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Modeling the prescription opioid epidemic

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Abstract Opioid addiction has become a global epidemic and a national health crisis in recent years, with the number of opioid overdose fatalities steadily increasing since the 1990s. In contrast to the dynamics of a typical illicit drug or disease epidemic, opioid addiction has its roots in legal, prescription medication - a fact which greatly increases the exposed population and provides additional drug accessibility for addicts. In this paper, we present a mathematical model for prescription drug addiction and treatment with parameters and validation based on data from the opioid epidemic. Key dynamics considered include addiction through prescription, addiction from illicit sources, and treatment. Through mathematical analysis, we show that no addiction-free equilibrium can exist without stringent control over how opioids are administered and prescribed, in which case we estimate that the epidemic would cease to be self-sustaining. Numerical sensitivity analysis suggests that relatively low states of endemic addiction can be obtained by primarily focusing on medical prevention followed by aggressive treatment of remaining cases

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- even when the probability of relapse from treatment remains high. Further empirical study focused on understanding the rate of illicit drug dependence versus overdose risk, along with the current and changing rates of opioid prescription and treatment, would shed significant light on optimal control efforts and feasible outcomes for this epidemic and drug epidemics in general.

Keywords Population Biology · Dynamical Systems · Epidemiology · Compartmental Model · Mathematical Biology · Prescription Drug Addiction

1 Introduction

Starting in the mid 1990s, allegations arose that the medical field systematically under-treated pain, and the American Pain Society (a professional organization) lobbied to have pain recognized as a 5^{th} vital sign which, if adopted, would require all physicians to accept and treat patient pain reports - naturally leading to an increase in opioid prescriptions and increasing profits for drug manufacturers (Zee, 2009; Mandell, 2016). Meanwhile, confounding medical literature appeared suggesting that cancer patients using prescription opioids to treat their chronic pain did not become addicted (Porter and Jick, 1980; Perry and Heidrich, 1982; Schug et al., 1992). One study found that only one participant out of 550 developed an addiction to their prescription painkillers (Schug et al., 1992). Another study found *no* cases of addiction among 10,000 burn victims using prescription opioid drugs (Perry and Heidrich, 1982). With this data, it began to appear as though physicians could safely prescribe opioids to those in chronic pain without fear of addiction.

By 2000, the Joint Commission began requiring that health care organizations assessing and treat pain in all patients (Mandell, 2016). OxyContin prescriptions for noncancer-related pain increased from $670,000$ in 1997 to nearly 6.2 million in 2002 (Zee, 2009). This trend continued through the early 2000s, and in 2012, it was discovered that 259 million opioid prescriptions had been written - enough for every adult in America to have at least one bottle of pills (CDC, 2014). By 2014, almost 2 million Americans abused or were dependent on prescription opioids (Hughes et al., 2016).

Unfortunately, the increase in opioid prescriptions has led to an increase in opioid addiction and abuse, affecting all age demographics. Large quantities of unused prescription drugs are currently available in many prescribed users' homes (Bicket et al., 2017), and in 2015, $276,000$ American adolescents were abusing painkillers for non-medical reasons (Hughes et al., 2016) - many of whom obtained them from a friend or relative who had a prescription (Twombly and Holtz, 2008; Han et al., 2017). In older age groups, regular, long-term opioid use is more common (Campbell et al., 2010) with possibly one in four long-term opioid users struggling with addiction (Boscarino et al., 2010). Geographically, the opioid epidemic not only affects densely populated areas, but hits rural areas especially hard as well (Keyes et al., 2014).

Misconceptions regarding prescription opioids make them especially dangerous and include the following: (1) Since opioids are medically prescribed

they are safe, (2) you cannot get addicted to prescription painkillers if taken as prescribed, (3) a person is able to safely self-medicate for pain with opioids, (4) only long-term use of certain opioids produces addiction (Twombly and Holtz, 2008; Volkow and McLellan, 2016). The coupling of these misconceptions with the general availability of opioids makes this epidemic unlike previous drug waves. To make matters worse, many opioid addicts switch to heroin as a cheaper alternative to prescription opioids (Muhuri et al., 2013), with estimates suggesting that as many as 4 out of 5 new heroin users had abused prescription painkillers prior to starting heroin (Jones, 2013). This is contrary to previous trends of addiction moving from heroin use to prescription painkillers abuse in the mid-1950s (Hughes et al., 1972; Lankenau et al., 2012).

As of October 26, 2017, the US Department of Health and Human Services has declared the opioid crisis a public health emergency (Davis, 2017). Yet despite the current seriousness and scale of the opioid epidemic, the need for effective intervention strategies, and an abundance of literature on mathematical epidemiology for infectious diseases, rigorous mathematical theory has yet to be applied to opioid addiction as it has for other diseases. In fact, very little has been published applying mathematical epidemiology to the problem of drug use in general. White and Comiskey (2007) published perhaps the first such model, mathematically describing the heroin epidemic as a system of differential equations resembling the classic SIR model of Kermack and McKendrick (1927). Alterations of this model were subsequently studied by several authors including Nyabadza and Hove-Musekwa (2010), Samanta (2011), Huang and Liu (2013), Bin et al. (2015), and Ma et al. (2017), all targeting heroin. In 2012, Njagarah and Nyabadza (2013) described a model exploring the dynamics of drug abuse epidemics more generally, focusing on the interplay between light users, heavy users, and rehabilitation. However, to our knowledge no one to date has developed and analyzed a compartmental differential equation model specifically for prescription opioids with the intent of better understanding the dynamics involved. Since opioids are regularly prescribed to a broad demographic segment of the population and addiction can arise directly from medical prescription, we expect the dynamics of this epidemic to be significantly unlike any purely illicit drug epidemic that has been studied in the past.

In this paper, we investigate the dynamics driving the opioid epidemic by formulating and analyzing an SIR-inspired model (Kermack and McKendrick, 1927; Anderson and May, 1979) based on White and Comiskey (2007) and built specifically to study addiction to a general class of prescription drugs. Our model includes multiple routes leading to dependency and addiction that are specific to prescription medication, including a "prescribed" class that both directly feeds the addicted population and contributes secondary cases via unsecured or unused drugs. We then analyze the model for key properties and conditions that may lead to a meaningful reduction in the number of addicted people and discuss our conclusions. Our results include a detailed description of equilibrium solutions under different model-structure scenar-

ios and extensive numerical analysis describing parameter sensitivity and 10 year projections under a large variety of realistic and hypothetical parameter choices. We emphasize that the goal of this paper is to investigate broad trends in prescription opioid addiction rather than localized interactions in order to narrow down possible national strategies for arresting the epidemic long-term. A discussion of our findings in this context is included in the Discussion and Conclusion section.

2 Mathematical Methods

We begin by defining 4 population classes:

1. S (*"susceptibles"*): This represents the proportion of individuals who are not using opioids or actively recovering from addiction. They may be prescribed opioids at a fixed rate (α).
2. P (*"prescribed users"*): This represents the proportion of individuals who are prescribed opioids but do not have an addiction to them. Members have some inherent rate (γ) of becoming addicted to their prescriptions, and a rate of finishing their prescription without addiction (ϵ).
3. A (*"addicted"*): This compartment represents the proportion of addicted opioid users, regardless of if their drugs are prescribed. There are multiple routes to this class in our model. One is prescription-induced (γ) addiction, while two other routes from S do not go through the P compartment: one based on interactions with addicted users or their dealers (β_A) and another based on the presence of opioid patients (β_P) in the form of unsecured or extra drugs (Hughes et al., 2016). Addicted users enter treatment at rate (ζ). Here, we define an addicted individual as someone exhibiting a pattern of continued nonmedical use with potential for harm (Vowles et al., 2015). We will assume throughout this paper that the term "pain reliever use disorder", which appears regularly in government reports (Hughes et al., 2016), satisfies this definition and that persons who "misuse" prescription opioids without further explanation do not satisfy the definition.
4. R (*"rehabilitation/treatment"*): This compartment represents the proportion of individuals who are in treatment for their addiction. We include an inherent, linear rate of falling back into addiction (σ) in contrast to White and Comiskey (2007) who only allow for a nonlinear rate. Also different in our model: members of the recovering class who complete their treatment can return to being susceptible (at rate δ). We note that structurally, this rate simply augments μR and so may also be thought of as an enhanced death rate for R (in the case that prior opioid addiction is related to a higher mortality risk) or be set to zero without any drastic change expected in the dynamics.

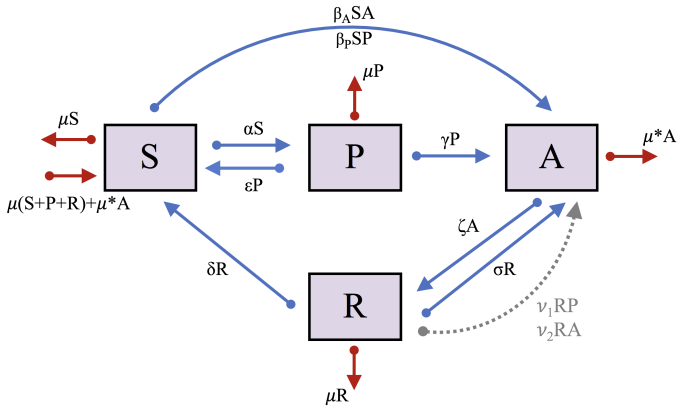


Fig. 1 Opioid Model Schematic. A schematic diagram showing the relationships between all the classes in the compartmental model of opioid addiction given by Eqns. 1-4. Red arrows denote death rates, which are passed back into S to maintain a constant population. The grey arrow represents nonlinear relapse rates which will be considered in an expanded version of the model for analysis purposes.

The system is illustrated in Fig. 1 and is specified via four continuous-time differential equations

$$\dot{S} = -\alpha S - \beta_A SA - \beta_P SP + \epsilon P + \delta R + \mu(P + R) + \mu^* A \tag{1}$$

$$\dot{P} = \alpha S - (\epsilon + \gamma + \mu)P \tag{2}$$

$$\dot{A} = \gamma P + \sigma R + \beta_A SA + \beta_P SP - (\zeta + \mu^*)A \tag{3}$$

$$\dot{R} = \zeta A - (\delta + \sigma + \mu)R. \tag{4}$$

where we set $S + P + A + R = 1$ so that S, P, A, and R represent the mean expected fraction of the population for each class. We note that $\dot{S}+\dot{P}+\dot{A}+\dot{R} = 0$ implies that $S + P + A + R = 1$ for all time, and positivity of the solution set is assured because of the density-dependent decay terms: for each variable $S, P, A, R \geq 0$, $S = 0$ implies $\dot{S} = 0$, $P = 0$ implies $\dot{P} = 0$, etc. Taken together, these facts bound each of S, P, A, R above by 1 and consequently, also below by zero. Time t is understood to be in years, and all rates can be assumed to be yearly rates.

