SYSTEMS SCIENCE APPROACHES TO THE OPIOID CRISIS:
EXPLORING ITS MULTIFACETED NATURE THROUGH
AGENT-BASED MODEL SIMULATIONS

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Abstract

Although opioids prescribed for medicinal purposes have shown temporary pain relief, they can lead to severe physical and psychological effects, addiction, and even death due to misuse, abuse, addiction, and overdose. The euphoric effects of opioids can drive individuals to seek street opioids, leading to a cascade of consequences that extend beyond personal health and are accompanied by a negative societal stigma, which can impede efforts to overcome the vicious cycle.

The central features of the opioid crisis reflect its complex nature, which can be effectively understood through the application of systems science methods. Purpose-specific simulation models can be created to replicate the key characteristics of the opioid crisis and used to analyze the behavior of the system, identify potential unintended consequences of different policy options, and evaluate alternative strategies. This work contributes three agent-based models, each addressing a different facet of the opioid crisis.

The first model examines the impact of COVID-19-related school closures on nonmedical prescription opioid use among youth. Grounded in social impact theory, this model explores the dynamics that may influence opioid use following school closures. By combining opinion dynamics and acute withdrawal intensity, the model simulates youth decision-making regarding opioids use. It suggests that lifting school closures could significantly increase non-medical prescription opioid use among youth. Effective interventions targeting risk factors at home can help prevent increased youth opioid use after school closures.

The second model evaluates the effectiveness of prescription regimes utilizing machine learning monitoring programs in identifying patients at risk of opioid abuse during treatment. It incorporates a hidden Markov model into an agent-based simulation to classify patients’ underlying states of prescription opioid use. A synthetic data experiment was conducted using the calibrated agent-based simulation model to generate time series data for feature selection. Lowering prescription doses yields favorable results in terms of overdose rates, escalation to street opioids, and prescription legitimacy, emphasizing the need for comprehensive evaluation of public health interventions.

The third model focuses on modified opioid agonist therapy (OAT) guidelines during the COVID-19 pandemic. It simulates individuals receiving OAT, including those with increased take-home doses. The model assesses the impact of increased take-home doses on treatment retention and opioid-related harms. Model findings suggest that increasing take-home doses could enhance treatment retention. However, the increased opioid-related harms among certain groups of patients receiving higher take-home doses of OAT underscores the importance of expanding naloxone availability within the networks of OAT patients.

At a methodological level, this dissertation demonstrates the integration of opinion dynamics theories, AI-based health policies, and hierarchical state-charts to enhance the utility of agent-based models in addressing public health issues. It highlights the models’ ability to generate time series data for machine learning techniques and evaluate the long-term impacts of AI-based healthcare policies. Furthermore, the modular design patterns used in the models facilitate comprehensive policy assessment while retaining generality.
List of the peer-reviewed publications with contents from this dissertation


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To the three-year-old princess
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<td>Agent-Based Modeling</td>
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<tr>
<td>AI</td>
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<td>AUC</td>
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<td>ICES</td>
<td>Institute for Clinical Evaluative Sciences</td>
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<td>MMEs</td>
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<td>National Drug and Alcohol Research Centre</td>
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<td>OSDUHS</td>
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<td>OAT</td>
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<td>OUD</td>
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<td>PDMP</td>
<td>Prescription Drug Monitoring Program</td>
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Chapter 1

Introduction

Opioids [256, 255, 336] are a broad group of drugs that are prescribed by healthcare professionals to relieve moderate to severe pain in patients. Opioid drugs mimic the actions of natural opioids in the body by binding to receptors in the central nervous system, which leads to changes in the perception of pain. Opioids can also produce and amplify feelings of euphoria, which can lead to an irresistible craving for this feeling and excessive, persistent, and compulsive use of the drug. When activated, this vicious cycle increases the risk of developing opioid tolerance -- whereby escalating doses are required for the same physiological effect -- dependence, addiction, and opioid related death [256, 255, 336].

In Canada, opioids can only be sold, manufactured, or used for industrial, scientific, or medicinal purposes. However, over the past 25 years, there has been a dramatic increase in opioid-related morbidity and mortality in the country [38, 326, 133]. The initial surge in opioid-related hospitalizations and fatalities was primarily linked to the increased availability of prescription medications in the late 1990s [73]. In 2010, various interventions and policies were implemented with the aim of reducing the distribution of prescribed opioids. However, these actions had adverse consequences, resulting in an increase in the use of illegal opioids, particularly heroin [38]. Although there was a temporary decrease in opioid-related mortality rates from 2017 to 2019, there has since been a resurgence in fentanyl and other synthetic opioid overdoses, and the COVID-19 pandemic has further elevated the health burden of opioids [60, 189].

The widespread use of prescription opioids and the dramatic increase in accessibility of illegal opioids have led to what has been referred to as the “opioid crisis” [127, 208]. As a result, healthcare professionals have begun to question the use of long-term, high-dose prescription opioids in treating chronic pain. Some proposed solutions, such as the restriction of prescription opioids, may lead to unintended consequences, such as where people using prescription opioids with opioid use disorder (OUD) turn to illegal opioids [265, 217, 124]. Along with increasing illegal opioid use, there is also a growing demand for drugs to temporarily reverse the effects of opioid overdoses and medications for OUD [58, 319]. Additionally, exposure to opioids prescribed to family members among adolescents and young adults is a growing concern as it can place adolescents and young adults at risk of addiction and overdose, even if the substances are prescribed to family members for medical reasons [85, 242, 42].

The complexities of addressing a highly interconnected system that underlies the opioid crisis can lead to unpredictable responses to policy interventions. This problem is exacerbated by fluctuations in the avail-
ability of opioid drugs and the emergence of synthetic opioids. Therefore, this interconnected nature of the components in the opioid crisis motivates the use of utilizing systems science approaches to explore its complexities [151, 115]. Systems science was developed to investigate the non-linear relationship between the structure of a system and its behavior, in which changes and evolution of the system can give rise to surprising behavior. This is particularly relevant when relationships between system components change over time, feedback loops are present, there are substantial delays between causes and effects, and changes in one area of the system may have unintended implications in another [180, 54, 343]. Systems science methods can be used to uncover the consequences of interactions between the various components involved in the opioid crisis, each with their own set of behaviors [205].

Through the use of systems science methods, it is possible to create simulation models that replicate differing key characteristics of the opioid crisis. These models can then be used to analyze the behavior of the system and identify potential unintended consequences of different policy options, as well as to evaluate trade-offs and explore alternative strategies for prevention and treatment. This is particularly valuable given the complexity of public health problems such as the opioid crisis [168].

1.1 Motivation

Systems science tools, such as simulation modeling and other computational techniques, have been widely used in public health to clarify existing mental models about public health problems, simulate their possible dynamics, estimate underlying parameters, and answer 'what-if' policy questions. Simulation models [30], including System Dynamics, agent-based modeling, and discrete-event simulation have been employed to model infectious diseases [224], non-infectious diseases [338, 243] and mental health issues [196]. The use of these methods has led to effective strategies for reducing the impact of diseases by assessing the outcomes and effectiveness of specific interventions. Simulation models can further help anticipate and avoid potential unintended consequences in addressing complex social and public health problems and suggest effective solutions that are sustainable in the long-term [205, 55, 270]. Such techniques are well-suited for analyzing the coupled and ever-changing nature of public health issues. Public health challenges often involve highly coupled dynamics and multifaceted interactions, and these modeling methods provide valuable tools for comprehensively studying and understanding these complex issues [202, 51].

The Canadian opioid crisis is characterized by a staggering number of fatal overdoses on prescription opioids, addiction, and social harm, and has been ongoing for the past quarter century [38, 73]. This crisis is being exacerbated by growing usage of powerful synthetic opioids, an increase in polydrug use, -- both intentional and unintentional -- and low rates of treatment admission and retention [312]. The COVID-19 pandemic has exacerbated and complicated the opioid crisis. Some measures to prevent the spread of COVID-19 -- such as social distancing and reduced access to harm reduction services -- have created unintended consequences for mitigating the ongoing opioid crisis, creating a dual public health crisis [189]. Furthermore,
the COVID-19 pandemic has resulted in a rise in stress and anxiety levels, which in turn can exacerbate opioid use and addiction [252].

