

- $\mathscr{F}_i(x, y) \geq 0$, $\forall x, y \geq 0$, $i = 1, 2, 3$ since these represent new addictions.

- $\mathscr{V}_i(x, y) \leq 0$ whenever $x_i = 0, i = 1, 2, 3$ since there must be inflow only when the respective compartment is empty.

- $\sum_{n=1}^{3} \mathscr{V}_i(x, y) \geq 0$, $\forall x, y \geq 0$ since this represents the total outflow from all addicted compartments.

- The addiction-free system, $\frac{\mathrm{d}S}{\mathrm{d}t}\Big|_{A,H,R=0}$ and $\frac{\mathrm{d}P}{\mathrm{d}t}\Big|_{A,H,R=0}$ has a unique equilibrium, $(\frac{\epsilon+\mu}{\alpha+\epsilon+\mu}, \frac{\alpha}{\alpha+\epsilon+\mu})$ that is asymptotically stable.

Taking $F = \frac{\partial \mathscr{F}_i}{\partial x_j}(0, y_0)$ and $V = \frac{\partial \mathscr{V}_i}{\partial x_j}(0, y_0)$, $i, j = 1, 2, 3$, where $(0, y_0) = (\frac{\epsilon+\mu}{\alpha+\epsilon+\mu}, \frac{\alpha}{\alpha+\epsilon+\mu}, 0, 0, 0)$ is the addiction-free equilibrium, we calculated the following [37]:

$$F = \begin{pmatrix} \beta S^* & 0 & 0 \\ 0 & \theta_1 S^* + \theta_2 P^* & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

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

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

$$\sigma(FV^{-1}) = \{0, \frac{(r+s)-\sqrt{(r-s)^2+4\beta S^* z \sigma_A \zeta \sigma_H \nu}}{2det(V)}, \frac{(r+s)+\sqrt{(r-s)^2+4\beta S^* z \sigma_A \zeta \sigma_H \nu}}{2det(V)}\}$$

where $a = \zeta + \mu + \mu_A$, $b = \nu + \mu + \mu_H$, $c = \delta + \sigma_A + \sigma_H + \mu$, $z = \theta_1 S^* + \theta_2 P^*$, $r = \beta S^*(bc - \sigma_H \nu)$, $s = z(ac - \sigma_A \zeta)$, and $det(V) = a(bc - \sigma_H \nu) - \sigma_A \zeta b$.

$\mathscr{R}_0$ 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 :

$$\mathscr{R}_0 = \frac{(r+s)+\sqrt{(r-s)^2+4\beta S^* z \sigma_A \zeta \sigma_H \nu}}{2det(V)}.$$

This value is the spectral radius since it is the largest eigenvalue greater than 0. We can see this by first noting that the radicand $(r - s)^2 + 4\beta S^* z \sigma_A \zeta \sigma_H \nu$ is positive, since all parameters are positive. In addition, r is positive because in the multiplication of $bc = \delta\mu + \delta\nu + \delta\mu_H + \mu^2 + \mu\nu + \mu\mu_H + \mu\sigma_A + \mu\sigma_H + \nu\sigma_A + \boxed{\sigma_H \nu} + \mu_H \sigma_A + \mu_H \sigma_H$, all terms are positive and the highlighted term cancels with $-\sigma_H \nu$, leaving only a positive sum. Multiplying by βS^*, the resulting value r is positive. Similarly, s is positive because in the multiplication of $ac = \delta\mu_A + \delta\mu + \delta\zeta + \mu_A\mu + \mu_A\sigma_A + \mu_A\sigma_H + \mu^2 + \mu\zeta + \mu\sigma_A + \mu\sigma_H + \boxed{\sigma_A \zeta}$ $+\zeta\sigma_H$, all terms are positive and the highlighted term cancels with $-\sigma_A \zeta$, again resulting in a sum of only positive terms. Multiplied against positive value z, this results in s being positive. Finally, the expansion of $det(V)$ is positive. This is because bc is a positive sum containing a term that cancels with $-\sigma_H \nu$ as described above and ac shown above contains the term $\sigma_A \zeta$ which multiplied with b cancels with $-\sigma_A \zeta b$, thus resulting in a positive determinant. Need to prove AFE is stable if $\mathscr{R}_0 < 1$ and unstable if > 1?

Sensitivity Analysis

In order to explore the sensitivity of each of the population classes to each of the parameters, we implemented Sobol sensitivity analysis in which the Saltelli sampler is utilized to generate $N(2D+2)$ parameter samples where N=FILL IN is the number of sample points and D=16, the number of parameters in the model for a total of FILL IN samples [17]. Saltelli are the statistically good points chosen in the parameter space to test and records S, P, A, H and R at the final time (t=10 years) for the parameter choices. Samples N points from the problem and returns a matrix of parameter values. Look into total order indices: total variance (sum?), expectation (variance), normalized sum. Look at Saltelli reference, equation 44: term+complement+interaction terms
Once have baseline parameters, do +/- 50% for each parameter and cut off μ so does not go all the way to 0? Both μ_A and μ_H were restricted to the domain $[0, 0.1]$ with the remaining parameters ranging on the entire domain $[0, 1]$. 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.
Change time step to -1: result[0][-1] I believe, because want to see how outputs (S,P,A,H,R) are affected at the FINAL time