This model assumes that any mortality due to opioid-related overdose is insufficient to significantly change total population proportions (S, P, A, and R), and all deaths are recycled back into the S class to maintain the relation $S + P + A + R = 1$. Additionally, we attempt to simply the system by considering only a first-order addiction rate γP from the P class to the A class, assuming that prescribed medication (perhaps from multiple doctors) is the primary source of opioids for most of these users. Second order effects due to mass action with A and P in the $P \to A$ route would likely also need to include feedback effects including a dynamic whereby large numbers of addicted promote additional caution in the prescribed and susceptible class, and we felt that this study was beyond the scope of a first model for prescription opioid

addiction. In a departure from the approach taken by White and Comiskey (2007), we assume that relapse from R to A would occur even in the absence of other prescribed or addicted individuals at an intrinsic rate σ. As far as we are aware, this is the first time such a linear rate has been considered in a mathematical model of opioid or heroin addiction, and we will also consider a case of the model (Eqns. 8-11) that includes mass action terms RA or RP, which may be considered to represent higher-order relapse effects.

In order to properly contextualize the epidemic model presented here within the existing, heroin-addiction based literature, we note that our model differs from the (White and Comiskey, 2007) model by initially replacing the nonlinear relapse term $\nu_1 RA$ with a linear one, and by adding a prescribed class with numerous interactions with the other classes. Eqns. (8-11) build on this model by adding nonlinear relapse terms, with the result that the model then becomes a direct extension of (White and Comiskey, 2007) to prescription drugs. In our analysis (Section 3.1), we will also consider various subsets of these models purely for the purpose of better understanding the structure and dynamics of the full model. These reduced models will be similar to (White and Comiskey, 2007), but with the possibility of linear relapse and P acting as something of a temporary holding state.

While the model is rich enough so that many of its submodels can have interesting features, our main purpose here is to better understand the dynamics involved in a prescription drug epidemic as seen on a coarse, national level. In particular, we will use data sourced from the literature to show that prescriptions (as opposed to illicitly sourced drugs) appear to be the essential driver behind the current opioid epidemic, and extensive numerical results will identify key aspects of the model important for control efforts including a large array of model projections based on data and numerous parameter regimes of interest.

2.1 Model parameters

We estimated parameter values from the literature wherever possible with the goal of focusing our attention on a neighborhood of likely values. These estimations are given in Table 1. U.S. national-level data was used in all cases as a matter of availability, with local municipality data being hard to acquire if it is available at all. Our goal therefore is to demonstrate that our model produces reasonable results in an approximately average scenario with social and demographic stratification left as a matter for future work.

The 2017 CDC Annual Surveillance report states that in 2016, 19.1 out of 100 persons received one or more opioid prescriptions (CDC, 2017). As some of these will have been continuing patients from the previous year, we assume that α, our yearly rate of moving from S to P, is less than 19.1. We were unable to find more specific data on this rate and so estimated that $\alpha = 0.15$. ϵ, the rate of ending opioid prescription use per prescription user-year, was even more difficult to find data on. Most patients end opioid use in less than a

month, while a smaller fraction can continue using opioid for over three years (Shah et al., 2017). For this reason, we explored a range of values for ϵ from 0.8 to 8 representing a general belief that most users will quit using prescription opioids in under a year if they have not become addicted.

Our prescription-induced addiction rate ($\gamma = 0.00744$) is based off of a comprehensive review (Vowles et al., 2015) which sifted through many opioid patient addiction studies of varying quality and methodology and found significant variance in the addiction rates of prescription opioid users who had been on their prescriptions for at least 90 days (95% confidence interval would have a rate of approximately 0.057-0.169 in an unweighted collection of studies). Taking only the high quality studies and an average of the minimum and maximum percents, we estimated that 9.3 percent of chronic, non-cancer pain patients become addicted to their opioid prescriptions. Using data that 0.75 of people using prescription opioids for 3 months go on to use for a year and that 0.06 of all initiates to prescription opioids use for a year (Shah et al., 2017), we arrived at our value for γ as a rate for addictions per prescribed user-year.

We then derived an illicit-induced addiction rate (0.0036) based on the ratio of physician-based sources of prescription opioids to other sources among adults reporting prescription opioid use disorder (Han et al., 2017), and given that the Substance Abuse and Mental Health Services Administration (SAMHSA) suggests that 2.1 million people abused prescription opioids for the first time in 2015 out of a population of 320 million (Hughes et al., 2016). Using this same source data (Han et al., 2017), the illicit-induced rate was then subdivided by differentiating the cases in which a user primarily obtains opioids from friends, relatives, or other similar prescribed individuals (β_P) or from a source related to general addictive demand (drug dealers) (β_A). Based on this data, we were able to estimate that 74% of users primarily obtain illicit opioids from friends/ relatives/ other verses drug dealers or strangers, resulting in $\beta_P = 0.00266$ and $\beta_A = 0.00094$. These parameter estimates are only meant to be rough starting points for the purpose of basic analysis, particularly as we expect these numbers to vary with both time and location.

The literature broadly suggests that approximately 90% of those entering treatment relapse during the first year in recovery (Smyth et al., 2010; Bailey et al., 2013; Weiss and Rao, 2017). Acute stage withdrawal lasts at most a few weeks (Gossop et al., 1987), and studies on heroin addicts suggest that up to 70% of recovering addicts may relapse during the first month after treatment ends (Smyth et al., 2010; Bailey et al., 2013). A study on US prescription opioid addicts (no heroin) similarly found that 8 weeks after cessation of treatment, only 9% had not relapsed (Weiss and Rao, 2017). We could not find published data on 4 weeks post-treatment. While we assume that this rate would be lower if the overall supply and demand of illicit drugs was reduced, it is hard to tease out to what extent. Therefore, we took the timescale of recovery and relapse to be approximately one year and made an estimate of 0.9 for the base relapse rate σ, the estimated yearly proportion of R that relapse. While this is certainly a very rough estimate that neglects nonlinear factors such as temporally dependent stages of withdrawal, environmental effects, and

Table 1 Estimated parameters for the opioid model (all rates per-capita yearly)

	Description	Est. Value	Ref.
α	prescription rate per person per year	0.15	CDC, 2017
ϵ	end prescription without addiction (rate)	$0.8 - 8$	Shah et al. 2017
β_P	illicit addiction rate based on P-class	0.00266	Han et al. 2017; Hughes et al. 2016
β_A	illicit addiction rate based on A-class	0.00094	Han et al. 2017; Hughes et al. 2016
γ	prescription-induced addiction rate	0.00744	Vowles et al. 2015; Shah et al. 2017
ζ	rate of A entry into rehabilitation	0.2–2	
δ	successful treatment rate	0.1	Weiss and Rao 2017
σ	natural relapse rate of R-class	0.9	Smyth et al. 2010; Bailey et al. 2013; Weiss and Rao 2017
μ	natural death rate	0.00729	Kochanek et al. 2017
μ^*	death rate of addicts	0.01159	Gwira Baumblatt et al. 2014; Hughes et al. 2016; Kochanek et al. 2017; Seth et al. 2018

discrepancy in treatment methodology over both time and location, we believe it to be a reasonable enough guess to serve as a gross estimate in this first model. For completeness, we also examine the addition of both a $\nu_1 RP$ and $\nu_2 RA$ relapse term to the model structure in Section 3 and Appendix A.4, but with the note that the model was not sensitive to these terms compared to σR (see Fig. 4) and that any estimation of the associated parameters is likely to be extremely difficult from an empirical point of view.

To estimate μ^*, the overall death rate for prescription opioid addicts, we started by making a rough estimate that 0.546 of all opioid deaths in the United States are attributed to addicted persons based on (Gwira Baumblatt et al., 2014). The prescription opioid death rate for the entire population is estimated to be 5.2 out of every 100,000 people per year (Seth et al., 2018), or 0.000052 deaths per person per year. We then used an estimate for the number of people with a prescription drug use disorder contemporary to the previous data (and an estimated US population of 300 million) to find the rate of prescription opioid deaths for the addicted class (Hughes et al., 2016). We then added the natural yearly death rate (obtained from Kochanek et al. (2017) by discounting addiction-related opioid deaths), to arrive at a total yearly death rate for the addicted class, e.g.

$$\begin{aligned}
&\frac{0.546 \text{ add. opioid deaths}}{1 \text{ opioid death}} \cdot \left(\frac{5.2 \text{ opioid deaths}}{100,000 \text{ people}} \right) \cdot \left(\frac{300 \times 10^6 \text{ people}}{2.0 \times 10^6 \text{ addicted}} \right) \\
&\quad + \left(\frac{728.8 \text{ deaths} - 0.546 \cdot 5.2 \text{ add. opioid deaths}}{100,000 \text{ addicted}} \right) \\
&= 0.01152 \ \frac{\text{deaths}}{\text{addicted} \cdot \text{year}}.
\end{aligned}$$

Since μ and μ^* represent continuous-time rates, we then assumed that $A_1 = A_0 e^{\mu^*}$ where $A_1 = (1-0.01152)A_0$ and similarly for μ. Solving these equations yields the values given in Table 1.

3 Results

The model was validated against national data for prescription opioid deaths between 1999 and 2016 (Hedegaard et al., 2017). To estimate the proportion of these fatalities that could be attributed specifically to addicted individuals rather than misuse by others, we adopted the percentage of prescription opioid deaths (54.6%) attributed to persons who had one or more high-risk factors, such as greater than 4 prescribers, 4 different pharmacies, or a daily dosage greater than 100 morphine milligram equivalents (MME) (Gwira Baumblatt et al., 2014). Simulations were then carried out using the estimated parameter values from Table 1 (see Fig. 2) and initial conditions chosen to approximate the proportion of each model compartment class present in 1999 (see Appendix A.1). In each simulation, we varied the rates of ending opioid prescriptions without addiction (ϵ) and treatment initiation (ζ). The number of simulated opioid related deaths were then found by computing $pop(t) \times (\mu^* - \mu)A(t)$, where $pop(t)$ was computed by taking the US population between 1999 and 2016 and finding the best fit line through the data (U.S. Census Bureau: International Database, 2018).

Each color in Fig. 2 corresponds to a particular ϵ value with $\zeta \in [0, 1]$. Our model generally agrees with the data for over a range of ϵ and ζ values. Additionally, we explored which combinations of α, ϵ, and ζ would exactly

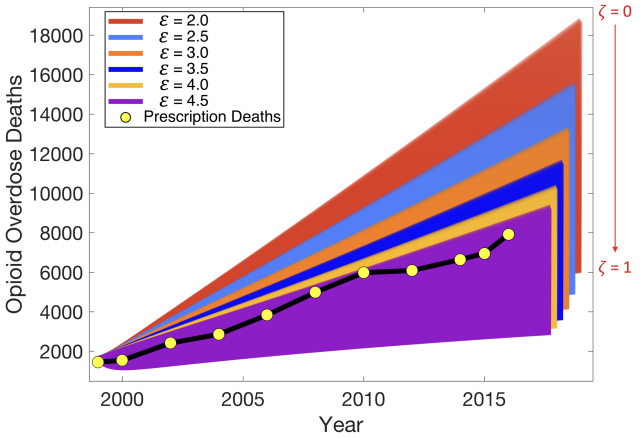


Fig. 2 Model Validation. Time-series model results varying $\epsilon \in [2, 4.5]$ (colors) and $\zeta \in [0, 1]$ (patch height) compared with prescription opioid death data from Hedegaard et al. (2017) (yellow circles). Note that $\zeta = 0$ at the top of each color patch with ζ increasing to 1 towards the bottom; this is illustrated in-figure for the $\epsilon = 2$ case.

predict the number of 2016 opioid overdose deaths attributed to individuals who are addicted. These relationships are found in Fig. 3. A few of the points on the feasibility curves were also chosen to highlight population fractions within realistic ranges. For example, when $\alpha = 0.05$, $\epsilon = 0.30$, and $\zeta = 1.32$, we find population fractions of $S(2016) = 0.8518$, $P(2016) = 0.1353$, $A(2016) = 0.0057$, and $R(2016) = 0.0072$. Or when $\alpha = 0.25$, $\epsilon = 5.40$, and $\zeta = 0.220$, we predict population fractions of $S(2016) = 0.9493$, $P(2016) = 0.0438$, $A(2016) = 0.0057$, and $R(2016) = 0.0012$. Roughly 2 million Americans had a substance abuse disorder involving prescription opioids in 2016, hence roughly $2 \times 10^6 / 300 \times 10^6$ US Pop $= 0.0066$ of Americans were actually addicted to prescription opioids, though this number is for the entire year. Between 1998 and 2006, one estimation for P is that 2% of adults were taking an opioid in any given week (Boudreau et al., 2009), so we might expect the actual value for P to be somewhat greater than 0.02 in 2016.