Policy makers are seeking a deeper understanding of the various factors that can lead to opioid use and misuse, including the potential impact, pathways, progression, outcomes, and consequences of opioid use and misuse. A systems science approach, with guidance from experts in epidemiology, prevention, and treatment services, is necessary to gain a comprehensive understanding of the evolving trajectories of the crisis and identify potential mitigating factors. Current simulation models, while able to depict certain aspects of the opioid crisis in the United States [286], do not fully capture the unique dynamics of the crisis in Canada [73].

The majority of current simulation models on the impact of opioid use in North America are based on data from the United States [69]. While the opioid crisis in the United States may have similarities with Canada in some aspects, such as its origins in the widespread use of prescription opioids, there are also significant differences [73, 162]. These include variations in access to public and private healthcare [144], direct-to-consumer advertising [337], electronic prescribing systems [15, 110], and addiction treatment options [269]. Furthermore, the nature of illicit drug production, manufacturing, and distribution differs greatly between the two countries [348]. Thus, additional simulation models are necessary to accurately understand and address the opioid crisis in Canada, particularly in terms of the design and implementation of prevention and treatment services.

To effectively develop a simulation model to study public health problems, a meaningful level of abstraction is required. Early and most subsequent simulation models of the opioid crisis primarily used aggregate compartmental or System Dynamics modeling [69] that cannot effectively trace individual histories or incorporate individual-level perception, network context, and data. Family, peers, social identity, and demographic factors at the individual level influence the development of overlapping syndromes of opioid misuse as it evolves and resulting future drug misuse within populations. Agent-based modeling (ABM) [49, 126, 274] as a core systems science methodology can capture a deep representation of the social contextual circumstances of opioid use and misuse at the individual and population level in terms of different geographical, demographic, and social factors. ABM can help understand the role of localized social context and individual history in relation to engagement in prevention and treatment services. Therefore, further studies specifically investing in ABM to develop simulation models of the opioid crisis to inform policy decision-making in Canada are valuable, particularly in an integrated approach that combines the contributions of knowledge derived from healthcare, education, policing and justice, and social service systems.

The dissertation argues that the use of systems science, through the use of simulation modeling both alone and with support by relevant machine learning methods, can help in developing and utilizing effective models to enhance decision-making in addressing the opioid crisis and bridge existing knowledge gaps on various aspects of the opioid crisis.
1.2 Problem Statement

Despite attempts to curb the opioid crisis and mitigate its effects, the rates of opioid misuse and opioid-related deaths remain alarmingly high in Canada [38, 73]. This crisis in Canada and other countries has led to an increase in the development of dynamic simulation models to better understand the nature of the opioid crisis in recent years. A comprehensive study of current modeling methods, model conceptualization and implementation, and policy interventions is necessary to identify areas for improvement and opportunities for future dynamic computational models of the opioid crisis. In order to gain an understanding of the current state of the art in systems science methodologies used to study the opioid crisis, a review of the literature on dynamic computational models of the opioid crisis [302] was performed with the aim of addressing the following research question.

**Research Question 1**: What are the current dynamic computational models for the opioid crisis, considering their representation of study populations, data sources, and their conceptualization and formulation? How are these models used to design and analyze policy scenarios? Furthermore, what are the future research directions in this field based on established niches?

The dissertation aims to use simulation modeling to investigate three key aspects of the opioid crisis: the impact of COVID-19-related health policies such as in person school closures on youth substance use, the potential outcomes for patients who are prescribed opioids, and the effectiveness of modified opioid agonist therapy (OAT) that was implemented during the COVID-19 pandemic on treatment retention among OAT recipients. We now cover the research questions addressed in successive components of this dissertation.

**Research Question 2**: How can systems science methodologies be utilized to examine the impact of in-person school closures on non-medical prescription opioid use among youth, and what do such methodologies suggest about the effectiveness of potential interventions or measures that can be implemented to mitigate any risks or improve the situation?

The COVID-19 pandemic had a significant impact on the lives of people, including youth, through the implementation of policies such as in-person school closures. Such closures may impact the access to prescription opioids. The closure of in-person schools during the COVID-19 pandemic has in particular raised concerns about the potential impact on non-medical prescription opioid use among youth. This study aims to use simulation modeling to investigate impact of in-person school closures on non-medical prescription opioid use among youth, and to identify potential interventions or measures to mitigate risks or mitigate opioid-related harms. The outcomes of this study can be utilized to inform policies and interventions intended to decrease the risk of nonmedical prescription opioid use among young people during and following the closure of in-person schools.

**Research Question 3**: How can systems science methodologies be utilized to examine the impacts of established policies like prescription drug monitoring programs and reduced prescribing on overdose and escalation to street opioids among patients treated with prescribed opioids? Through the incorporation of
simple machine-learning techniques into a simulation model, can we use that model to identify effective machine-learning informed prescription drug monitoring programs?

The opioid crisis in Canada was initially exacerbated by the widespread prescription of opioid medications, making it challenging for healthcare providers to determine the legitimacy of opioid prescriptions. This research emphasizes the usefulness of integrating dynamic modeling, simulation, and machine learning techniques to evaluate the impact of policies aimed at regulating opioid prescription practices. The goal of this research is to assess the effectiveness of incorporating machine learning techniques into a simulation model for the purpose of enhancing prescription drug monitoring programs and to further explore how well-established policies -- such as reduced prescribing and prescription drug monitoring programs -- might be impacting overdose and escalation to street opioids among patients treated with prescription opioids.

**Research Question 4:** How can systems science methodologies be utilized to examine the impacts of new guidelines for administering higher take-home doses of OAT on treatment retention and opioid-related harms among OAT recipients, and what do such methods suggest about the advisability of continuing to maintain such recommendations after the acute phase of the COVID-19 pandemic has passed?

The COVID-19 pandemic has led to significant modifications in the healthcare system, one of which is the alteration of opioid agonist therapy (OAT) guidelines. The modified OAT guidelines aimed to reduce the risk of treatment interruption and support physical distancing by allowing increased take-home doses for OAT recipients during the COVID-19 pandemic. Assessing the impact of the new guidelines on treatment retention and opioid-related harms among OAT recipients is crucial to determine whether the new recommendations should be continued in the future.

It is crucial to emphasize that while the current problem statements in this dissertation focus on the aforementioned topics, the scope of the opioid crisis is vast, and exerts diverse and far-reaching effects on individuals, families, and communities within Canada. The rapidly evolving nature of the opioid crisis, marked by the introduction of new drug combinations into the illicit market (such as between fentanyl and stimulants, opioids and benzodiazepines, and opioids and tranquilizers such as Xylazine), presents an ever-expanding challenge. Furthermore, the roles of incarceration, law enforcement policies, and correctional facilities in both exacerbating and ameliorating overdose prevalence have not been addressed in this dissertation, nor have the key pathways associated with early-life trauma. Each of these represents limitations on the generalizability of the results included here. However, in the Computational Epidemiology and Public Health Informatics Laboratory (CEPHIL) in which the author works, with heavy early as well as ongoing involvement of the author, a project is in progress to implement and simulate diverse facets of polydrug use in Canada. This simulation model offers a far broader exploration of the intricate and interrelated dimensions of the opioid crisis, shedding light on the complexities of co-occurring polydrug-using opiate dependents, including their interfaces with legal system factors, hospitalization, treatment and harm reduction programs.
1.3 Research Methodology

To address the research questions at hand, agent-based modeling was chosen due to its ability to capture the emergence of complex system behaviors from behaviors of individual interacting agents, thus providing more information than solely focusing on aggregate system behavior. This approach is advantageous as it can represent each agent individually, allowing for more favourable capturing of heterogeneity than is viable for aggregate approaches; the capacity of agent-based models to readily capture aspects of individual history, network and spatial context was additionally an asset. Furthermore, agent-based modeling provides a flexible and generative framework for considering a wide range of agent behaviors and interactions, including influences on the decision-making of agents based on individual contexts, histories and localized perceptions. An agent-based model and simulation framework enables experimentation by enabling the execution of virtual experiments to investigate model behavior under various conditions, permitting exploration of multiple scenarios and explanations from the level of individual agents up to the aggregated level.