Future Work/Ideas
-Obtain local data from Knox County/East Tennessee, can calculate $\mathcal{R}_0$ from there (would expect < 1 b/c prescriptions seem to be a huge driving force behind addiction to opioids and individuals switching to heroin use. Contact with Davide Stern (UT hospital), Paul Erwin, Agricola Odoi, Kelly Cooper
-Perform sensitivity analysis to determine the sensitivity of each of the classes to the parameters (i.e. the contribution of each of the parameters to the sizes of the classes). Plan to use Sobol sensitivity analysis in which the saltelli sampler is utilized to generate (statistically good) parameter samples. Will only perform on the full odel, not the AFE b/c that would require t very large and we want to look at shorter term, such as $t = 10$ years. Will perform first, second and total indices.
-Fit parameters to data that are difficult to find in literature.
-Explore management strategies for how to best treat pain with prescriptions while reducing opioid addiction and heroin use (optimal control or scenario analysis).
Possible extentions:
-Break recovery class into two different classes for opioid addicts and heroin users (look at pain management and why people relapse: START paper and Addiction Treatment

Study).

-Look into gender, race, socioeconomic class, incarceration or rural versus urban location to investigate differences; treatment programs/types of treatment/success rates (see Modeling Gender Differences in Drug Abuse Epidemics paper, paper copy in desk and Length of Stay in Different Drug Using States: Lifestyles of Problem and Recreational Drug Consumers for location, also see "future papers to read" in heroin folder) -Significance of naloxone for reversing effects of overdose -Consider Markov Chain model (Lou from oral exam) -Linda Allen slides from Stochastic Modeling of Biological and Ecological Systems 2018 MN workshop

For a paper: *Acknowledgements: The authors would like to thank Dr. Nicholas Battista and Leigh Pearcy for their contributions.*

References

[1] (2017). *Modeling approaches, challenges, and preliminary results for the opioid and heroin co-epidemic crisis.*

[2] Abdurahman, X., Shang, L., and Teng, Z. (2014). Global dynamics of a discretized heroin epidemic model with time delay. *Abstract and Applied Analysis*, 2014.

[3] Agar, M. H. (2001). Another complex step: A model of heroin experimentation. *Field Methods*, 13(4):353–369.

[4] American Pain Society Quality of Care Committee (1995). Quality improvement guidelines for the treatment of acute pain and cancer pain. *JAMA*, 274(23):1874–1880.

[5] Battista, N., Pearcy, L., and Strickland, W. C. (2018). Modeling the prescription opioid epidemic. *NEED TO UPDATE.*

[6] Centers for Disease Control and Prevention (2016). Synthetic opioid overdose data. Available at https://www.cdc.gov/drugoverdose/data/fentanyl.html (accessed 05/01/2018).

[7] Centers for Disease Control and Prevention (2017a). Opioid data analysis. Available at https://www.cdc.gov/drugoverdose/data/analysis.html (accessed 05/01/2018).

[8] Centers for Disease Control and Prevention (2017b). Opioid overdose. Available at www.cdc.gov/drugoverdose/opioids/index.html (accessed 07/16/2018).

[9] Centers for Disease Control and Prevention (2017c). Prescription painkiller overdoses. Available at https://www.cdc.gov/vitalsigns/PrescriptionPainkillerOverdoses/index.html (accessed 7/19/2018).

[10] Cicero, T. J., , Ellis, M. S., and Surratt, H. L. (2012). Effect of abuse-deterrent formulation of oxycontin. *New England Journal of Medicine*, 367(2):187–189. PMID: 22784140.

[11] Cicero, T. J. and Ellis, M. S. (2015). Abuse-deterrent formulations and the prescription opioid abuse epidemic in the united states: Lessons learned from oxycontin. *JAMA Psychiatry*, 72(5):424–430.

[12] Cicero, T. J., Ellis, M. S., Surratt, H. L., and Kurtz, S. P. (2014). The changing face of heroin use in the united states: A retrospective analysis of the past 50 years. *JAMA Psychiatry*, 71(7):821–826.

[13] Compton, W. M. (2017). Research on the use and misuse of fentanyl and other synthetic opioids. Available at https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2017/research-use-misuse-fentanyl-other-synthetic-opioids (accessed 07/18/2018).

[14] Fang, B., Li, X.-Z., Martcheva, M., and Cai, L.-M. (2015a). Global asymptotic properties of a heroin epidemic model with treat-age. *Applied Mathematics and Computation*, 263:315–331.

[15] Fang, B., Li, X.-Z., Martcheva, M., and Cai, L.-M. (2015b). Global stability for a heroin model with age-dependent susceptibility. *Journal of Systems Science and Complexity*, 28(6):1243–1257.

[16] Florence, C. S., Zhou, C., Luo, F., and Xu, L. (2016). The economic burden of prescription opioid overdose, abuse and dependence in the united states, 2013. *Medical Care*, 54(10):901–906.