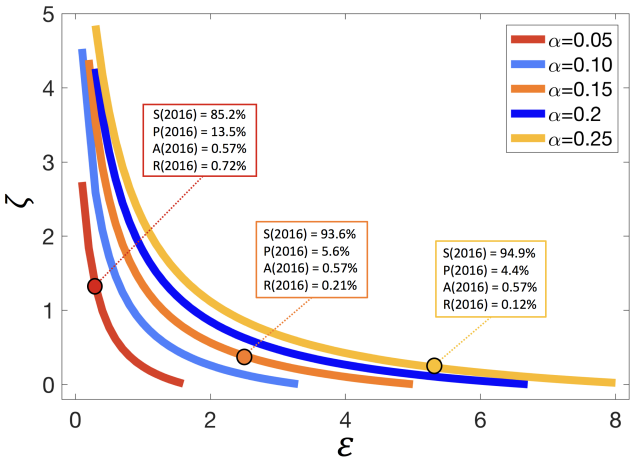


Fig. 3 Model Validation. 2016 model results based on 1999 initial conditions for various $\epsilon \in [0, 8]$, $\zeta \in [0, 5]$, and different choices of α that match prescription opioid death data from Hedegaard et al. (2017). Three specific cases where the addicted class matches the 2016 literature-estimated value for opioid use disorder are highlighted.

3.1 Addiction-free equilibrium

Existence of an addiction-free equilibrium (AFE) is dependent on the condition that $\alpha = 0$ (in which case opioid prescriptions have ceased and the AFE is given by $P, A, R = 0$ and $S = 1$), or $\gamma = 0$ and $\beta_P = 0$ (in which case P can be nonzero). With the latter condition, addiction can only occur through the black market (represented in our model by demand from current addicts). It also represents a special case of our equations that describes an illicit prescription drug epidemic sub-model which would be applicable to any epidemic where

the drug in question is available by prescription but prescribed users do not become addicted to their drug or contribute in a meaningful way to its misuse because of its general availability on the black market. In all cases, the AFE is given by

$$\begin{aligned} S^* &= \frac{\epsilon+\mu}{\alpha+\epsilon+\mu}, & A^* &= 0, \\ P^* &= \frac{\alpha}{\alpha+\epsilon+\mu}, & R^* &= 0. \end{aligned} \tag{5}$$

Traditionally, the basic reproduction number denotes how many secondary infections result from one infected individual within a population. When $\mathcal{R}_0 > 1$, the epidemic is expected to grow as more infections occur while for $\mathcal{R}_0 < 1$, the number of infected individuals declines. This remains consistent in the context of drug epidemics, where $\mathcal{R}_0$ can be understood to represent how many addictions there will be in the next generation (year) compared to the current one. Assuming that $\gamma = 0$ and $\beta_P = 0$, $\mathcal{R}_0$ can be found using the next generation method (Diekmann et al., 1990; van den Driessche and Watmough, 2002; Heffernan et al., 2005; Diekmann et al., 2010).

Remark 1 We mention here as a warning: the exact form of R_0 one obtains from the next generation method is dependent on whether or not certain classes are to be considered "infected" when applying this method. In order to satisfy all of the assumptions of the next generation method as described in (van den Driessche and Watmough, 2002), with no further assumptions on parameters (besides positivity) than $\gamma = \beta_P = 0$, one must take both A and R as "infected" classes with all others considered as "not infected." Biologically then, one should consider that those in recovery are still infected by addiction in some way, with the potential to fall back into full blown addiction on their own. However, they do not contribute to secondary cases. R_0 is then the ratio of new cases (caused by A) to the current number of cases, $A + R$.

In this case,

$$\begin{aligned} \mathcal{R}_0 &= \frac{\beta_A(\epsilon+\mu)}{(\alpha+\epsilon+\mu)(\mu^*+\zeta\Lambda)} = \frac{\beta_A S^*}{\mu^*+\zeta\Lambda} \\ \text{where} \quad \Lambda &= \frac{\delta+\mu}{\delta+\mu+\sigma},\ S^* = \frac{\epsilon+\mu}{\alpha+\epsilon+\mu}. \end{aligned} \tag{6}$$

A derivation of this result is given in Appendix A.3 and is consistent with spectral analysis. For parameter values estimated in Table 1, $\mathcal{R}_0 \approx 0.025 < 1$, and so in the absence of prescription-based primary and secondary addictions, we strongly expect the opioid epidemic to die out on its own. This result provides explicit mathematical backing to the idea that prescription opioid addiction is primarily caused by medical prescriptions and over prescribing.

Another potentially surprising result of this calculation for $\mathcal{R}_0$ is that increasing α, the rate at which opioids are prescribed to the general population,

actually reduces $\mathcal{R}_0$ and can thus act as a control on the epidemic. This behavior is a result of the AFE-required assumptions that $\beta_P = 0$ and $\gamma = 0$ (when $\alpha > 0$): if no prescribed users can become addicted to their drugs and their prescriptions do not cause other people to become addicted either, then the prescribed class effectively becomes a safe haven from opioid addiction. If this is altered by adding a $\beta_A PA$ pathway moving prescribed users to the addicted class based on the number of addicted (e.g., from prescribed users taking illicit drugs), then Eqn. 6 changes so that only β_A is left in the numerator. For expected parameter values, $\mathcal{R}_0$ still remains close to its original value. In general, we have left this pathway out of our first model for prescription opioid dynamics because it is higher-order in comparison to γP, and since prescription opioids always contribute something to their users' eventual dependency, it is difficult to parse primary cause between prescription-based usage and black-market based usage - especially when a prescription makes acquiring opioids easier. In the hypothetical case that $\gamma = 0$, one would need to examine the specifics of how $\gamma = 0$ was accomplished and what the implications are for prescribed users who may have a source of opioids on the black market before modeling the dynamics.

Comparison of Eqn. 6 for our $\gamma = \beta_P = 0$ sub-model to the form of $\mathcal{R}_0$ found by White and Comiskey (2007) (Eqn. 7) in their model of a non-prescription, heroin epidemic, the contribution of the linear relapse rate σR and the addition of the P class to the dynamics become immediately apparent. Specifically, in our equation for $\mathcal{R}_0$, α represents the contribution of the P-class to the dynamics while σ represents the contribution of the R-class via the linear relapse rate. Removing these pieces by setting $\alpha = \sigma = \gamma = \beta_P = 0$, or by setting $\sigma = \gamma = \beta_P = 0$ and adding a $\beta_A PA$ pathway from P to A (so that P is essentially a second class of S), the AFE sub-model reduces to the model of (White and Comiskey, 2007), giving us $\mathcal{R}_0 = \mathcal{R}_{0,WC}$.

$$\mathcal{R}_{0,WC} = \frac{\beta_A}{\mu^* + \zeta} \tag{7}$$

Following the method described by Castillo-Chavez and Song (2004) with β_A as the bifurcation parameter when $\mathcal{R}_0 = 1$, we can show that a backward bifurcation cannot occur in our model as described by Eqns. (1)-(4); the reader is directed to Appendix A.4 for details. However, if we expand our model with a nonlinear relapse term $\nu_2 RA$, then a backward bifurcation becomes possible.

Consider the following system of equations with additional relapse terms $\nu_1 RP$ and $\nu_2 RA$,

$$\dot{S} = -\alpha S - \beta_A SA - \beta_P SP + \epsilon P + \delta R + \mu(P + R) + \mu^* A \tag{8}$$

$$\dot{P} = \alpha S - (\epsilon + \gamma + \mu)P \tag{9}$$

$$\dot{A} = \gamma P + \sigma R + \beta_A SA + \beta_P SP + \nu_1 RP + \nu_2 RA - (\zeta + \mu^*)A \tag{10}$$

$$\dot{R} = \zeta A - (\delta + \sigma + \mu)R - \nu_1 RP - \nu_2 RA. \tag{11}$$

It is worth noting that this model is now a direct extension of White and Comiskey (2007) as we use a nonlinear relapse rate of the same form. Calculating the basic reproduction number $\mathcal{R}_0$ using the next generation method, we arrive at

$$R_{0,ext} = \frac{\beta_A(\epsilon+\mu)}{(\alpha+\epsilon+\mu)(\mu^*+\zeta\widetilde{\Lambda})} = \frac{\beta_A S^*}{\mu^*+\zeta\widetilde{\Lambda}}$$
$$\text{where} \quad \widetilde{\Lambda} = \frac{\delta+\mu}{\delta+\mu+\sigma+\nu_1 P^*},\ S^* = \frac{\epsilon+\mu}{\alpha+\epsilon+\mu},$$

so the addition of $\nu_1 RP$ contributes to $\mathcal{R}_0$ in a way similar to σ (but scaled by P^*), while the addition of $\nu_2 RA$ does not contribute to $\mathcal{R}_0$. The condition for existence of a backward bifurcation is now

$$\widetilde{\Lambda}\widetilde{\Gamma}\nu_2 > (1+\widetilde{\Gamma})(\mu^*+\zeta\widetilde{\Lambda}+\widetilde{\Lambda}\widetilde{\Gamma}P^*\nu_1) \tag{12}$$

where

$$\widetilde{\Gamma} = \frac{\zeta}{\delta+\mu+\sigma+\nu_1 P^*}.$$

Practically speaking, this implies that when Eqn. 12 is satisfied, a positive, stable, endemic equilibrium exists simultaneously with the stable AFE, raising the possibility that additional effort beyond achieving $\mathcal{R}_0 < 1$ may be required to eliminate addiction. It is interesting to note that the possible existence of a backward bifurcation is primarily driven by ν_2; however, for parameter values that we estimate to be realistic (see Table 1), such a bifurcation is unlikely to occur. While it is feasible within our numerical analysis parameter ranges, it requires minimal values for the parameters in Eqn. 12 other than ν_2, especially ζ. Of course, for the model given in Eqns. (1)-(4) where ν_2 functionally equals zero, it is not possible for a backward bifurcation to occur. With that said, our suggested parameter ranges are only estimates, and it remains a distinct possibility that a backward bifurcation occurs within biologically feasible parameter scenarios. However, we do not wish to overly dwell on analysis of the AFE in this paper as $\gamma = \beta_P = 0$ remains an unlikely special case of the model, and therefore we leave exploration of a backward bifurcation for future study.

