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A Markov Chain Approach for Forecasting Progression of Opioid Addiction

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A Markov Chain Approach for Forecasting Progression of Opioid Addiction

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Abstract

The U.S. is currently facing an opioid crisis. Naltrexone is a common treatment for drug addiction; it reduces the desire to take opiates. However, addicts often stop treatment or continue to use opioids while in treatment. This results in increased fatalities and associated costs. A Markov-chain model is presented to analyze the progression of opioid addiction to assist the medical community in developing appropriate treatments. The model includes patients who continue opiate use while on naltrexone (*blocked* patients) and those who use opiates after missing naltrexone doses (*unblocked* patients). The other types of patients are *abstinent* (the best-case scenario) and *dropout* (the worst-case scenario). The Markov-chain model is built on probability estimates of transitions from one stage to another; the model predicts the proportion of patients in the different stages for a given rate of intervention on dropouts. Many factors, including psychological, environmental, sociodemographic, and access-to-healthcare, impact transition probabilities and thereby the observational data used for constructing the Markov-chain model. Markov chains have been used successfully in predicting the progression of HIV (Human Immunodeficiency Virus) and other diseases. Modeling statistically provides an offline method, based on existing data, to develop successful strategies for addressing this public-health crisis.

Keywords
healthcare; Markov chains; opioid; interventions; addiction

1. Introduction

The U.S. is currently facing an opioid crisis in which significant sections of society are getting addicted to chemicals that affect the brain, making opioid abuse a growing public health problem [1]. More than 702,000 persons have died from drug overdoses in the last 18 years since 2017 for which data are available with the Centers for Disease Control and Prevention. This number appears to be increasing every year. In 2017 alone, the number of casualties has exceeded 70,000; this makes opioid abuse one of the leading causes of injury-related casualties in the country [2]. There are two types of addictions that come under the purview of opioid abuse: (a) abuse of prescription medications, methamphetamine, (meth for short), tranquilizers, and stimulants (collectively called opioids) and (b) substance (opiate) abuse. Two widely used prescription medications that often get abused are hydrocodone and oxycodone [1]. Typically, by substance abuse, one means addiction and overdose of alcohol or drugs such as heroin, cocaine, and/or marijuana. These three drugs (heroin, cocaine, and marijuana) are natural products and are technically called opiates, while opioids are essentially synthetic products that behave like opiates but are not fully natural and contain one or more synthetically produced ingredients. Collectively, addiction to opiates and opioids is generally called *opioid abuse*, and in this paper, the term "opioid" will mean opiates and/or opioids. Opioid abuse is quite prevalent in the young adult age group [3]. This work seeks to build upon the research based on sociodemographic risk factors that

increase susceptibility to such addictions and further use a statistical model rooted in Markov chains for (a) better understanding the different stages of opioid addiction and (b) potentially determining the rates of intervention needed to reduce the severity of this disease. In general, addiction arises from psychological factors, demographic factors, environmental factors, income levels, and lack of access to healthcare and treatments. In particular, a large number of risk factors have been studied in the young adult population [4], which will be elaborated upon later. Many patients remain under the radar because of poverty, homelessness, and unwillingness to disclose drug abuse and/or sexuality due to the unfortunate social stigma attached to such disclosures.

Statistical models such as Markov chains have been widely used successfully in predicting the progression of different stages of HIV (Human Immunodeficiency Virus) [5] and other diseases and to analyze the different treatment procedures available. The goal with such models is to reduce the spread of the disease. This is crucial in diseases for which a cure has not been discovered or if the patient can quickly worsen and progress to a stage where interventions are not possible. A major merit to developing such *statistical* models that capture the behavior of patients within a mathematical (and typically computerized) model is that one can study the effects of clinical intervention strategies *offline*. Randomized controlled trials (RCTs) that have a long history in the medical community [6] can often provide the initial data for statistical models. An advantage of statistical models, such as Markov-chain and discrete-event simulation, is that they provide a high-fidelity mechanism to test different intervention strategies – *after a short RCT is conducted*. A short RCT, for instance, would be 4-6 months long, while a prolonged RCT would have a duration of 4-6 years. The results of *prolonged* RCTs can be quite negative for some of the patients involved, especially for those who did not receive the appropriate treatment, but which treatment was inappropriate became clear much later after all the results came in. Further, prolonged RCTs of this nature can take a long time-period (several months) and are usually expensive. In the case of opioid abuse and HIV, time is of essence, as the patient may get worse quickly beyond cure, or in the worst case, actually lose his/her life.