In addition, the choice of Hidden Markov Models (HMM) was made to investigate prescription drug monitoring in scenarios where the underlying legitimacy of opioid prescription cannot be directly observed from patient behavior observations. HMM is capable of capturing the concealed structure that exists in the datasets, and is especially suitable for modeling time series data where the underlying legitimacy of opioid prescription changes over time.

1.4 Contribution

The main contributions of this dissertation include the following:

1- A comprehensive survey of existing studies on dynamic computational modeling and simulation of the opioid crisis. This survey provides an overview of past and contemporary work contributing dynamic computational models and simulations concerning opioid-related harms, and analyzes their modeling techniques, model formulation, policy recommendations, data sources, and study populations. The survey suggests future directions and opportunities for dynamic computational models that can help mitigate the opioid crisis. The result of this literature review is published in [302] as a peer-reviewed journal paper.

2- Designing, implementing, calibrating, and extracting valuable insights from an agent-based model of the interaction of youth opioid use and school closures that makes several subcontributions. Specifically, this model serves as

- the first dynamic simulation model to investigate possible impacts of in-person school closures due to COVID-19 on the youth's risk of opioid use in Canada.
- the first agent-based simulation model grounded in social impact theory which shed light on the impact of pandemic-era school closures on overall opioid use of the youths' social circle.
• the first agent-based simulation model which combines theories of opinion dynamics with the intensity of acute withdrawal from the nonmedical use of opioids to depict the decision-making processes of youth regarding opioid use.

The result of this study is published in [303] as a peer-reviewed journal paper.

3- Designing, implementing, calibrating, and extracting valuable insights from an agent-based model of opioid prescription management that serves as

• the first agent-based model to examine the impacts of different prescription management strategies on opioid-related harms among patients receiving prescription opioids in Canada.

• the first agent-based model with an adequate configuration to generate patient-specific opioid prescription time series data to be utilized both for feature selection and to train a 2-states hidden Markov model on prescription legitimacy.

• the first agent-based model incorporating an AI-based health policy for prescription opioids to assess its impact on patients in the long term.

The result of this study is published in [305] as a peer-reviewed journal paper.

4- Designing, implementing, and extracting valuable insights from an agent-based model of OAT. This model serves as the first agent-based model investigating the impact of the increased use of take-home doses, recommended by the Canadian healthcare agreement during the COVID-19 pandemic, on treatment retention and opioid-related harm among individuals receiving opioid agonist therapy.

The result of this study is published in [304] as a peer-reviewed journal paper.

1.5 Dissertation Overview

The dissertation is manuscript-styled and consists of six chapters, including four manuscripts that form the main body of the dissertation. Chapter 1 gives the overall introduction to the dissertation, including the motivations behind the research, the problem statement, the research questions addressed, and the contributions of the studies. Subsequent chapters are discussed below.

Chapter 2 (Manuscript 1)


This chapter is part of the published comprehensive survey which conducts a comprehensive examination of the literature on simulation models of opioid crisis. The chapter provides background information and reviews of research studies in agent-based modeling aimed at mitigating the opioid crisis. It analyzes the various model frameworks, policy recommendations made by previous studies, and their data sources.
Chapter 3 (Manuscript 2)


Chapter 3 explores the potential impact of school closures and increased time spent at home, particularly in relation to the potential exposure of youth to available prescribed opioids within the home, and its effect on the prevalence of opioid use among youth. This chapter presents an agent-based simulation that utilizes social impact theory and incorporates data from the Ontario Student Drug Use and Health Survey (OSDUHS) to examine the accessibility of prescription opioids within the home. By simulating different lengths of school closures, the chapter provides valuable insights into the effects of this public health policy on a population level, which would not be possible to observe in real-life scenarios. Furthermore, the results obtained from the agent-based model simulation, which was developed based on the timeline of school closures in Ontario due to COVID-19, are validated by comparing them to data from the Ontario Student Drug Use and Health Survey and the projections of the model results are then extended up to 2025. Finally, this study examines the effect of varying degrees of reduced access to prescribed opioids within the home through the implementation of safe storage at different time points. In the model findings, the lifting of in-person school closures leads to a noticeable increase in the prevalence of youth with nonmedical prescription opioid use, but further suggest that this effect can be mitigated if the prescription opioids are securely stored during the time of in-person school closures.

Chapter 4 (Manuscript 3)


This chapter establishes an agent-based model to characterize and serve to evaluate impacts of Hidden Markov Model-aided prescription drug monitoring programs. The simulation assesses the impact of reducing opioid prescription dosage, shortening treatment duration, and implementing HMM-aided prescription drug monitoring programs on overdose and transition to illicit opioid use among patients taking prescribed opioids, and furthermore evaluates the legitimacy of prescription opioid fulfillment. The agent-based model incorporates the distributions of prescribed dosages and durations for both new and established patients who received prescription opioids that were obtained from a study by the Canadian Institute for Health Information (CIHI). The findings of the model indicate that reducing prescription dosages had the largest impact on the outcome of interest over a five-year period while having minimal adverse effect on patients with a legitimate need for pharmaceutical opioids.

Chapter 5 (Manuscript 4)

Cite: Narjes Shojaati and Nathaniel D. Osgood. Evaluating the impact of increased dispensing of opioid agonist therapy take-home doses on treatment retention and opioid-related harm among opioid agonist

This chapter presents an agent-based model to examine the effects of increasing the number of take-home doses of methadone and buprenorphine/naloxone on treatment retention and opioid-related harm among individuals receiving opioid agonist therapy. The agent-based model examined the impact of elevated use of take-home doses -- such as that recommended by the current healthcare agreement during the COVID-19 pandemic -- to determine whether increased take-home doses of OAT should be continued in future. The data utilized for the agent-based model discussed in this research was obtained from a published study of the Institute for Clinical Evaluative Sciences (ICES) databases that includes a vast array of Ontario’s health-related data. In the simulation model, the extended take-home doses policy is varied to initiate after the second, third, and fourth month of treatment; and these three scenarios are further paired with varying levels of naloxone accessibility to assess the effect of naloxone distribution among OAT patient networks. Model findings suggest that longer-duration take-home doses may have helped sustain treatment, but higher rates of opioid-related overdoses and fatalities among some OAT patients who received increased dispensing highlights the need for increasing the availability of naloxone within patient networks.

Finally, chapter 6 concludes the findings of this dissertation and summarizes the dissertation components and contributions.
CHAPTER 2

BACKGROUND AND LITERATURE REVIEW

This chapter is part of a published comprehensive survey on dynamic simulation models for the opioid crisis [302] and provides background information and reviews of research studies in agent-based modeling for the opioid crisis.

2.1 Systems Science

Fostering critical, forward and strategic thinking in the context of real-world problems is greatly facilitated by systems science [115, 54, 143] and its subset known as complexity theory [151, 231] which provide concepts and methodologies to help comprehend complex phenomena in the real world. A system consists of a collection of interrelated elements, often with intricate relationships and connections [222, 117, 54]. Such interconnections between elements distinguish the system from a mere collection of such elements. Systems are characterized by inputs, outputs, and boundaries that delineate the system from its external environment [222]. Selecting the appropriate level of analysis that a system requires considering the system’s complexity. The level of complexity (i.e., coupling) within a system is an indicator of the numerous inter-relationships present within it, behaving often in non-linear and unexpected ways [180, 54, 343].

Systems science is an interdisciplinarity field that centers on studying the nature of systems, particularly complex systems, by examining the interrelationships and interactions between their various components [306], and how such relationships relates to properties of the system as a whole. Simple systems are characterized by low complexity and high predictability. They typically have a small numbers of components that interact in a predictable and well-understood manner. Examples of simple systems might include the isolated system of a pendulum or a simple circuit. These systems are often easy to analyze and understand, and their behavior can be modeled using simple mathematical equations [67]. Complex systems are characterized by the prominent presence of intricate relationships. They typically have elements that interact in a nonlinear manner. Some complex systems include a large number of such elements, but some complex systems have just a few. Examples of complex systems can be found in many spheres, including ecosystems, social networks, and features of the atmosphere. These systems often exhibit emergent behavior that arises from the interactions between their elements but is not reducible to such elements, and their behavior cannot be fully predicted or understood using simple mathematical models [287]. For example, the dynamics of a
traffic jam is a higher-level phenomenon cannot be reduced to the characteristics of the cars that make it up, and the behaviours – such as oscillations – seen in ecological systems lies beyond the sum or average of the characteristics of the species of which it is composed. Similarly, epidemiology tipping points associated with herd immunity are not a function at the level of elements (here, individuals), but of the population.