3.2 Endemic equilibrium

Theorem 1 *For the system in Eqns. (1)-(4) with $S+P+A+R = 1$; $\mu, \mu^*, \beta_A > 0$; and all other parameters non-negative, there exists an equilibrium solution in the closed hypercube $\{0 \le S, P, A, R \le 1\}$ given by*

$$S^* = \frac{\beta_A + (1+\Theta)K + \gamma\Theta(1+\Gamma) - \sqrt{(\beta_A + (1+\Theta)K + \gamma\Theta(1+\Gamma))^2 + 4K(\beta_P\Theta(1+\Gamma) - \beta_A(1+\Theta))}}{2(\beta_A(1+\Theta) - \beta_P\Theta(1+\Gamma))}$$

if $\beta_A(1+\Theta) - \beta_P\Theta(1+\Gamma) \neq 0$ or

$$S^* = \frac{K}{\beta_A + (1+\Theta)K + \gamma\Theta(1+\Gamma)}$$

otherwise, with

$$P^* = \Theta S^*, \quad A^* = \frac{1-(1+\Theta)S^*}{1+\Gamma}, \quad R^* = \Gamma A^*$$
$$\Lambda = \frac{\delta+\mu}{\delta+\sigma+\mu}, \quad \Gamma = \frac{\zeta}{\delta+\sigma+\mu}, \quad \Theta = \frac{\alpha}{\epsilon+\gamma+\mu}, \quad K = \zeta\Lambda + \mu^*.$$

Furthermore, if there exist both an addiction-free equilibrium (AFE) and an endemic (non-AFE) equilibrium in the hypercube, the equations above yield the AFE only when it is stable, and otherwise yield the endemic equilibrium. There are never more than two coexistent equilibrium solutions, and there is never more than one endemic solution in the interior of the hypercube. In particular, if $\gamma = \beta_P = 0$ or $\alpha = 0$ then the AFE always exists, and an unique, interior, endemic equilibrium exists if and only if $\mathcal{R}_0 > 1$.

Proof Setting Eqns. (1)-(4) equal to zero, Eqns. (2) and (4) quickly give us the given expressions for P^* and R^*, and using these expressions together with $S + P + A + R = 1$ gives us A^*. Combining the equations for P^* and R^* with Eqn. (1) and setting equal to zero, we have

$$0 = A(\beta_A S - K) + \Theta S(\gamma + \beta_P S). \tag{13}$$

If $\alpha = 0$ then $\Theta = 0$, and we have the AFE $P, A, R = 0$ and $S = 1$. Additionally, given that $\beta_A > 0$, we have an endemic equilibrium defined by $S = K/\beta_A$ which will lie in the unit hypercube by the equations for P^*, A^*, and R^* if $K/\beta_A < 1$ (in which case, it is this equilibrium which is given by the statement of the theorem instead of the AFE with $S^* = 1$). Note that for the AFE with $S = 1$, $\mathcal{R}_0 = \beta_A/K$ so we expect the AFE to be unstable precisely when the endemic equilibrium represented by $S = K/\beta_A$ crosses into the hypercube.

If $\gamma = \beta_P = 0$ instead, then $A = 0$ yields the AFE described in Eqn. (5) and there is once again a second equilibrium defined by $S = K/\beta_A$. Note that when $\gamma = 0$, the AFE has $S = 1/(1+\Theta)$ so $\mathcal{R}_0 = \beta_A/(K(1+\Theta))$. It is easy to verify that when $\mathcal{R}_0 > 1$, the theorem yields the $S^* = K/\beta_A$ equilibrium and when $\mathcal{R}_0 < 1$, it yields the AFE $S^* = 1/(1+\Theta)$. One can also quickly verify that if $0 \leq S^* \leq 1/(1+\Theta) \leq 1$ ($= 1$ when $\alpha = 0$), $0 \leq A^* \leq 1$ and substituting the equation for A^* into R^*, one can easily see that $0 \leq R^* \leq 1$ as well. The equation for P^* implies that $P^* \geq 0$ and $S^*(1+\Theta) = S^* + P^* \leq 1$ implies that $P^* \leq 1 - S^* \leq 1$, which taken together shows that $0 \leq S^* \leq 1/(1+\Theta) \leq 1$ is a sufficient condition for the corresponding equilibrium to lie in the closed hypercube. Finally, $\mathcal{R}_0 > 1$ implies that $K/\beta_A < 1/(1+\Theta) \leq 1$ and $0 < \mathcal{R}_0 < 1$ implies that $0 < K/\beta_A < 1/(1+\Theta)$, which in turn implies that the AFE is unstable whenever the endemic equilibrium is inside the open unit hypercube and stable otherwise.

If $\alpha \neq 0$ and γ, β_P are not both zero, using the relation for A^* in Eqn. (13) results in a degree-two polynomial equation for S

$$0 = K - (\beta_A + (1+\Theta)K + \gamma\Theta(1+\Gamma))S + (\beta_A(1+\Theta) - \beta_P\Theta(1+\Gamma))S^2.$$

If $\beta_A(1+\Theta) - \beta_P\Theta(1+\Gamma) = 0$, it is easy to see that $0 < S \leq 1$ (note that $K > 0$ for all parameter choices). Solving the quadratic equation yields the expression for S^* given in the statement of the theorem but with both a plus and minus before the radical. The discriminant can be rewritten as

$$(\beta_A - (1+\Theta)K)^2 + \Theta(1+\Gamma)[4\beta_P K + \gamma(2\beta_A + 2K(1+\Theta) + \gamma\Theta(1+\Gamma))] \geq 0,$$

so the roots are always real. Considering in turn cases where $\beta_A(1+\Theta) - \beta_P\Theta(1+\Gamma)$ is greater than zero and less than zero, it can easily be seen that S^* with the negative square root is positive in both cases. Similarly, S^* with the positive square root is negative if $\beta_A(1+\Theta) - \beta_P\Theta(1+\Gamma) < 0$. We now show that $S^*(1+\Theta) \leq 1$ for the S^* with the negative root.

First, in the case where $\beta_A(1+\Theta) - \beta_P\Theta(1+\Gamma) = 0$ it is easy to see that the relation holds. Now assume that $\beta_A(1+\Theta) - \beta_P\Theta(1+\Gamma) > 0$. Isolating the radical in S^*, the inequality $S^*(1+\Theta) \leq 1$ is equivalent to the condition that

$$\sqrt{\cdots} \geq \frac{2\beta_P\Theta(1+\Gamma)}{1+\Theta} + (1+\Theta)K + \gamma\Theta(1+\Gamma) - \beta_A \tag{14}$$

Squaring both sides, numerous terms cancel and we are left with an expression that can be reduced to

$$0 \geq \Theta\left(\beta_P\Theta(1+\Gamma) - \beta_A(1+\Theta)\right)\left(\beta_P + \gamma(1+\Theta)\right).$$

We can see that this is true given our assumption, which shows that the magnitude of the right hand side of Eqn. (14) is less than or equal to that of the left hand side. However, since the left hand side is positive, the relation holds in all cases. Now assume that $\beta_A(1+\Theta) - \beta_P\Theta(1+\Gamma) < 0$. Then the inequality for $S^*(1+\Theta) \leq 1$ in Eqn. (14) is reversed. Similarly as before, we can show that the magnitude of the right hand side is larger than the magnitude of the left by isolating the radical and squaring both sides,

$$\sqrt{\cdots} \leq \left|\frac{2\beta_P\Theta(1+\Gamma)}{1+\Theta} + (1+\Theta)K + \gamma\Theta(1+\Gamma) - \beta_A\right|$$

but then multiplying both sides by $(1+\Theta)$, we can see that the interior of the absolute value is positive by our assumption $\beta_P\Theta(1+\Gamma) - \beta_A(1+\Theta) > 0$. So the relation holds for all cases of $\beta_A(1+\Theta) - \beta_P\Theta(1+\Gamma)$, and we have shown $S^*(1+\Theta) \leq 1$, where S^* takes the negative square root solution to the quadratic equation above, as given in the statement of the theorem.

We have already shown that the condition $S^*(1+\Theta) \leq 1$ is sufficient for the corresponding equilibrium to lie inside the closed unit hypercube, and we now note that it is also a necessary condition, since otherwise $A^* < 0$. As a result, if we consider the positive square root version of S^* for the case where it is positive ($\beta_A(1+\Theta) - \beta_P\Theta(1+\Gamma) > 0$), we quickly get the same expression as in Eqn. (14), but with the inequality reversed. As a result, this equilibrium value is only feasible in the case of equality, e.g. when $\alpha = 0$ or $\beta_P = \gamma = 0$. In both cases, this equilibrium corresponds to the AFE as found

earlier in the proof, with the other equilibrium $S^* = K/\beta_A$ (as given in the statement of the theorem) representing the endemic state. As this is the only case in which there are simultaneously two feasible equilibrium solutions, and we have already examined stability of the AFE in this case, this concludes the proof.

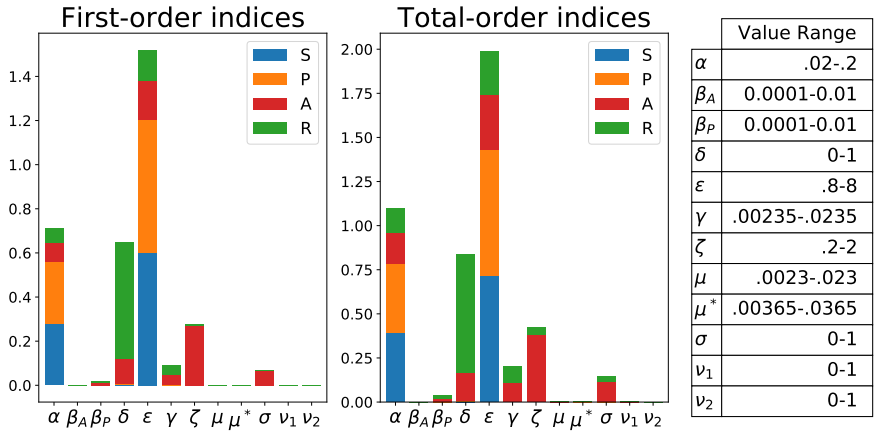
We note that stability of the AFE as described in the previous result is local in nature, and any rigorous proof of global asymptotic stability would require further analysis. Additionally, none of our analysis considers the stability (either local or global) of the endemic equilibrium. However, our numerical results suggest that the endemic equilibrium is always globally asymptotically stable when (1) it is feasible and (2) the AFE is either unstable or does not exist (see Eqn. 12 for a condition under which both the AFE and endemic equilibrium may feasibly exist and be stable).

3.3 Numerical Sensitivity Analysis

To assess the overall 10 year sensitivity of the model to its parameters, we used Saltelli's extension of the Sobol sequence (Saltelli, 2002; Saltelli et al., 2010) to vary each parameter within a range about its estimated value. We then conducted Sobol sensitivity analysis (Sobol, 2001) on the resulting values of S, P, A, and R after 10 years. This is a variance-based sensitivity analysis that has become extremely popular in recent years. One of its greatest strengths is the ability to efficiently calculate not just first-order sensitivity of the parameters (that is, perturbations of one parameter at a time), but also second-order (two at a time) and total-order (all combinations of other parameters) indices Saltelli et al. (2010). An immediate consequence of this functionality is that the presence of higher-order interactions can be inferred by comparing first-order sensitivity indices with total-order indices. If significant higher-order interactions between the parameters are present, these results will be notably different.