The progression of opioid addiction has been studied via Markov chains in [7], where a short RCT that was 26 weeks (approximately 6 months) long was conducted. Patients who have dropped out, called *dropouts*, typically remain in that stage, as it is naturally difficult to track such patients. Dropping out of treatments for opioid addiction is clearly the least desirable outcome, as it leads to fatalities in a high proportion of cases. The overarching goal of social programs is to minimize the probability of this outcome and maximize that of *abstinence*, i.e., the stage in which the patient has stopped abusing opioids. The dataset in [7] provides a window to the world of opioid abuse. Very importantly, this dataset can be analyzed further, via the model presented here, to study and determine the appropriate *rate of intervention on the dropouts* (RID) in order to obtain a desired social outcome. RID will be defined herein as the proportion of the dropped-out patients who are brought back, via active interventions, to the *blocked* stage, where the patient returns to taking medications consistently but is still abusing opioids occasionally. Such interventions include active social interaction with the vulnerable population, as well as hard-copy advertisements (e.g., flyers) for getting tested and free counselling in locations frequented by vulnerable populations, along with follow-up of patients through other mechanisms, such as searches in existing databases. For instance, if the patient is homeless, it is likely that he/she has a history of different shelters visited in the past. In case the patient is a student still enrolled in college, there are numerous ways to try and reach out to the individual. Clearly, this kind of an intervention requires time, effort, and money. However, the model presented here shows how critically important interventions of this nature are if one desires to bring this problem under control in the long run. HIV treatments that have sought to reduce the spread of the virus have made active efforts to track vulnerable populations, and those efforts have produced a significant impact on reducing the spread of the virus [8, 9]. Similarly, RID is clearly an important strategy that can help produce a similar impact on reducing fatalities. In this paper, the goal is to predict the long-term outcomes, i.e., what proportion of patients will eventually become abstinent and what proportion will drop out, for a given rate of intervention on the dropout. In other words, the goal is thus to forecast the proportion of patients who will drop out of treatments and how many will cease using opiates for a given value of RID.

2. Background and Literature Review

A large number of factors, including sociodemographic status, homelessness, parental abuse of drugs, parental mental health (anxiety, depression, and anger), and prescription history, have been cited as major indicators of increased risk for opioid abuse within vulnerable populations [4, 10]. Young adults, it has been observed in [11]-[13], are a particularly vulnerable group for opioid abuse, and some of the factors named below apply specifically to them. The main sociodemographic and environmental factors considered in the literature are enumerated below via a numbered list, where the name of the factor is provided in each numbered item and the different categories for the factor concerned are provided within brackets:

(i) gender (male, female, gender-variant)
(ii) race (White, Hispanic/Latino, African-American, Multi-Racial, Asian/Pacific Islander, Native American, and Other)
(iii) sexual identity (heterosexual, homosexual, bisexual, questioning)
(iv) housing status (homeless in the last year, never homeless, ever in foster care)
(v) income level of parents when growing up (middle/high, low)
(vi) prescription history of patient and parents (patient prescribed, patient never prescribed, parents prescribed, parents never prescribed, parents abused drugs)
(vii) student status (attending college, completed college, college dropout, never attended college)

A so-called *risk profile* can be constructed for any individual (typically a young adult) based on the information gathered via the above list. The risk profile can be used to gauge the probability of getting addicted. The risk profile is directly related to how vulnerable an individual is to addiction and hence can become very useful in (a) demarcating patients into different risk groups that share similar characteristics and (b) in developing treatment options (procedures) for the different groups in the vulnerable population when diagnosed.

Naltrexone is commonly used to reduce addiction to opiates. It diminishes the desire to take opiates and is also used to treat alcohol addiction, which is often of a less severe magnitude than addiction to the other drugs mentioned above (marijuana, cocaine, and heroin), and addiction to prescription medications (opioids). Prescription medications that can become addictive are loosely called opioids and include painkillers and central nervous system depressants, such as benzodiazepines (Xanax, Valium, and Ativan) used to treat anxiety and sleep disorders. The focus in this study is on the drugs and opioids, rather than alcohol. Patients who continue to use opiates while on naltrexone treatment therapy are referred to as *blocked* patients in the literature, while those who use opiates after having missed numerous naltrexone doses are called *unblocked* patients. There are thus two classes of patients using opioids, although they are under treatment. The best-case scenario is that of patients who are *abstinent*, while the worst-case scenario is that of *dropout*, i.e., dropping out of treatments. The patients who have dropped out are those who were formerly undergoing treatment but are no longer with the medical care providers. The abstinent patients are those who are responding to the treatment and have stopped using opiates. Overall, thus, there are four major stages in the process of treatment: (1) abstinent, (2) blocked, (3) unblocked, and (4) dropout. A clear demarcation of this nature helps the medical community understand the disease better, as well as diagnose the current state of the patient and determine which steps can potentially be undertaken to help the patient eventually become abstinent.