Systems science knowledge facilitates systems thinking as a cognitive process to analyze complex systems with emphasis on their key concepts, including holism, feedback loops, and non-linear relationships [306]. There is interdependence between system components, which is not possible to understand the system behavior by analyzing their individual components in isolation [222]. This brings forward the concept that the entirety of a system is more than just the sum of its individual components, known as holism [223]. Furthermore, feedback loops often create circular causality that drives systems behavior toward either reinforcing by amplifying change, which leads to exponential growth or decline or balancing, which counteracts change and promotes stability [117].

The behavior and outputs of a complex system emerge [130, 87] from the interaction of the parts, and these properties do not exist at the level of the individual parts. The interactions between the micro-level components in a complex system result in macro-level emergent properties and behaviors that are spontaneous, and these properties do not exist at the level of the individual parts [150, 181, 197]. If these emergent dynamics exhibit nonlinearity, then small perturbations can lead to disproportionately large effects, and the system self-organizes [93] into new structures and patterns without external control [141, 211].

Traditional approaches to problem-solving often prove inadequate as they fail to understand complex systems in terms of their interacting components, relationships, and overall behavior [233]. Many traditional scientific endeavours have pursued reductionist methodologies, in which the behavior of a whole is understood primarily by understanding the pieces of which it is composed. Such approaches offer much insight, particularly for simple systems. But with complex systems, systems science provides significant benefits over reductive approaches by helping to understand the ways in which the interactions between the pieces in such systems drive the behaviours of the whole.

Understanding the core concepts of complex systems, such as emergent behavior and feedback loops, requires more than statistical models alone. Traditional statistical modeling typically focuses on a single level of analysis [153], tends to be reductionist by centering on individual parameter estimates [267], and emphasizing correlational relationships between variables [333]. Such models are often limited in their ability to provide a holistic and integrated perspective that reflects the dynamic complexity of systems, as they cannot account for circular causality, changes from micro to macro levels, and other aspects of non-linearity [317, 205]. Nonetheless, strong empirical data and appropriate research questions are crucial for the effectiveness of statistical models in analyzing data and identifying patterns of association within them [97, 204].

The simulation of dynamic systems imitates the evolution of systems using an abstract representation of the system’s key elements, behaviors, and characteristics, referred to as a model [29, 30]. The modeling and simulation of complex dynamic systems aim to depict the underlying mechanism of complex systems as
they evolve over time, illustrate the possible future of these processes, and understand the limitations of such results [33].

Some of the common methods used in systems science research include system dynamics modeling [318], agent-based modeling [81], and system mapping tools like causal loop diagrams [138]. System dynamics modeling uses stocks, flows, feedback loops, and time delays to understand how systems change over time [154]. Agent-based modeling simulates the actions and interactions of autonomous agents to assess their effects on the system [238]. Causal loop diagrams are visual models that show how variables in a system are linked through positive and negative feedback loops [31].

2.2 Agent-based Modeling

Agent-based modeling, as a systems science methodology, is a computational method for modeling and simulating complex dynamic systems. The notion of an agent is the central concept in agent-based modeling and represents an actor, commonly one exhibiting some degree of autonomous evolution. Insights into such an actor being modeled can be achieved by simulating the actions and interactions of the agents [49, 126, 274]. Despite varying definitions of agents in the literature [98, 172, 207, 226], the following components are often central to defining agents in public health simulation models: incorporating heterogeneity in both agent characteristics and their environment, giving agents the ability to make decisions based on programmable rules, and taking into account their social networks and the agent environment [28]. The individuals represented in the model, known as agents, exhibit various distinct characteristics, referred to as heterogeneity. The autonomous agents in the model possess internal behaviors in the form of a set of potential actions they can perform in response to any given situation within the model. Agents can be positioned in varying spatial environments and engage in interactions with other agents through various network configurations [49, 126, 274]. These self-contained, self-directed, and often social agents operate and interact in virtualized time within the model’s simulation [207]. The use of virtualized time, or simulation time, enables the simulation of long time periods within a relatively short time frame.

Agent-based models use micro-level assumptions to generate macro-level structures through computational simulations, resulting in often unexpected population-level dynamics known as emergent behavior. Additionally, the agents in the model can exhibit adaptive behaviors in response to changes in their social or spatial environment [206]. Hence, the emergence of autonomous patterns resulting from the micro-macro transition can be observed in the outcomes of agent-based models [126]. A historical example of using an agent-based model to demonstrate adaptation and emergence is the segregation model [288]. While the segregation model characterizes very stylized preferential mobility on the part of dichotomously heterogeneous agents, a modest agent discriminatory preference to move in order to have neighbours similar to them can give rise to marked patterns of segregation over a landscape [266]. This considerable complexity arises from myriad interactions, each of which is individually very simple, demonstrating that simple procedures are
sufficient to cause complex phenomena in real-world systems.

Modeling the emergence of macro-level structures from the actions of individual agents in the real-world requires writing algorithms that capture the generative sufficiency [315] of these agents. These algorithms can be readily executed in object-oriented programming languages or using commercially available or open-source simulation software packages [4, 40]. Expectations are that regardless of the preferred aspects of a toolkit by different users [245], the outcome of an agent-based modeling and simulation remains constant across various platforms with equivalent capabilities, ensuring the consistency of the simulation's results.

Agent-based models can serve as simplified representations for theory development, requiring little or no calibration to empirical data. Alternatively, they may contain highly calibrated stochastic elements to produce results relevant for decision-making [206]. As the wide spectrum of agent-based model implementations offers various uses, domain experts can provide valuable feedback through face validity to validate agent behaviors and emergent phenomena, as well as system-level model outcomes. The model's accuracy can be further improved by employing other forms of validation, such as internal validity, historical data validation, sensitivity analysis, and predictive validation [30, 355, 331].

The use of agent-based modeling and its concepts for understanding the behavior of complex systems holds a significant importance in the field of public health research [205, 282, 308]. Infectious diseases [163, 301], obesity [191, 311], and substance use [152, 23, 24] are only a few areas where health policymakers find it beneficial to adopt a system thinking approach and explore the use of agent-based models. Agent-based modeling allows policymakers to form a clearer understanding of the underlying mechanisms behind observed patterns by testing their hypotheses, identifying new questions and areas of exploration, improving data collection for more effective analysis [307], and informing the development or evaluation of interventions [108]. Furthermore, agent-based modeling offers valuable insights into the underlying mechanisms, leverage points and future opportunities for policy intervention. It also helps explain the success or failure of previous policies or interventions and identifies potential outcomes of various interventions [215].

Different forms of integration between agent-based modeling and machine learning can be conceptualized [14, 258, 310]. Machine learning can assist in multiple stages of agent-based models development and implementation, including exploration of parameter spaces and calibration [259, 193], and reducing computational demands [283]. Additionally, machine learning needs large amounts of data to apply statistical methods for learning about a system or its behavior without prior knowledge of the model or theory [19]. Agent-based modeling simulations can therefore provide practical datasets for training machine learning algorithms [248, 84]. Machine learning also can be incorporated into agent-based modeling to determine agent rules [16, 5] and assess the efficacy of combining machine learning algorithms and agent-based models in analyzing the target system [16, 5, 26]. One possible application of integration between machine learning and agent-based modeling is the combination of the hidden Markov model (HMM) [82] and an agent-based model. To employ HMM as a statistical model in machine learning, acquiring intensive longitudinal data is of utmost importance [273]. In such instances, a detailed set of data is utilized for estimating the probability of a
sequence of observations, decoding the most likely sequence of hidden states underlying such a sequence, and training the HMM parameters based on those observations (Refer to [82] for HMM algorithms and equations). An appropriate agent-based modeling framework has the potential to generate high-quality data specifically for these purposes [183, 57]. Subsequently, the integration of HMM into an agent-based model can enable a simulation-based evaluation of HMM, which assesses both the proximal and distal impact of the HMM's predictions on both the macro and micro levels within the system being studied [229].