Initial conditions were chosen to reflect estimations of recent U.S. population fractions in each class around the year 2016: $P_0 = 0.05$ (Boudreau et al., 2009) (some increase added for passage of time), $A_0 = 0.0062$ (Hughes et al., 2016), and $R_0 = 0.0003$ (SAMHSA-CBHSQ, 2016) resulting in $S_0 = 0.9435$ so that $S + P + A + R = 1$. Relative sensitivity of the parameters can be seen in Fig. 4, where longer bars of a given color denote higher sensitivity to that parameter. The reported results for all sub-bars in this figure are within a 95% confidence interval of 0.0053. For parameter sensitivity analysis with respect to the model's AFE, see Appendix A.5. To conduct this sensitivity analysis, we used the expanded version of the model given in Eqns. (8)-(11) to illustrate the fact that the model is insensitive to choices of ν_1 and ν_2 compared to σ; results without these nonlinear replase terms (as in the original specification of the model, Eqns. (1)-(4)) are the same, minus the two parameter bars in the plot. Similarly, if the linear relapse rate σ is set to zero and the nonlinear

relapse rates remain, the sensitivity results are similar with very low to no sensitivity to ν_1 and ν_2.



	Value Range
α	.02-.2
β_A	0.0001-0.01
β_P	0.0001-0.01
δ	0-1
ε	.8-8
γ	.00235-.0235
ζ	.2-2
μ	.0023-.023
μ^*	.00365-.0365
σ	0-1
ν_1	0-1
ν_2	0-1

Fig. 4 Sensitivity of 10 year values for S, P, A, and R to model parameters using expanded Eqns (8)-(11). See Fig. 1 or Table 1 for parameter definitions. First-order indices do not take into account interactions with other parameters, while total-order indices measure sensitivity through all higher-order interactions

3.4 Simulation Results Around Realistic Parameters

The parameters ϵ (the rate at which prescribed persons complete their opioid prescription(s)) and ζ (the rate that addicts enter treatment) are difficult to parse out from data so in the following results, we varied them in the space of $\epsilon, \zeta \in [0.8, 8.0] \times [0.2, 2.0]$ while simultaneously considering changes in one other parameter at a time: β_P, β_A, γ, δ, and α. The combined results are shown in Fig. 5. Whenever unspecified by the plot, all parameters were held constant as in Table 1.

The first row of Fig. 5 examines the effect of varying the addiction rate due to opioids from excess prescriptions (β_P) while holding $\beta_A = 0.00094$, which dictates the rate of addiction due to black-market prescription opioids. The second row similarly examines the effect of varying β_A while holding β_P constant. As suggested by Fig. 4, model results do not appear to be sensitive to β_A, and are only somewhat sensitive to β_P compared to γ, δ, or α. In every case, to minimize the number of opioid addicts a high prescription completion rate and a high rate of entering treatment is required (upper-right region of each subplot).

As β_P increases, there exists a higher addicted class for low values of ϵ and ζ, suggesting that left-over prescriptions could exacerbate the number of addicted in certain circumstances - a scenario that was not apparent from

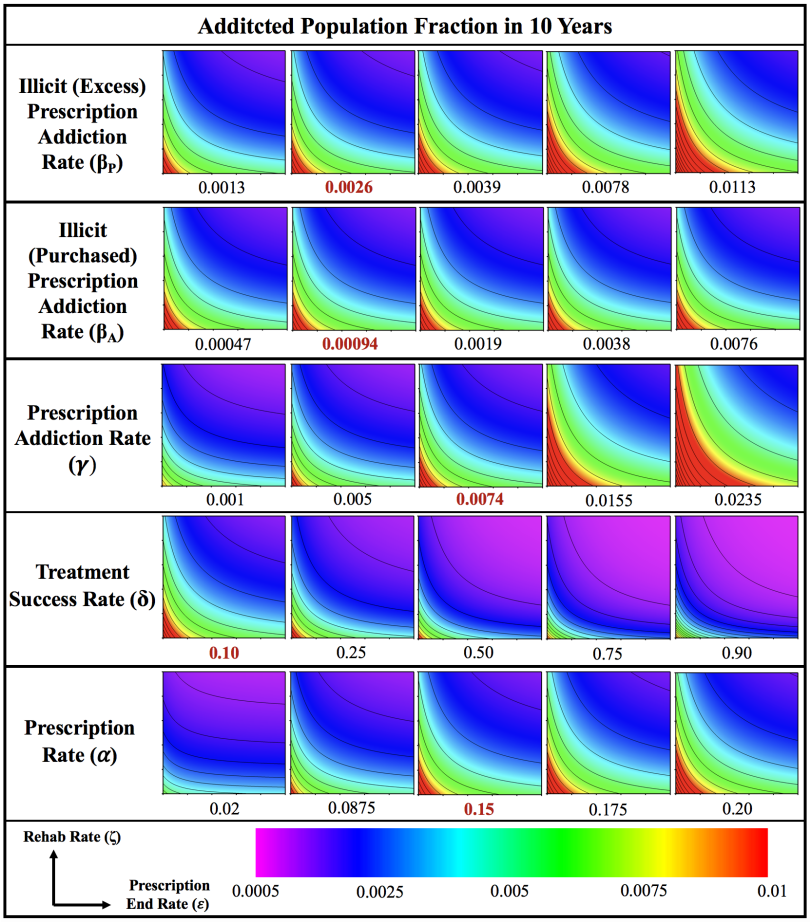


Fig. 5 Varying the Illicit Addiction Rate Due to Excess Prescriptions (β_P), Addiction Rate Due to Illicit Purchases (β_A), Prescription Addiction Rate (γ), Treatment Success Rate (δ), and Prescription Rate (α). Colormaps illustrate the predicted 10 years addicted population fraction for prescription completion rates (ϵ) and rehabilitation rates (ζ) between [0.8,8.0] and [0.2,2.0], respectively, while varying the other parameters one at a time

the Sobol analysis in Fig. 4 which was conducted within a larger feasibility space of all parameters rather than the estimated values in Table 1. Even more striking, the third row of Fig. 5 suggests that for estimated parameters, the rate at which medically prescribed opioid users become addicted (γ) very significantly affects the number of addicted. When γ doubles from its assumed realistic value of 0.00744 to 0.015, the number of addicts virtually doubles as well. Assuming that the treatment success rate δ is difficult to move, our numerical analysis strongly suggests that γ and α, the prescription addiction rate and the prescription rate respectively, are the parameters to focus on. This result strongly reinforces and extends the AFE finding that this epidemic is es-

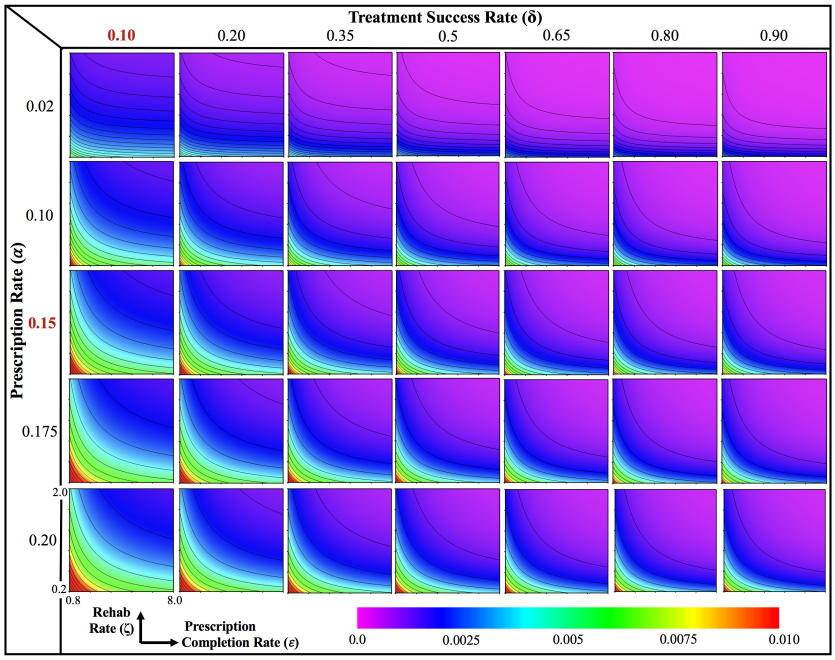


Fig. 6 Varying the the Prescription Rate (α) and Treatment Success Rate (δ) in tandem with varying prescription completion rates (ϵ) and rehabilitation rates (ζ) between [0.8,8.0] and [0,1]. Colormaps illustrate the predicted 10 years addicted population percentage

sentially driven by prescriptions and prescription-induced addictions, both in the hypothetical case where the prescription addiction rate is low and around realistic, data-estimated parameter values. It is also clear that even when the treatment success rate δ is low, or the prescription rates γ and α are as expected or high, the addicted population can be greatly reduced through a combination of a high rehab-entry rate ζ and a high rate of finishing opioid prescriptions and returning to the S-class (ϵ).

Finally, we explored the relationship between α, ϵ, δ, and ζ in detail, as these parameters are most likely to be the target of control efforts. The results can be seen in Fig. 6. Even with current level prescription rates (estimated to be $\alpha \sim 0.15$), decreased addicted population percentages can be achieved with sufficient prescription completion rates, rehabilitation initiation rates, and treatment success rates.

4 Discussion and Conclusion

In this paper, we present a first model for the opioid epidemic which utilizes the successful mathematical epidemiology approach popularized by Kermack and McKendrick (1927) for the spread of infectious disease. Parameters are

estimated from the literature and simulation results are compared with mortality data and estimates for current population fractions of our given model compartments. Analysis of our model shows that maintenance of an addiction-free population (the addiction-free equilibrium, or AFE) requires at minimum the elimination of both patient prescription-induced addiction ($\gamma = 0$) as well as secondary, non-patient addictions attributable to filled prescriptions ($\beta_P = 0$). Parameter sensitivity analysis indicates that the first of these is far more important, with near-AFE endemic states possible even if β_P is significantly greater than zero as long as $\gamma = 0$ (see Fig. 7 in Appendix A.5). This result strongly suggests that reducing the number of addictions among opioid-prescribed patients is a critical first step in combating the crisis.

Even in the hypothetical case where both prescription-induced addiction and addiction resulting from leftover prescription opioids are eliminated, the threat of ongoing, endemic addiction persists due to illicit availability of these drugs. In this case, our model reduces to an illicit drug addiction model except that prescribed opioid users are considered safe from addiction since they are closely monitored to prevent addiction to the drugs they are taking. Our calculation of the basic reproduction number, $\mathcal{R}_0$, then provides a metric by which we can determine if overall addiction will eventually die off or persist based upon model parameters.

A key result of our addiction-free equilibrium analysis using parameters estimated from the literature is that we strongly expect $\mathcal{R}_0$ to be less than one ($\mathcal{R}_0 \approx 0.025$ for estimated values) and thus, we expect that a black-market only prescription opioid epidemic is not self sustaining. This result provides mathematical backing to the conventional wisdom that unlike previous drug epidemics, prescription opioid addiction is essentially a by-product of primary and secondary addictions caused by medical prescription and likely would not be self-sustaining absent these prescriptions.