3. A Markov-Chain Model

Key numerical outcomes from developing a Markov chain model are: the likelihood of a patient staying in a given state and the frequency with which the patient can transition to a different state. Markov-chain models can capture the behavior of a large number of biological systems, and, as stated above, have been utilized in studying the progression of diseases. A finite discrete-time Markov chain, which will be used in this study, is defined by a finite number of distinct *states* of the system, where the state of the system is typically the condition of the system. In this case, the stage of treatment (abstinent, blocked, unblocked, or dropout) will be equivalent to the state. Thus, there will be four distinct states in the system under consideration.

3.1. Transition Probabilities

The key to using a Markov chain model is developing estimates of probabilities of transition from one state to another. In a Markov chain, the underlying assumption in a transition from one state (i) to another (j) is that regardless of where the system has been in the past before coming to i, its probability of transition to j is a constant that depends on i and not on where the system has been before coming to i [14]. Thus, if $P(i,j)$ denotes the probability of transition from i to j, then the value of $P(i,j)$ depends only on i and j. Since these transition probabilities depend on two discrete variables (i and j), they can be written in the form of a matrix, $\boldsymbol{P}$, whose element in the ith row and jth column will equal $P(i,j)$.

3.2 Steady-State Probabilities

An advantage of setting up the transition probabilities is that one can then compute the long-run or steady-state behavior of the underlying system. Then, steady-state analysis can estimate what proportion of the affected population can be found in each of these four states in the *long run*, i.e., if the system is observed for a long time. The well-known steady-state equations for computing these proportions, also called steady-state probabilities, are given by (see e.g., [14]):

$$\Pi \boldsymbol{P} = \Pi \tag{1}$$

$$\sum_{i=1}^{n} \Pi(i) = 1 \tag{2}$$

where $\boldsymbol{\Pi}(\boldsymbol{i})$ denotes the *i*th element of the row vector $\boldsymbol{\Pi}$, $\boldsymbol{n}$ denotes the number of states in the system, and $\boldsymbol{P}$ denotes the transition probability matrix. In the above, $\boldsymbol{\Pi}(\boldsymbol{i})$ will denote the steady-state probability of state *i*, i.e., the proportion of time the system can be found in state *i* in the long run. The equations defined by (1) and (2) can be solved easily as they form a linear system of equations, allowing for the computation of the values of the steady-state probabilities after all the elements of the matrix $\boldsymbol{P}$ are estimated.

4. Numerical Results

The numerical results in this work are based on the data drawn from the short RCT conducted in [7]. It is to be noted that typically in an RCT, there is a main trial in which a medicinal drug is used for treatment and another trial on different patients in which either a placebo is used or a milder form of the treatment (or the medicinal drug) is used. Since naltrexone is known to be very effective, the two different types of treatment in [7] differed in the nature of the social interactions performed to help the patient rather than on the medicinal drug. The stronger (main) trial resulted in statistically better outcomes, and hence results from that trial are used here. As discussed above, the RID is *not* studied in [7], and the novelty of this work is to determine the intensity of RID needed for desirable outcomes. The data for the Markov chain used in the analysis here are shown via Figure 1, where each transition takes approximately 22 weeks. Note, however, that the transitions from the dropout stage (i.e., RID-related transitions) are *not* considered in [7], and this is where this model deviates from the literature. The RID (rate of intervention of dropouts) is the probability of returning a patient who has dropped out to the blocked state. This probability is denoted by x in the model, as shown in Figure 1. Consequently, the probability of a patient remaining in the dropout state is clearly $(1 - x)$. Death has not been accounted for *separately* in this model or in [7], as it is typically associated to the dropout state discussed above; those in the dropout state will essentially lose their life from the effects of this disease with a high likelihood. Also, death is an absorbing state that poses a modeling challenge in this setting.

The steady-state probabilities are computed using the matrix equations (1)—(2). A computer program was written in MATLAB and implemented on a computer using 2.60 GHz Intel Core i7-6700HQ processor and a 64-bit Windows operating system. The run time of the computer program is very short (a few microseconds), which indicates that this model can be used easily in practice. Table 1 shows the results of two different RID strategies (named A and B for convenience) for illustration. In Strategy A, the RID probability (x) is 0.01, i.e., 1 out of 100 dropouts are effectively transferred to the blocked stage. In Strategy B, the RID probability (x) is 0.5, i.e., half of those who have dropped out return to the blocked stage. Clearly, Strategy B would require a significantly higher amount of money and effort, as discussed above in Section 1.