2.3 Nature and Potential Risks of Opioids

Opioids are a type of drug that act by binding to natural mu, kappa, and delta receptors in the brain and exhibit similar clinical effects such as analgesia, sedation, constipation, and respiratory depression [256, 255, 336]. Opioids can be categorized into four main groups: endogenous opioids that are naturally occurring in the body, opium alkaloids like codeine and morphine that are derived from the opium poppy, semi-synthetic opioids like oxycodone and heroin that are modified forms of opium alkaloids, and fully synthetic opioids like methadone and fentanyl, which are entirely man-made but exhibit similar properties and effects as the alkaloids and semi-synthetics [352]. Proteins on the surface of neurons, or other cells, that respond to endogenous opioids, such as endorphins, and opioid drugs -- such as heroin -- are called opioid receptors. These receptors have subtypes, which include mu, kappa, and delta [255].

In spite of the fact that opioids prescribed for medicinal purposes have been shown to temporarily reduce the severity of pain, they can lead to severe adverse physical and psychological effects or even death through misuse, abuse, short- or long-term dependence, and one-time or recurrent overdose [289, 290]. Opioids can induce euphoria and can lead to a craving for this feeling. As a result, patients may engage in the misuse or abuse of opioids. Generally, misuse refers to the use of opioids in manners that differ from the intended use as instructed by the prescribing physician. Abuse, on the other hand, entails the self-administration of medication (such as methadone) for non-medical reasons like altering one's state of consciousness, and using illegal drugs like heroin [177, 347, 104]. Over time, increased amounts of the drug are required to maintain a given level of analgesic and euphoric effects [347, 104, 187]. When faced with such situations, patients may experience symptoms of tolerance and withdrawal, and develop mental or physical dependence and addiction [241].

Tolerance is the state of adaptation to a drug, which results in a decrease in one or more of its effects over time, while withdrawal is a characteristic syndrome that occurs when the drug is abruptly stopped [236]. Addiction is a condition that involves behavioral, cognitive, and physiological changes resulting from repeated opioid use [342, 159]. This may manifest in difficulties controlling opioid use, persistent use despite negative consequences, and withdrawal symptoms when use is reduced or stopped. Addiction involves both physical and mental dependence on a particular substance [342, 159, 268]. This common definition of addiction is generally applicable to all addictive substances, although different substances may affect the brain and...
behaviour differently [241].

An overdose occurs when a person uses enough of a drug to produce a life-threatening reaction or death, whether accidentally or intentionally [280]. A potentially lethal opioid overdose can happen unawares through its depressant action on the central nervous system, including breathing [290]. Naloxone can be administered to temporarily reverse an opioid overdose effect [36]. Naloxone is a fast-acting drug that works by displacing opioids from the opioid receptors in the brain and binding to those receptors instead; however, it requires administration by another party, such as a companion, bystander, or first responder [32]. Therefore, it is strongly recommended that clinicians exercise caution when prescribing prescription opioids, given their highly addictive potential and significant side effect profile [268, 39].

Patients with opioid use disorder can benefit from available treatment centers and harm reduction programs for substance use disorders. Such centers and programs can offer access to peer support groups and networks, mental health professionals, and individual and group therapy [320]. Although patients may experience long periods of abstinence, relapse is a common occurrence [159]. Opioid-based medications can help treat opioid use disorder by reducing withdrawal symptoms, cravings, and blocking opioid effects in case of relapse [262].

The opioid crisis is defined as the dual impact of the health risks and fatalities associated with opioid abuse and the significant financial burden it imposes on the healthcare and criminal justice systems [127, 208]. The issue of the opioid crisis has persisted in Canada for more than a decade, leading to the deaths of tens of thousands of Canadians [38, 326, 133]. Despite the mixed effect of the COVID-19 pandemic on opioid use in Canada [120, 162], the opioid crisis remains one of the most complicated public health challenges in the country [112].

Prescription opioids are known as a common source of opioids used for non-medical reasons [289, 264]. Such use of pharmaceutically supplied opioids can also serve as a gateway to the use of heroin and synthetic opioids [289]. Despite caution advanced in many quarters regarding chronic, long-term use of opioid-based painkillers, some opioid patients remain on long-term prescriptions of opioid analgesic regimens [179]. This long-term opioid exposure may cause opioid abuse for patients [94, 353] or diversion of the leftover prescription opioid to other people without a prescription [75, 242, 293]. Common street-obtained opioids are another potential source used for non-medical reasons [264]. Dealers are the main access points of powerful synthetic opioids, such as fentanyl [253]. When taking these illegal opioids, the risk associated with users is often high, both because of the tremendous but variable potency of the drugs themselves, as well as the risk of impurity [254]. Moreover, the varying availability of street opioids can pose particular risks in light of the waning of tolerance over time and established dose preferences on the part of the user.

The opioid crisis can be particularly challenging to reason through, given the legality, routine medical use and easy accessibility of many opioid drugs [94]. The existence of multiple and, at times, competing theories to explain a single real-world situation, and starkly divergent policy prescriptions may indicate that there is difficulty establishing a robust way of reasoning about it. Researchers seeking a robust understanding of the
underlying causes of the opioid crisis and identifying high-leverage policy options have benefited from the availability of computational tools and methods to characterize the process and underlying theory behind the opioid crisis.

### 2.4 Agent-based Modeling of the Opioid Crisis

Table 2.1 provides an overview of all identified agent-based models of the opioid crisis. A total of 17 models have been included in this review. Netlogo [329] was used as an agent-based modeling and simulations tool [4] for several agent-based models in the existing literature and face validity [79] of the results was accepted as the only type of validation [331] in several models. Other validation techniques, including sensitivity analysis, predictive validation and code verification are also conducted in the existing literature.

**Table 2.1**: Agent-based models of the opioid crisis and their technique, platform, drug type, and validation

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Technique</th>
<th>Platform</th>
<th>Drug Type</th>
<th>Model Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>[7]</td>
<td>ABM</td>
<td>Netlogo</td>
<td>Heroin</td>
<td>Face validity</td>
</tr>
<tr>
<td>[10]</td>
<td>ABM</td>
<td>Starlogo</td>
<td>Heroin</td>
<td>Face validity</td>
</tr>
<tr>
<td>[12]</td>
<td>ABM</td>
<td>SWARM</td>
<td>Heroin</td>
<td>Face validity</td>
</tr>
<tr>
<td>[47]</td>
<td>ABM</td>
<td>Netlogo</td>
<td>Pharmaceutical opioid</td>
<td>Sensitivity analysis</td>
</tr>
<tr>
<td>[48]</td>
<td>ABM</td>
<td>Netlogo</td>
<td>Heroin, Methamphetamine</td>
<td>Face validity</td>
</tr>
<tr>
<td>[70]</td>
<td>ABM</td>
<td>LISP</td>
<td>Drug-Heroin</td>
<td>Face validity</td>
</tr>
<tr>
<td>[99]</td>
<td>ABM</td>
<td>Cormas</td>
<td>Heroin</td>
<td>Sensitivity analysis</td>
</tr>
<tr>
<td>[100]</td>
<td>ABM</td>
<td>Cormas</td>
<td>Heroin</td>
<td>Sensitivity analysis</td>
</tr>
<tr>
<td>[140]</td>
<td>ABM</td>
<td>Not specified</td>
<td>Heroin</td>
<td>Predictive validation</td>
</tr>
<tr>
<td>[145]</td>
<td>ABM</td>
<td>Not specified</td>
<td>Heroin</td>
<td>Face validity</td>
</tr>
<tr>
<td>[146]</td>
<td>ABM</td>
<td>Not specified</td>
<td>Heroin</td>
<td>Face validity</td>
</tr>
<tr>
<td>[147]</td>
<td>ABM</td>
<td>Not specified</td>
<td>Heroin</td>
<td>Face validity</td>
</tr>
<tr>
<td>[149]</td>
<td>ABM</td>
<td>Not specified</td>
<td>Heroin</td>
<td>Not specified</td>
</tr>
<tr>
<td>[182]</td>
<td>ABM</td>
<td>Netlogo</td>
<td>Opioid</td>
<td>Not specified</td>
</tr>
<tr>
<td>[240]</td>
<td>ABM</td>
<td>Netlogo</td>
<td>Heroin</td>
<td>Code verification, Predictive validation</td>
</tr>
<tr>
<td>[261]</td>
<td>ABM</td>
<td>Cormas</td>
<td>Heroin</td>
<td>Predictive validation, Sensitivity analysis</td>
</tr>
<tr>
<td>[285]</td>
<td>ABM</td>
<td>Netlogo</td>
<td>Pharmaceutical opioid</td>
<td>Sensitivity analysis</td>
</tr>
</tbody>
</table>
2.4.1 Data Sources

In total, five models [7, 48, 70, 145, 146] are classified as “middle-range models,” as these models are based on a qualitative ‘understanding’ of its research problem and aim to create hypotheses and test different interpretations of the opioid crisis; therefore, they did not provide any data sources. Two models [47, 285] benefited from published literature and expert opinion. The references of their parameters consist of extrapolated or calculated from the literature and derived from a panel consensus. Data sources for other models can be divided into two overall categories: (i) ethnographic case studies and interviews conducted by researchers working collaboratively, (ii) open-access online data sources.