[17] Herman, J. and Usher, W. (2017). Salib-sensitivity analysis library in python. Available at https://salib.readthedocs.io/en/latest/ (accessed 05/01/2018).

[18] Ihongbe, T. O. and Masho, S. W. (2016). Prevalence, correlates and patterns of heroin use among young adults in the united states. *Addictive Behaviors*, 63:74–81.

[19] Liu, J. and Zhang, T. (2011). Global behaviour of a heroin epidemic model with distributed delays. *Applied Mathematics Letters*, 24:1685–1692.

[20] Ma, M., Liu, S., and Li, J. (2017). Bifurcation of a heroin model with nonlinear incidence rate. *Nonlinear Dynamics*, 88(1):555–565.

[21] Mandell, B. (June 2016). The fifth vital sign: A complex story of politics and patient care. *Cleveland Clinic Journal of Medicine*, 83(6).

[22] Muhuri, P. K., Gfroerer, J. C., and Davies, M. C. (2013). Associations of nonmedical pain reliever use and initiation of heroin use in the united states.

[23] National Institute on Drug Abuse (2018a). Heroin. Available at https://www.drugabuse.gov/publications/drugfacts/heroin#ref(accessed 07/17/2018).

[24] National Institute on Drug Abuse (2018b). Heroin. Available at https://d14rmgtrwzf5a.cloudfront.net/sites/default/files/828-heroin.pdf (accessed 7/18/2018).

[25] National Institute on Drug Abuse (2018c). Opioid summaries by state. Available at https://www.drugabuse.gov/drugs-abuse/opioids/opioid-summaries-by-state (accessed 7/18/2018).

[26] National Institute on Drug Abuse (2018d). Prescription opioids and heroin. Available at https://d14rmgtrwzf5a.cloudfront.net/sites/default/files/19774-prescription-opioids-and-heroin.pdf (accessed 04/16/2018).

[27] Samanta, G. (2011). Dynamic behaviour for a nonautonomous heroin epidemic model with time delay. *Journal of Applied Mathematics and Computing*, 35(1-2):161–178.

[28] Smith, H. L. (1995). *Monotone dynamical systems: an introduction to the theory of competitive and cooperative systems*, volume 41. American Mathematical Society, Rhode Island.

[29] Substance Abuse and Mental Health Services Administration (2015a). Medication and counseling treatment. Available at https://www.samhsa.gov/medication-assisted-treatment/treatment (accessed 07/16/2018).

[30] Substance Abuse and Mental Health Services Administration (2015b). Substance use disorders. Available at https://www.samhsa.gov/disorders/substance-use (accessed 07/16/2018).

[31] Substance Abuse and Mental Health Services Administration (2017a). 2016 NSDUH report: America's behavioral health changes and challenges. Available at https://www.samhsa.gov/sites/default/files/topics/data_outcomes_quality/nsduh-ppt-09-2017.pdf (accessed 06/26/2018).

[32] Substance Abuse and Mental Health Services Administration (2017b). Key substance use and mental health indicators in the united states: Results from the 2016 national survey on drug use and health. Available at https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf (accessed 06/14/2018).

[33] Substance Abuse and Mental Health Services Administration and Center for Behavioral Health Statistics and Quality (2015). 2016 national survey on drug use and health (nsduh): Final approved cai specifications for programming (english version). Available at https://www.samhsa.gov/data/sites/default/files/NSDUHmrbCAIquex2016v2.pdf (accessed 06/14/2018).

[34] United States Drug Enforcement Administration. Drug scheduling. Available at https://www.dea.gov/druginfo/ds.shtml (accessed 07/17/2018).

[35] U.S. Department of Health and Human Services (2017). Hhs acting secretary declares public health emergency to address national opioid crisis. Available at https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html (accessed 04/16/2018).

[36] U.S. Food and Drug Administration (2018). Timeline of selected fda activities and significant events addressing opioid misuse and abuse. Availabe at https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM566985.pdf (accessed 06/13/2018).

[37] van den Driessche, P. and Watmough, J. (2008). *Mathematical Epidemiology*, chapter 6: Further Notes on the Basic Reproduction Number, pages 159–178. Springer, Berlin, Heidelberg.

[38] Volkow, N. D. (2016). What science tells us about opioid abuse and addiction. Available at https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2018/what-science-tells-us-about-opioid-abuse-addiction (accessed 07/17/2018).

[39] Vowlesa, K. E., McEnteea, M. L., Julnesa, P. S., Frohea, T., Neyb, J. P., and van der Goes, D. N. (2015). Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *PAIN*, 156(4):569–576.

[40] Wang, X., Yang, J., and Li, X. (2011). Dynamics of a heroin epidemic model with very population. *Applied Mathematics*, 2(6):732–738.

[41] Wangari, I. M. and Stone, L. (2017). Analysis of a heroin epidemic model with saturated treatment function. *Journal of Applied Mathematics*, 2017.

[42] White, E. and Comiskey, C. (2007). Heroin epidemics, treatment and ode modelling. *Mathematical Biosciences*, 208:312–324.