Due to the form discovered for $\mathcal{R}_0$ in Eqn. 6, the ratio of the addiction rate due to black-market opioids (β_A) to the death rate of addicts (μ^*) appears to be critical. If this ratio is less than one, the opioid epidemic is not self-sustaining without prescription drugs no matter the prescription rate or addiction treatment rate. This precise ratio β_A/μ^* may be somewhat artificial due to the recycling of overdosed persons back into the susceptible class (done in order to maintain an overall static population size), but the suggestion of a natural balance between a drug's infectiousness and potential for addiction verses its potential to be lethal is not far-fetched and could merit further study to better understand addiction in the context of an infectious social disease.

Given the difficulties of completely eradicating prescription-based addiction ($\gamma = 0$ and $\beta_P = 0$), the idea of reaching an addiction-free state remains improbable. Relaxing these assumptions, our numerical analysis suggests that control efforts should focus on reducing the average prescription length (ϵ) and increasing the rate addicts enter treatment (ζ), even if treatment is often unsuccessful (Fig. 5), followed by decreasing the number of prescriptions written (α). Reducing both ϵ and α could help naturally decrease the rate of prescription-induced addiction, γ. In one typical case where $\epsilon = 3.0$ and

$\zeta = 0.25$, doubling the rate that users enter treatment to $\zeta = 0.5$, resulted in a 21% decrease in the addicted population after 5 years, despite the fact that treatment success was held at 10%. If the treatment success rate also doubles to $\delta = 0.2$, the addicted population decreases another 8.7% (or by 27.5% of where it was initially) after 5 years.

Following this, we found that increasing the success rate of rehabilitation (δ) should also be a priority (Fig. 10 in the Appendix A.6). The beneficial effect of decreasing overall prescription lengths (via increasing ϵ) is particularly pronounced when either the rate of starting rehabilitation (ζ) is low or the success rate of rehabilitation (δ) is low, regardless of the prescription rate (α). On the other hand, our model suggests that neither the mode of relapse nor illicit opioids, whether from leftover prescriptions or demand-driven market, have much impact on the total fraction of addicted (Fig. 4 and Fig. 7 in the Appendix).

To simplify the dynamics for this first model, we neglected potential effects due to gender, race, and geographical location. Additionally, our model did not attempt to capture how prescription drug addicts may move to heroin or vice versa, leaving this study to future work. This dynamic has important ramifications for public health as heroin use is associated with high rates of overdose, especially when laced with fentanyl (Gladden et al., 2016; Peterson et al., 2016; O'Donnell et al., 2017), and could be particularly lethal for users who have first built up an opioid tolerance and then increase their doses on heroin (Muhuri et al., 2013). While many have modeled the heroin epidemic previously (D. Mackintosh, 1979; White and Comiskey, 2007; Battista, 2009; Nyabadza and Hove-Musekwa, 2010; Huang and Liu, 2013; X. Abdurahman, 2014), we are not aware of studies that incorporate effects of fentanyl, methadone, and prescription opioids all together, or studies that explicitly consider demographic effects. Our model is meant to provide a starting point for this larger, more detailed work.

Another simplification we made for the presentation of this first model was the implicit assumption that parameter values are constant with respect to time. This is obviously not the case in for many of our parameters, in particular the prescription initiation rate (α) (Pezalla et al., 2017), the prescription completion rate (ϵ) (Scully et al., 2018), the rehabilitation initiation rate (ζ), and the rehabilitation success rate (δ). Despite the large amount of public interest in prescription opioid addiction, we found it quite difficult to obtain our ball-park estimates for many of the parameters, as prescription and addiction statistics are often given in yearly aggregate numbers and survey studies are not typically designed with the intent to parameterize mathematical models. For other parameters such as β_A, β_P, ν_1, and ν_2, data is almost wholly absent by nature; fortunately, our results suggest that the model is relatively insensitive to these parameters. While beyond the scope of this particular study, we believe that a rigorous, time-sensitive estimation of model parameters is an important next step and represents a significant work on its own.

In summary, our main results confirm that necessary measures to combating the opioid epidemic include lowering the number and duration of medi-

cally prescribed painkillers, more successful treatment regimens, and increasing the availability, ease, and motivation for opioid addicts to enter treatment (Watkins et al., 2017). Our findings also provide a direct measure of the epidemic's sensitivity to each of these efforts which may be useful in allocating available resources, especially for small rural towns, cities, or states combating the epidemic. Better estimates of model parameters from data could prove crucial in developing management strategies and refining our modeling approaches - given the role of non-prescription opioids such as heroin and fentanyl to the overall epidemic and the unique effects of geography and population demography, we believe that the model presented here represents only the beginning in a larger mathematical exploration of opioid addiction dynamics.

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A Appendix

Here we present supplemental material to support our findings including additional model analysis and validation, numerical stability analysis, and simulation data. We also provide details for the calculation determining a condition for backward bifurcation, the explicit Jacobian used in our stability analysis, and simulation results illustrating system sensitivity to the prescription addiction rate (γ), treatment success rate (δ), and prescription rate (α). Futhermore, we explore the and the relationship between prescription rate (α) and prescription addiction rate (γ).

A.1 Initial Conditions for Validation

We estimated the initial prescribed population, P_0, based off of the percentage of U.S. population to whom were prescribed opioids at any given week in 2009 (2%) (Boudreau et al., 2009). Since there were more prescriptions given in 2009 than 1999 (Shah et al., 2017), we estimated that roughly $0.40 \times 2\%$ of the population were prescribed opioids at any time in 1999, hence $P_0 = 0.008$. Note we estimated the coefficient of 0.40 by using the ratio of total opioids MME sold in 1999 to 2009 (U.S. Food and Drug Administration, 2018).

We backed out the initial addicted population from the number of prescription opioid deaths in 1999 (2749) (Hedegaard et al., 2017), and normalized it by the fraction of deaths attributed to addicted persons (54.6%) (Gwira Baumblatt et al., 2014) and the predicted number of deaths from our model with the age-adjusted U.S. population in 1999 (259×10^6) (U.S. Census Bureau: International Database, 2018), e.g., $A_0 = \frac{(0.546)(2749)}{(259\times 10^6)(\mu^* - \mu)} = 0.00136$. We then assumed $R_0 = 0.1A_0$ (Office of the Surgeon General, 2016) (fraction of population in treatment), making $S_0 = 0.990504$.

A.2 Analysis of the Addiction-Free Equilibrium

Here we derive conditions on the existence of an addiction-free equilibrium (AFE) within the system defined by Eqns.1-4. To begin, we set each equation to zero and require that $A = 0$. Eqn. 3 becomes $0 = -(\delta + \sigma + \mu)R$, and since $\mu > 0$ as a natural death rate, this implies that $R = 0$ at any AFE (conversely, $R = 0$ requires that either $A = 0$ or $\zeta = 0$, which my apply at the beginning of an epidemic). We are left with the system

$$\begin{aligned} 0 &= -\alpha S^* - \beta_P S^* P^* + \epsilon P^* + \mu P^* \\ 0 &= \alpha S^* - (\epsilon + \gamma + \mu) P^* \\ 0 &= P^*(\gamma + \beta_P S^*). \end{aligned}$$

$P^* \neq 0$ since otherwise the only solution is $S^* = P^* = A^* = R^* = 0$ and we require that $S + P + A + R = 1$. Then $0 = \gamma + \beta_P S$. Since all our parameters and dependent variables are non-negative by definition, $\gamma = \beta_P = 0$. In this case, opioids are available only through the presence of current addicts (e.g. on the black market due to illicit demand) and not through currently prescribed users. We can now use our assumption that $1 = S + P + A + R$ to find that

$$\begin{aligned} S^* &= \frac{\epsilon + \mu}{\alpha + \epsilon + \mu} & A^* &= 0 \\ P^* &= \frac{\alpha}{\alpha + \epsilon + \mu} & R^* &= 0. \end{aligned}$$

A.3 Calculating the Basic Reproduction Number, R_0

Assuming that $\gamma = \beta_P = 0$, the necessary and sufficient conditions for the AFE to exist, Eqns. 3 and 4 reduce to

$$\begin{aligned} \dot{A} &= \sigma R + \beta_A S A - (\zeta + \mu^*) A \\ \dot{R} &= \zeta A - (\delta + \sigma + \mu) R. \end{aligned}$$

Using the next generation method (Diekmann et al., 1990; van den Driessche and Watmough, 2002; Heffernan et al., 2005; Diekmann et al., 2010) with both A and R treated as "infected", we compute the matrices F and V as

$$F = \begin{bmatrix} \frac{\beta_A(\epsilon+\mu)}{\alpha+\epsilon+\mu} & 0 \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} \zeta + \mu^* & -\sigma \\ -\zeta & \delta + \sigma + \mu \end{bmatrix}.$$

Then R_0 is given by the spectral radius of FV^{-1},

$$\begin{aligned} R_0 &= \frac{\beta_A(\epsilon + \mu)}{(\alpha + \epsilon + \mu)(\mu^* + \zeta \Lambda)} = \frac{\beta_A S^*}{\mu^* + \zeta \Lambda} \\ \text{where} \quad \Lambda &= \frac{\delta + \mu}{\delta + \mu + \sigma}, \; S^* = \frac{\epsilon + \mu}{\alpha + \epsilon + \mu}. \end{aligned}$$

Prevalence of opioid addicts will rise when $R_0 > 1$ and fall when $R_0 < 1$.

A.4 Jacobian Analysis and Alternative Relapse Models

Consider an alternative form for the model with the addition of two relapse rates $\nu_1 SP$ and $\nu_2 SA$,

$$\begin{aligned}
\dot{S} &= -\alpha S - \beta_A SA - \beta_P SP + \epsilon P + \delta R + \mu(P+R) + \mu^* A \\
\dot{P} &= \alpha S - (\epsilon + \gamma + \mu)P \\
\dot{A} &= \gamma P + \sigma R + \beta_A SA + \beta_P SP + \nu_1 RP + \nu_2 RA - (\zeta + \mu^*)A \\
\dot{R} &= \zeta A - (\delta + \sigma + \mu)R - \nu_1 RP - \nu_2 RA.
\end{aligned}$$

The AFE for this system remains the same (with the same conditions for existence) as in Eqn. 5. Calculating the basic reproduction number $\mathcal{R}_0$ using the next generation method, we arrive at

$$R_0 = \frac{\beta_A(\epsilon+\mu)}{(\alpha+\epsilon+\mu)(\mu^*+\zeta\widetilde{\Lambda})} = \frac{\beta_A S^*}{\mu^*+\zeta\widetilde{\Lambda}}$$
$$\text{where} \quad \widetilde{\Lambda} = \frac{\delta+\mu}{\delta+\mu+\sigma+\nu_1 P^*},\ S^* = \frac{\epsilon+\mu}{\alpha+\epsilon+\mu},$$

so the addition of $\nu_1 RP$ contributes to $\mathcal{R}_0$ in a way similar to σ (but scaled by P^*), while the addition of $\nu_2 RA$ does not contribute to $\mathcal{R}_0$. We will now conduct further analysis on this model which, as a direct extension of our model given in Eqns. (1)-(4), will include it as a subcase.