2.4.1.1 Ethnographic Case Studies and Interviews

The setting of seven studies is based on different ethnographic studies of users, dealers, or treatment provider samples in the United States which corresponding researchers conducted. Surveys and interviews were chosen as appropriate methods to elicit applicable data given the hidden nature of opioid use. Various parameters and variables used in these models were informed by results obtained from these ethnographic case studies. These ethnographic case studies are discussed in this section.

Ethnographic case study of heroin users and dealers in Denver, Colorado, the United States

An 18-month ethnographic case study in Denver, state of Colorado, the United States, during the 1990s [148] formed data for three models [140, 147, 149]. This data source represents the historical account of users and dealers who operated in the Larimer area heroin market. These models [140, 147, 149] were calibrated with different numbers of customers to produce the observable rates of drug arrests and treatment admission.

Ethnographic survey of active heroin users in Cleveland, OH, the United States

In one model presented in [240], the dataset used to develop the model was obtained via an ethnographic survey of active heroin users who visited a syringe exchange point in Cleveland, OH, between September 2015 and July 2016 [240]. Their responses related to buying and brokering frequency were mainly used to parameterize the network nodes. Exploratory data analysis on some features of this ethnographic survey data also was conducted to understand market behavior. It is noteworthy that a comparison of this survey to the national Morbidity and Mortality Weekly Report (MMWR) population survey [174] showed that this local survey yielded nationally representative data while revealing increasing heroin use over time and the gender ratios of the users.

Ethnographic research with youthful heroin experimenters in Baltimore County, Maryland, the United States

Two models [10, 12] took advantage of knowledge gained from interviewing a sample of youthful heroin experimenters in Baltimore County, state of Maryland, the United States [11]. This ethnographic research with the 1990s youth revealed the importance of the local reputation of illicit drugs. To pin down quantitative data gained from this interview, the model presented in [12] benefited from fuzzy logic [221] and assigned
numbers to probabilities of drug experience and attitude changes. Furthermore, the model [10] produced various S-curves of experimentation using realistic settings of the parameters gained from this study.

**Interview with substance abuse treatment providers and opioid users in Southwestern Pennsylvania, the United States**

One model [182] was parameterized using data obtained from interviews with substance abuse treatment providers and opioid users at high risk for opioid overdose in Southwestern Pennsylvania between July 2016 and September 2016 [182]. The behavioral variables used in the model [182] were informed using an exploratory sequential mixed-methods design that emerged from the qualitative results of the interview. These variables include fear of calling emergency response, as well as opportunities for naloxone distribution through community sites, via secondary networks utilizing opiate using bystanders, and with access to multiple kits at a time.

### 2.4.1.2 Open-access Online Data Sources

Open-access online data sources can provide timely and comprehensive data on opioid use, treatment, and overdose deaths. In total, three models use a variety of online data sources to study the scope of the opioid crisis.

**The National Drug and Alcohol Research Centre (NDARC) in Australia**

Three models [99, 100, 261] employed data sources from the NDARC in Australia [96]. Three variables comprising fatal overdose, non-fatal overdose, and user’s readiness for treatment are calibrated to these reference data.

### 2.4.2 Conceptualization and Formulation

This section provides an overview of the model conceptualization and formulation for the agent-based model of the opioid crisis. These studies are broadly categorized based on their scope.

#### 2.4.2.1 Illicit Drug Market Characteristics

The drug availability in society is affected by the dynamics of the drug market. Several micro-interactions between active individuals in the drug market lead to different patterns of available drugs. The role of ‘brokers’ and the influence of police activity in the drug market are the primary concerns for different models in the existing literature. Hoffer et al. [149] started implementing the rough idea of a square geographical area where an individual can jump to nearby squares while looking for heroin. Moreover, a detailed state diagram for a customer is presented that involves different states, such as moving around, buying heroin, and using heroin. The processes of satiation, withdrawal, tolerance, and habit were implemented using an ordinary differential equation. Six types of agents are present in the model: customers, street dealers, street brokers, private dealers, police, and homeless people. Customers purchase heroin with their income. After a while, they develop an addiction, and their purchase amount changes to match their addiction level. Individuals’
addiction can grow or diminish based on the use of the drug. Brokers are heroin users who play a role as intermediaries between customers and dealers for transferring money and purchasing the drug. They take a portion of heroin as their wage for their personal use. They are also the only ones to introduce a customer to a private dealer. Although private dealers have their own specific customers (i.e., private market), street dealers work in an open-air (public) market to sell their available heroin repository. They stop working when they sell all their resources or when their shift ends. Police patrol the whole area and randomly select people for inspection. If a person is caught with heroin, the police arrest the person. Therefore, the person becomes inactive for an interval based on his heroin repository. The homeless population does not have any specific roles except making noise or crowding the environment. There is no clear information about the implemented networks between agents in these articles. However, besides any other networks, it seems that a network between a private dealer and customers can be shaped through running the model.

Even though the implemented model in [149] concentrated on the social aspect of the market dynamics, the one presented in [147] focused on the inverse relationship, that is, the individual neurophysiological factors shaped by market activities and studied different patterns (e.g., stepped and stable, and crash patterns) in customer addiction levels based on drug availability. For this reason, the model [147] represents a simple equation based on drug concentration in the body to describe satiation and withdrawal. Unlike [149], customers in [147] have the memory to keep track of previous successful purchases and their sellers. Most of the model specifications for these two models [147, 149] are the same. The difference lies in customer behaviors and environmental properties.

Customer interactions with other agents in two previous models [147, 149] are a big overload. Thus, the model presented in [140] simplifies this excess using a probabilistic rather than algorithm-based approach. The goal was to maintain simulation fidelity while reducing computational complexity. This reduction involved identifying key summary quantities of individual customer behavior as well as an overall market activity using regression models and replacing some agents with probability distributions. Statistical approximations were computed for some outcomes, eliminating the need for the function of the police, street brokers, street dealers, and homeless agents. Meanwhile, it reintroduced the street dealers and police busts into the reduced model. This new extension is straightforward, in the way that the new model only keeps the number of street dealers currently in the market and the number who are currently arrested. Social networks exist among customers in obtaining heroin, and there is a probability assigned to joining a new network.

The studies [145, 146] are an attempt to implement illicit drug market characteristics using three agents – the customer, the broker, and the dealer – with simple rules. Customers buy heroin indirectly from a broker. A loyal customer can develop a direct relationship with the dealer. A busy dealer can create new branches and change their prices. There is also some possibility for the dealer to be arrested based on the size of their customer base. The network was implemented in three levels: customers with a broker, customers with dealers, and customers with peers (other customers). The model in [146] highlighted the existence of two different types of social networks: static and dynamic. The dynamic network reflected the possibility
of disconnection between individuals after having a certain time of bad experiences. Dealers are unaware of other dealers’ sales; therefore, they adjust their price based on their own sales on the previous day and continue competing for customers.

In a study, Nassani [240] aimed to simulate local heroin market growth and stability. The model [240] captured both the population-at-risk and dealers. A scale-free network was introduced with individuals at its nodes, some of which are randomly identified as dealers. Nassani [240] chose the spring layout algorithm to display the resulting graph. Furthermore, new connections can be created when individuals have a mutual friend, and friendship is based on a probability. Connections can also be randomly removed from the network, whereas new users are created when dealers sell their product to their social connections. Some individuals can also be marked as ‘inactive’ if they are currently not using or have never used drugs. Individuals known as ‘population-at-risk’ can be labeled as ‘brokers’ if they have a direct connection to a dealer as well as to a user. This model [240] employs graph theory metrics [118], such as clustering coefficients, betweenness, and degree distribution, to study the network topology created among local heroin market participants.