Table 1 shows the dramatically different results from Strategies A and B. Strategy A is reflective of a situation in which very little effort is made to track the patients who have dropped out, while Strategy B is reflective of that in which a significant amount of effort is made in this direction. The steady-state percentage for each stage is shown in Table 1, which essentially equals the steady-state probability, obtained from solving Equations (1)—(2), multiplied by 100. It is clear from the results in Table 1 that it is imperative to make strong efforts to track the dropouts if one wishes to reduce the fatalities. With a low effort (Strategy A), a very high percentage of patients (82.27%) will eventually die, while this percentage is significantly reduced with high effort (Strategy B) to a lower percentage (8.49%); of course, additional efforts can bring this rate of fatalities even lower. At the same time, the results show that with a low effort (Strategy A), a very low percentage of patients (13.23%) will eventually become abstinent, while

this percentage is significantly increased with high effort (Strategy B) to a higher percentage (68.28%). Figure 2 shows how the steady-state percentages of patients being in the abstinent state and in the dropout state change as the RID value (x) is varied on a continuous spectrum. The resulting data from Figure 2 can help determine the RID needed to achieve a desired level of abstinence. It can also be potentially used in public-policy analysis to motivate the need for additional funds for social programs that can help reduce the intensity of this problem in the long run *without waiting to see the impact of a prolonged RCT.*

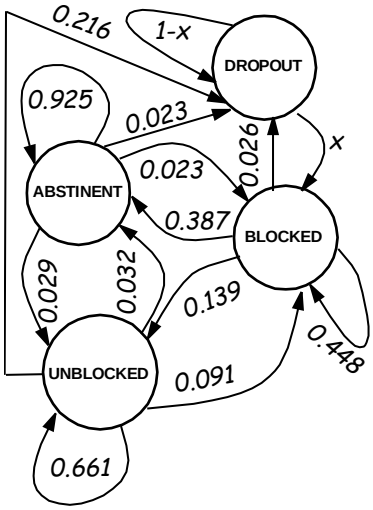

Figure 1: A schematic for the Markov chain in which the four states (abstinent, blocked, unblocked, and dropout) are denoted by four different circles and the number on the connecting arc represent the probability of the associated transition.

Table 1: Results of the numerical results with the two strategies are shown here.

RID	x	$\Pi(Abstinent)$	$\Pi(Blocked)$	$\Pi(Unblocked)$	$\Pi(Droput)$
Strategy A	0.01	13.23%	2.39%	2.11%	82.27%
Strategy B	0.5	68.28%	12.33%	10.9%	8.49%

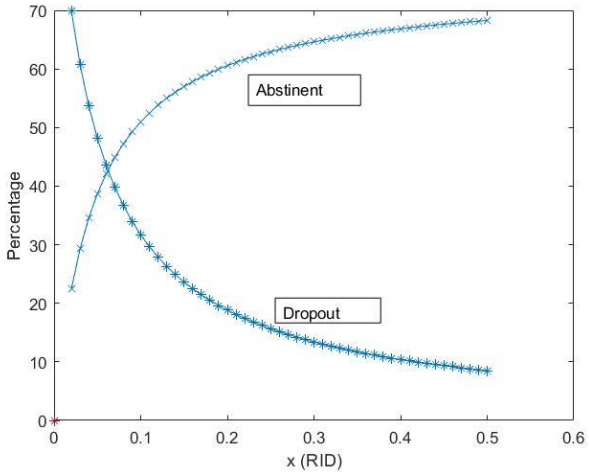

Figure 2: The figure shows how the percentages of abstinent and dropout change as RID is varied.

5. Conclusions

The opioid crisis is a significant public health issue facing the nation. A significant proportion of patients suffering from opioid abuse remain under the radar because of social stigma and other factors such as homelessness. The opioid crisis has been getting increasing media attention and needs public health and strategic initiatives for resolution. However, the existing work does not study the rates of intervention on the dropouts, which can lead to a systemic understanding of the effort needed to bring about a desired long-run goal of abstinence. This work sought to provide numerical insights on the rates of intervention on the dropouts in order to reduce the probability of deaths. Industrial and systems engineers have been studying stochastic processes for many years and have a unique opportunity to team up with psychologists and the medical community and economists to help develop solution strategies.

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