Reducing the system to three equations for S, A, R using $P = 1 - S - A - R$ gives us

$$\begin{aligned}
\dot{S} &= -\alpha S - \beta_A SA - \beta_P S(1-S-A-R) \\
&\quad + (\epsilon+\mu)(1-S-A-R) + (\delta+\mu)R + \mu^* A \\
\dot{A} &= \gamma(1-S-A-R) + \sigma R + \beta_A SA \\
&\quad + \beta_P S(1-S-A-R) + \nu_1 R(1-S-A-R) + \nu RA - (\zeta+\mu^*)A \\
\dot{R} &= \zeta A - \nu_1 R(1-S-A-R) - \nu_2 RA - (\delta+\sigma+\mu)R,
\end{aligned} \tag{15}$$

The Jacobian, J, of this system is

$$\begin{bmatrix}
-\alpha - \beta_A A + \beta_P(S-P) - (\epsilon+\mu) & (\beta_P - \beta_A)S - (\epsilon+\mu) + \mu^* & \beta_P S + \delta - \epsilon \\
-\gamma + \beta_A A + \beta_P(P-S) - \nu_1 R & -\gamma + (\beta_A - \beta_P)S - \nu_1 R + \nu_2 R - (\zeta+\mu^*) & -\gamma + \sigma - \beta_P S + \nu_1(P-R) + \nu_2 A \\
\nu_1 R & \zeta + \nu_1 R - \nu_2 R & -\nu_1(P-R) - \nu_2 A - (\delta+\sigma+\mu)
\end{bmatrix}$$

Evaluated at the AFE given by Eqns. 5 with $\gamma = \beta_P = 0$, the Jacobian $J(x_0)$ is

$$\begin{bmatrix}
-(\alpha+\epsilon+\mu) & -\beta_A S^* - (\epsilon+\mu) + \mu^* & \delta - \epsilon \\
0 & \beta_A S^* - (\zeta+\mu^*) & \nu_1 P^* + \sigma \\
0 & \zeta & -\nu_1 P^* - (\delta+\sigma+\mu)
\end{bmatrix}.$$

Following Castillo-Chavez and Song (2004), we now take β_A to be the bifurcation parameter (given the form of $\mathcal{R}_0$) and conduct analysis around

$$\beta_A^* = \frac{\mu^* + \zeta\widetilde{\Lambda}}{S^*}.$$

to analyze the bifurcation of this system when $R_0 = 1$ and determine the bifurcation's direction (Castillo-Chavez and Song, 2004). First, we define the matrix $\mathcal{A}$ as in Castillo-Chavez and Song (2004) but, via a change of coordinates, taking x_0 to be the AFE and

the bifurcation parameter to be β_A. Writing our system of differential equations (including nonlinear relapse terms) as $dx/dt = f(x, \beta_A)$, we have

$$\begin{aligned}\mathcal{A} &= \frac{\partial f_i}{\partial x_j}(x_0, \beta_A = \beta_A^*) = J(x_0, \beta_A = \beta_A^*) \\ &= \begin{bmatrix} -(\alpha+\epsilon+\mu) & -\zeta\widetilde{\Lambda} - (\epsilon+\mu) & \delta - \epsilon \\ 0 & \zeta(\widetilde{\Lambda}-1) & \sigma + \nu_1 P^* \\ 0 & \zeta & -(\delta+\sigma+\nu_1 P^* + \mu) \end{bmatrix}. \end{aligned} \tag{16}$$

It is easy to check that zero is a simple eigenvalue of $\mathcal{A}$ and that all other eigenvalues of $\mathcal{A}$ have negative real parts. $\mathcal{A}$ has right eigenvector $\mathbf{x} = (-S^*(1+\widetilde{\Gamma}), 1, \widetilde{\Gamma})^T$ and left eigenvector $\mathbf{y} = (0, 1, 1-\widetilde{\Lambda})$ where $\widetilde{\Gamma}$ is given by

$$\widetilde{\Gamma} = \frac{\zeta}{\delta+\mu+\sigma+\nu_1 P^*}$$

and once again

$$\widetilde{\Lambda} = \frac{\delta+\mu}{\delta+\mu+\sigma+\nu_1 P^*}.$$

The first component of $\mathbf{x}$ is negative, but since $S^* > 0$ the analysis still applies (Castillo-Chavez and Song, 2004). We now let f_k be the kth component of f and set

$$\begin{aligned} a &= \sum_{k,i,j=1} y_k x_i x_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(x_0, \beta_A = \beta_A^*) \\ b &= \sum_{k,i=1} y_k x_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_A}. \end{aligned}$$

The non-zero derivatives are

$$\begin{aligned} \frac{\partial^2 f_1}{\partial S \partial A} &= \frac{\partial^2 f_1}{\partial A \partial S} = -\beta_A^* \\ \frac{\partial^2 f_2}{\partial S \partial A} &= \frac{\partial^2 f_2}{\partial A \partial S} = \beta_A^* \\ \frac{\partial^2 f_2}{\partial S \partial R} &= \frac{\partial^2 f_2}{\partial R \partial S} = \frac{\partial^2 f_2}{\partial A \partial R} = \frac{\partial^2 f_2}{\partial R \partial A} = -\nu_1 \\ \frac{\partial^2 f_2}{\partial R^2} &= -2\nu_1 \\ \frac{\partial^2 f_3}{\partial S \partial R} &= \frac{\partial^2 f_3}{\partial R \partial S} = \frac{\partial^2 f_3}{\partial A \partial R} = \frac{\partial^2 f_3}{\partial R \partial A} = \nu_1 \\ \frac{\partial^2 f_3}{\partial R^2} &= 2\nu_1 \\ \frac{\partial^2 f_2}{\partial A \partial R} &= \frac{\partial^2 f_2}{\partial R \partial A} = \nu_2 \\ \frac{\partial^2 f_3}{\partial A \partial R} &= \frac{\partial^2 f_3}{\partial R \partial A} = -\nu_2 \\ \frac{\partial^2 f_1}{\partial A \partial \beta_A} &= -S^* \\ \frac{\partial^2 f_2}{\partial A \partial \beta_A} &= S^*. \end{aligned}$$

Now,

$$\begin{aligned}
a &= (1)(-S^*(1+\widetilde{\Gamma}))(1)\beta_A^* + (1)(1)(-S^*(1+\widetilde{\Gamma}))\beta_A^* \\
&\quad + (1)(-S^*(1+\widetilde{\Gamma}))(\widetilde{\Gamma})(-\nu_1) + (1)(\widetilde{\Gamma})(-S^*(1+\widetilde{\Gamma}))(-\nu_1) \\
&\quad + (1)(1)(\widetilde{\Gamma})(-\nu_1) + (1)(\widetilde{\Gamma})(1)(-\nu_1) + (1)(\widetilde{\Gamma})^2(-2\nu_1) \\
&\quad + (1-\widetilde{\Lambda})(-S^*(1+\widetilde{\Gamma}))(\widetilde{\Gamma})(\nu_1) + (1-\widetilde{\Lambda})(\widetilde{\Gamma})(-S^*(1+\widetilde{\Gamma}))(\nu_1) \\
&\quad + (1-\widetilde{\Lambda})(1)(\widetilde{\Gamma})(\nu_1) + (1-\widetilde{\Lambda})(\widetilde{\Gamma})(1)(\nu_1) + (1-\widetilde{\Lambda})(\widetilde{\Gamma})^2(2\nu_1) \\
&\quad + (1)(1)\widetilde{\Gamma}\nu_2 + (1)\widetilde{\Gamma}(1)\nu_2 + (1-\widetilde{\Lambda})(1)\widetilde{\Gamma}(-\nu_2) + (1-\widetilde{\Lambda})\widetilde{\Gamma}(1)(-\nu_2) \\
&= -2S^*(1+\widetilde{\Gamma})\beta_A^* - 2\widetilde{\Lambda}\widetilde{\Gamma}(1+\widetilde{\Gamma})P^*\nu_1 + 2\widetilde{\Lambda}\widetilde{\Gamma}\nu_2 \\
&= -2(1+\widetilde{\Gamma})(\mu^* + \zeta\widetilde{\Lambda} + \widetilde{\Lambda}\widetilde{\Gamma}P^*\nu_1) + 2\widetilde{\Lambda}\widetilde{\Gamma}\nu_2 \\
b &= (1)(1)S^* > 0.
\end{aligned}$$

To make $a > 0$, we therefore need

$$\widetilde{\Lambda}\widetilde{\Gamma}\nu_2 > (1+\widetilde{\Gamma})(\mu^* + \zeta\widetilde{\Lambda} + \widetilde{\Lambda}\widetilde{\Gamma}P^*\nu_1). \tag{17}$$

If this condition is satisfied, there will be a backward bifurcation at $R_0 = 1$. Of course, for the model given in Eqns. (1)-(4) where ν_2 functionally equals zero, it is not possible for a backward bifurcation to occur.

A.5 Addiction Free Equilibrium Numerical Analysis

To examine the sensitivity of the model's addiction free equilibrium (AFE) to its parameters, we first ran simulations to see how the AFE changes when either γ or β_P shifts away from zero. Parameter values were chosen as in Table 1 with $\epsilon = 3$ and $\zeta = 0.25$. Our results show that for our estimated parameters resulting in $R_0 \approx 0.022$, shifting β_P away from zero has little noticeable effect while shifting γ away from zero strongly moves the equilibrium away from the addiction-free state (see Fig. 7). This suggests that in a nearly addiction-free population, prescription-induced addiction remains far more important than securing prescriptions away from non-prescribed users. Note that in the exact case of an AFE, it is always stable when $\gamma = \beta_P = 0$ for a parameter space centered around the other parameters listed in Table 1.

Further analysis of the model parameter space when $\gamma = \beta_P = 0$ was conducted using the Sobol method (Sobol, 2001). We chose $N = 700000$ and generated $N(2D+2)$ parameter sets (where $D = 9$ is the dimension of the parameter space) via Saltelli's extension of the Sobol sequence (Saltelli, 2002; Saltelli et al., 2010) for a total of 16 million samples. We then ran the model to 10000 years for each set of parameters to arrive at an equilibrium. We subsequently conducted Sobol analysis (Sobol, 2001) on the values for S, P, A, and R after the final year. Initial conditions for each simulation were $S(0) = 0.9435$, $P(0) = 0.05$, $A(0) = 0.0062$, and $R(0) = 0.0003$.