2.4.2.2 Unstable Availability of Illicit Drugs

The ‘heroin drought’ was a period when the global production and supply of opiates were sharply reduced [90]. The model presented in [261] concerns the drug market and issues around heroin use during the ‘heroin drought’ in Australia. The individual in this model [261] can be a user, a dealer, a wholesaler, a constable (police officer), or outreach worker. A user has some possibility to become an active user-dealer. Dealers work secretly or on the street, and they buy the drug from their wholesaler and sell it to users or user-dealers. All individuals are placed on a regular square mesh with many cells corresponding to street blocks. The cells form five suburbs with different sizes and shapes. Two cells represent the Police Station and the Treatment Centre. The Police Station stores information about the arrested individual as well as the quantity of the drugs seized. Three different kinds of treatment are available in the Treatment Centre which are differentiated by their duration and estimated success rates. Each cell stores some information about its own safety and wealth, which will lead to determining the attractiveness of drug dealing. The class diagram, the sequence diagram, and the activity diagram describe the functionalities of the model.

Later, a model presented in [99] inherited the main structure of [261]; it enhanced the law enforcement module of [261] by introducing complexity to the role of the police. Subsequently, Dray et al. [100] added two illicit drug types and variations to their availability in the marketplace. As a forcing factor, this model assumed that the availability of ‘other drugs’ (amphetamine-type stimulants) is inversely proportional to heroin. Furthermore, Dray et al. [100] examined whether this assumption affects street-level policing interventions.

2.4.2.3 Polydrug Users

Polydrug users are those who use more than one type of drug at either the same or different times with the same or different effects [142]. Polydrug use is a common problem in rural areas due to the price and
availability of drugs [48]. Bobashev et al. [48] examined this issue and tried to identify qualitative trajectories of the individual and collective responses to external interventions. For a population of polydrug users with three reinforcers – methamphetamine, opiates, and others – the model in [48] defines four non-overlapping states: never used, occasionally tried, continually used, and used in the past. The ethnographic research shaped behavior rules in the model; hence, the drug selection mechanisms are dictated by parameters such as drug liking, drug availability, drug cost, perception of health and other life consequences, perception of potential punishment, and peer pressure – calculated as the average of drug use in the community. The model [48] represents a close community in a way that everyone is connected to everyone else.

2.4.2.4 Opioid Outbreak Amongst Youth

A computational model of heroin use amongst youth can be helpful to study users’ experimentation, the influence of social network members, and prior drug experience in current drug use. Agar [10] highlighted the use of the computational modeling method as a possible way to explore the complex concept of drug addiction. In the model [10], youths and adults with the potential to start using the drug are divided into three groups: edge users (those who would try almost any drug that comes along), ordinary users (those who might use an illicit drug), and abstainers (those who never use drugs). They are placed in a rectangular plane that has been divided into sections. Individuals’ fixed social network facilitates traveling narratives about the drug. A user can get heroin indirectly within a heroin hotspot or directly from another user. If the experiment variable has a high value, an individual is more likely to try heroin. That value is determined by three concepts. The first is a risk variable taken from the diffusion of innovation (DOI) theory [277], indicating how likely the individual is to try something new. It draws from a normal distribution at the beginning, and it remains constant. The second concept is an attitude variable, representing the individual’s acceptance or rejection of illicit drug use. It can change based on the network connection effects and personal experience with drug use. The changes in the attitude variable are stochastic. The last concept is an outlaw variable, which represents the individual’s attitude toward social norms that can be followed or ignored. The changes in the outlaw variable are stochastic.

The categories for youths and adults are revised in [12] as follows: clean, experimenter, user, addict (i.e., a user who has used to a certain threshold value), and ex-addict. Furthermore, Ager [12] used trend theory [9] and further applied fuzzy logic [221] to rank the magnitude of heroin experimentation and then translated it into a static numerical form.

To show differences in the quality of the drug experience, Ager [7] added two concepts of ‘Goodstuff’ and ‘Badstuff,’ which reflects prospect theory [332], to the base model presented in [10]. A high Goodstuff rating indicates that the drug is a highly attractive product in the environment at this time, while a high Badstuff rating has the opposite meaning. They were set at an aggregated level (i.e., one for the whole model). Based on a simple algorithm, the individual’s experience with the drug can be good, bad, both, or none. The attitude variable is changing with the individual’s experience and with narratives of the drug. If
risk outweighs attitude, the individual uses the drug. This model [7] eliminates an outlaw variable from the base model [10].

It is fundamental to know that the credibility of the communication might be different for each type of individual. Therefore, Chattoe et al. [70] introduced this difference to the base model in [10]. Individuals are non-users, users, or addicts. Non-users and active users can say what they know, which has a direct influence on others. Non-users (again) and users with less experience can only gossip, which leads to much lower credibility. And, finally, addicts lack any credibility, based on labeling theory [134]. In this model [70], only two cognitive factors, risk attitude and drug attitude, are used.

2.4.2.5 Overdose Prevention Tool

Of particular concern is whether increasing support for naloxone distribution to laypersons via sites could save the lives of those opioid users who are at a higher risk of overdose. One model in the existing literature aimed to answer this question. In the model [182], individuals can be either an opioid non-user or an opioid user. There is some possibility for an opioid user to become bystanders (i.e., administer naloxone). The syringe exchange site distributes naloxone. Individuals are placed on a lattice grid with at most eight other neighbors at any given time. There is a dynamic social network connection between individuals; they move around the theoretical city and have contact with current neighbors. If any bystanders encounter an overdose, based on the bystander’s confidence level, a bystander will call emergency response or administer naloxone or do both.

2.4.2.6 Pharmaceutical Opioids for Chronic Pain

Prescribing opioids for chronic pain quickly places the patient at risk of addiction. An alternative tool for limiting chronic pain is self-management education [203]. The study [285] investigated how pain self-management education influences the prevalence of opioid prescriptions. The model utilizes Hovland’s theory [156] and the elaboration likelihood model (ELM) theory [263] to analyze attitude change via two processing routes: the central route and the peripheral route. In this model [285], opioid users with chronic non-cancer pain (CNCP) are located in a rectangular plane constructed with patches. There are a couple of patches willing to prescribe opioids, whereas some provide self-management education(al) messages as an alternative. When patients require treatment, they may establish the closest patch and relocate. They may then choose whether to accept the educational message from that patch or continue to use opioids. To clarify, there is no network within this model [285].

A more complex model formulation for the prescription of opioids is presented in the existing literature. Bobashev et al. [47] analyzed the dynamics of opioid use in a community while agents’ connections were implemented as networks. The model [47] contains two types of agents: user agents and distributor agents of opioids. User agents are patients, and distributed agents are drug dealers, physicians, pharmacies, and emergency departments. Supplies are prescription opioids, tamper-resistant prescription opioids, and heroin.
Patients fill their prescriptions at the pharmacy or are dispensed opioids by an emergency department. Each patient knows one or more physicians, one or more patients and nonpatients, dealers, and a pharmacy.

Moreover, a simplified version of the Prescription Drug Monitoring Program (PDMP) is implemented in this model [47]. Addiction and tolerance can be developed in patients; therefore, they may need a higher dose of opioid than prescribed. The desire for opioids exceeding a patient’s supply can be fulfilled by visiting additional physicians, visiting an emergency department, or buying from another patient or a dealer. The main progression of patients is stochastic, with some possibility to switch from pills to heroin if heroin is available.