A.6 Further Numerical Exploration of Parameter Space

In this section we expand our parameter space exploration for $\{\epsilon, \zeta\} \in [0.8, 8.0] \times [0.2, 2.0]$ by examining parameter sensitivity for each of S, P, A, and R instead of only the addicted class. More specifically, we examine the associated effects of ϵ and ζ on the predicted populations for 10 years into the future for each of the following cases:

1. Prescription Addiction Rate (γ),
2. Treatment Success Rate (δ),
3. Prescription Rate (α),

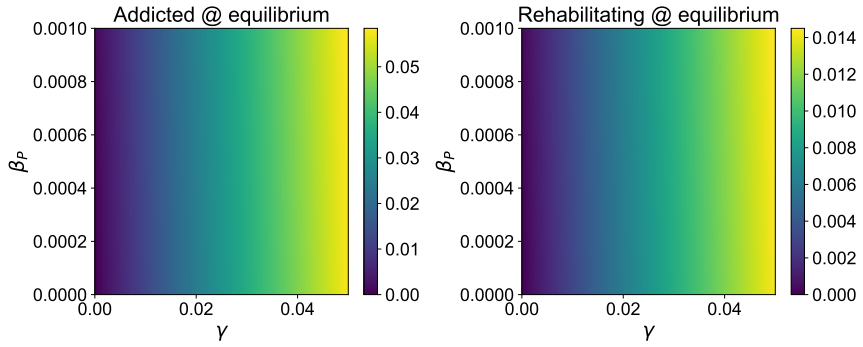
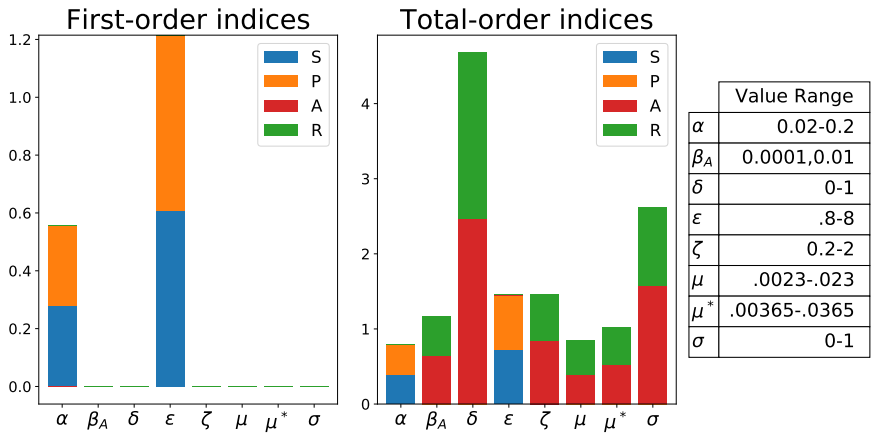


Fig. 7 Model Sensitivity to γ and β_P. Effect of moving γ and/or β_P away from zero when $R_0 \approx 0.085$ with likely parameter values, $\epsilon = 3$ and $\zeta = 0.25$



	Value Range
α	0.02-0.2
β_A	0.0001,0.01
δ	0-1
ε	.8-8
ζ	0.2-2
μ	.0023-.023
μ^*	.00365-.0365
σ	0-1

Fig. 8 Sobol sensitivity analysis for equilibrium values when $\gamma = \beta_P = 0$ (see Fig 1 or Table 1 for parameter definitions). First-order indices do not take into account interactions with other parameters, while total-order indices measure sensitivity through all higher-order interactions. The parameter ranges tested here are the same as in Fig. 4

4. Prescription Rate vs. Prescription-Induced Addiction (α vs. γ).

As in Fig. 5, Fig. 9 shows that as γ increases the addicted population grows. In particular, if γ doubles from its estimated value, there exists (ϵ, ζ) for which 2% of the population becomes addicted to opioids, which is approximately three times the number of addicts in 2016. Moreover, as γ increases, so does the rehabilitation class. Interestingly, for values of (ϵ, ζ) that make the addicted class roughly 2% of the population, the rehabilitation class makes up approximately 1%. On the other hand, when the rehabilitation class composes roughly 1.5% of the population, the addicted class makes up roughly the same percentage. When δ increases the rehabilitation class population decreases near zero. The population of the addicted class decreases towards zero as well, while the populations of the susceptible class and prescribed class appear unaffected (Fig. 10).

Fig. 11 shows that if the prescription rate α is small enough, the entire population almost remains in the susceptible class. However, for certain values of (ϵ, ζ) roughly 0.5% of the population can still remain in the addicted population. Moreover, for all cases of α and small ζ, the rehabilitation class' population remains near zero for almost all values of ϵ.

Finally, we explore the relationship between prescription-induced addiction (γ) and completing the prescription and heading back into the susceptible class (ϵ). Situations in which these two parameters do not add to one could be used to model long or short-term opioid prescription use. The data is presented in Fig. 12. It is clear that a decrease in ϵ corresponds to an increase in the number of addicts as might be expected for more chronic opioid prescription use. For large γ those differences are more subtle, as increasing γ leads to a profound escalation in the addicted population regardless of ϵ.

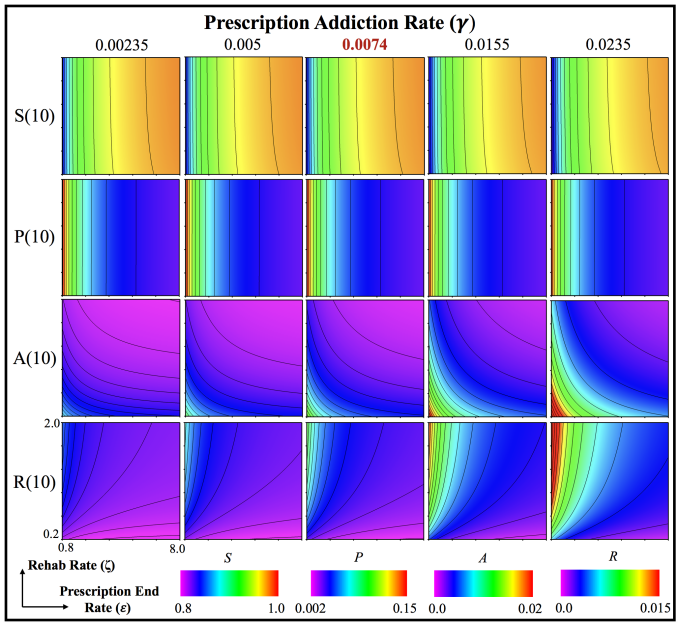


Fig. 9 Prescription Addiction Rate Colormaps illustrating the long-term equilibrium solutions (S^*, P^*, R^*, and A^*) for prescription-end rates (ϵ) and rehabilitation-start rates (ζ) between $[0.8, 8]$ and $[0.2, 2.0]$, respectively, and for various prescription addiction rates (γ)

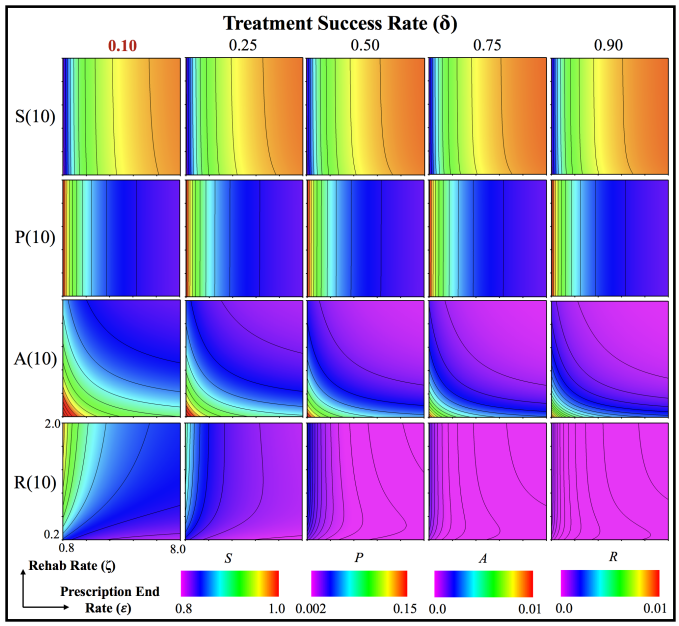


Fig. 10 Treatment Success Rate Colormaps illustrating the long-term equilibrium solutions (S^*, P^*, R^*, and A^*) for prescription-end rates (ϵ) and rehabilitation-start rates (ζ) between $[0.8, 8]$ and $[0.2, 2.0]$, respectively, and for various treatment success rates (δ)

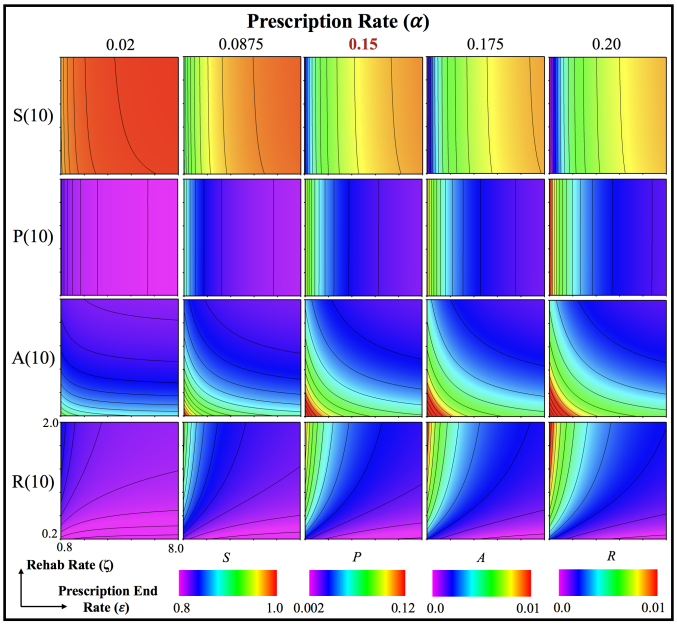


Fig. 11 Prescription Rate Colormaps illustrating the long-term equilibrium solutions (S^*, P^*, R^*, and A^*) for prescription-end rates (ϵ) and rehabilitation-start rates (ζ) between $[0.8, 8]$ and $[0.2, 2.0]$, respectively, and for various prescription rates (α)

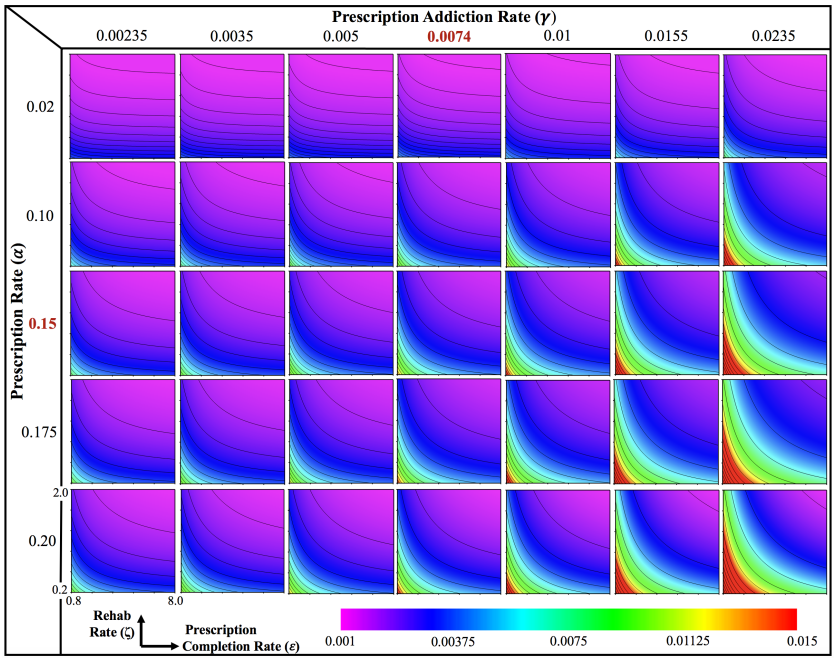


Fig. 12 Prescription-Induced Addiction vs. Prescription Completion. Colormaps illustrating the long-term equilibrium solutions (S^*, P^*, R^*, and A^*) for prescription rates (α) and rehabilitation rates (ζ) between 0 and 1 and for various rates of prescription-induced addiction (γ) and rates of finishing prescriptions (ϵ)

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