2.4.3 Experimentation and Simulation, Suggested Policies and Impacts on the Opioid Crisis

There is one study in the existing literature on agent-based modeling of the opioid crisis that develops computational modeling frameworks and concepts for commencing policy simulations. However, neither a numerical result nor policy suggestions were included [7]. Another example of what is meant by the experimental model is the model presented in [140] that tried to keep the result of two previously published models [147, 149] constant while making a model reduction to have a simpler and high-performance model. Table 2.2 lists applied interventions in the existing literature with its corresponding simulation models.
Table 2.2: A list of implemented interventions in agent-based models of the opioid crisis

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reducing the popularity of drug use within the community</td>
<td>[10, 12]</td>
</tr>
<tr>
<td>Different social network structures within the community</td>
<td>[10, 12]</td>
</tr>
<tr>
<td>PDMP</td>
<td>[47]</td>
</tr>
<tr>
<td>Tamper-resistant opioid formulations</td>
<td>[47]</td>
</tr>
<tr>
<td>Reducing initial doses of pharmaceutical opioids</td>
<td>[47]</td>
</tr>
<tr>
<td>Increasing naloxone availability in the community</td>
<td>[47, 182]</td>
</tr>
<tr>
<td>Elimination of methamphetamine from the illegal drug market</td>
<td>[48]</td>
</tr>
<tr>
<td>Increasing drug education among susceptible individuals</td>
<td>[70]</td>
</tr>
<tr>
<td>Different policing strategies</td>
<td>[99]</td>
</tr>
<tr>
<td>Different numbers of outreach workers</td>
<td>[100, 261]</td>
</tr>
<tr>
<td>Different numbers of constables</td>
<td>[100, 261]</td>
</tr>
<tr>
<td>Altering the weight of illegal drug units</td>
<td>[145]</td>
</tr>
<tr>
<td>Presence of street brokers</td>
<td>[145, 149]</td>
</tr>
<tr>
<td>Different network configurations within the illegal drug market</td>
<td>[146, 240]</td>
</tr>
<tr>
<td>Different probabilities of participation in drug dealing</td>
<td>[146, 240]</td>
</tr>
<tr>
<td>Absence of street brokers</td>
<td>[149]</td>
</tr>
<tr>
<td>Occurrence of a drug bust during a specific day</td>
<td>[149]</td>
</tr>
<tr>
<td>Secondary exchange of naloxone through social networks</td>
<td>[182]</td>
</tr>
<tr>
<td>Syringe exchange sites</td>
<td>[182]</td>
</tr>
<tr>
<td>Different opioid addiction treatment and different treatment capacities</td>
<td>[261]</td>
</tr>
<tr>
<td>Integration of self-management education into the care of prescription opioid patients</td>
<td>[285]</td>
</tr>
</tbody>
</table>

Problem-oriented policing (i.e., having high contributions between constables and outreach workers) is the most effective approach to disrupting street-level drug markets to reduce the availability of drugs in the streets, which will cause a visible effect on opioid harm reduction [99]. Moreover, the high number of outreach workers strongly reduces overdose rates by preventing users from quitting an unsuccessful treatment [261].

The combination of agent-based modeling and random graph theory can create a social network mimicking a local heroin market [240]. Furthermore, connection between the social dynamics of the heroin market and the physiological consequences of heroin addiction can be significant [147]. The increasing number of constables has a positive influence on the number of arrested dealers [261]. Nonetheless, arresting street-based dealers may not effectively disrupt market activities. The role of a broker in the illegal drug market is far more important than policymakers may know. Brokers stabilize heroin sales. Increasing brokering
trends cause more active dealers. Therefore, removing brokers from the market may have powerful policy implications [145, 146, 149].

Supply chain disruptions simply lead to displacement from one illicit drug to another [100]; therefore, law enforcement strategies to overcome the opioid crisis often fail. A reduction in a certain drug, such as methamphetamine, would increase the use of other reinforcements (drugs) available in society, especially heroin. Considering its higher addictive potential, these new heroin users would quickly develop an addiction to heroin. If methamphetamine is then reintroduced into the social network, many former methamphetamine users who are now on heroin will start using methamphetamine again. In other words, addiction to methamphetamine increases the chance of using methamphetamine and heroin in this context [48].

There is no correlation between the initial risk attitude of the person (i.e., prepared to use if exposed) and final drug use status (i.e., non-user, user, addicted); however, decreasing individual enthusiasm for using the drug by changing the drug attitude (i.e., acceptance or rejection of illicit drug use) has a significant effect on reducing the number of users and addicts [70]. The reason can be investigated in the social network connection. A simple circulation of drug-use stories is sufficient to produce an epidemic curve [10, 12]. However, a rapid negative trend based on gossip, negative experiences, and contact with addicts, could reduce willingness to use the drug among susceptible individuals [70]. Thus, high-density connected social networks result in less use, reflecting the anti-drug friends’ role. It means the social network role in the drug epidemic is contrary to its role in infectious disease epidemiology models [10, 12].

The positive effects of PDMP compliance could be seen in the long-term application. PDMP reduces rates of overdose and pharmaceutical opioid deaths. However, tamper-resistant medication increases heroin use and overdose rates. Naloxone availability reduces opioid and heroin death rates [47]. Thus, increasing naloxone distribution for laypersons might reverse opioid overdoses [182].

The overall results imply that careful screening of patients who receive opioid therapy is an effective way to reduce opioid overdose deaths among the medical and, surprisingly, the non-medical population. This result reflects the fact that opioid user patients have numerous sources of opioids. Moreover, the results of these models highlight the importance of the metrics for an intervention assessment. Eventually, there is no simple intervention that could be implemented to combat the opioid crisis. The overall conclusion highlights the absolute need for a combination of different interventions to mitigate the impacts of opioid addiction.
Chapter 3

An Agent-Based Social Impact Theory Model to Study the Impact of In-Person School Closures on Nonmedical Prescription Opioid Use among Youth

Abstract: Substance use behavior among youth is a complex peer-group phenomenon shaped by many factors. Peer influence, easily accessible prescription opioids, and a youth’s socio-cultural environment play recognized roles in the initiation and persistence of youth nonmedical prescription opioid use. By altering the physical surroundings and social environment of youth, in-person school closures may change risk factors for youth drug use. Acknowledging past research on the importance of the presence of peers in youth substance use risk behavior, this paper reports the findings from the use of an agent-based simulation grounded in social impact theory to investigate possible impacts of in-person school closures due to COVID-19 on the prevalence of nonmedical prescription opioid use among youth. The presented model integrates data from the Ontario Student Drug Use and Health Survey and characterizes the accessibility of within-home prescription opioids. Under the status quo, the lifting of in-person school closures reliably entails an increase in the prevalence of youth with nonmedical prescription opioid use, but this effect is ameliorated if the prescription opioids are securely stored during the in-person school closures period.
3.1 Introduction

Youth are among the high-risk population for substance use behaviors [83, 91]. Substance use behavior among youth is a complex phenomenon and involves diverse influential factors including the socio-cultural environment [92, 275], substance-using peers, and personal network characteristics [34, 186, 234]. Some youth initiate drug use because of friends and continue it to fit in with their social network and environment. Such initiation is of particular significance in that many adults have initiated substance use during their teen and young adult years [284, 178]. With growing appreciation for the impact of peers, families, and communities on youth substance use, schools are also recognized as important social environments affecting student knowledge, attitudes, and behavior toward substance use [271].

One of the initial actions taken during the COVID-19 pandemic to lower mortality and avoid unsustainable acute care service utilization was the implementation of public health orders that frequently included partial or full in-person school closures, and sometimes encouraged families to minimize socialization and remain at home where possible [309]. In Ontario, the first school closure was announced on 12 March 2020, in effect from 14 March 2020, and continued with several gradual and staggered reopening and closures throughout the course of the following two years, as shown in Figure 3.1 [121]. Finally, Ontario schools reopened for in-person learning on 17 January 2022 [41].

The presence of youth at home during in-person school closures may have positive and negative implications for their mental health and propensity to use substances. While a lack of in-person contact with classmates and instructors is likely to produce elevated anxiety, boredom, and discontent in some young people, others may have welcomed less stressful peer interaction and a temporary decline in bullying and other forms of unpleasant experiences associated with in-person learning [137]. Among youth, the adoption of unhealthy coping mechanisms, such as substance use, as a result of pandemic-related stress, are of particular concern, since they are less likely to consider the negative consequences of their action [171]. The increased risk of opioid use among youth could result from elevated accessibility of prescription opioids due to unsafe medication storage practices by family members at home [85, 242, 42], witnessing elevated parental nonmedical prescription opioid use [136], and increased alcohol and cannabis consumption among youth during the pandemic [59, 129, 250]. Such regularities and the prospects of requiring in-person school closures as part of future public health orders suggest the importance of understanding the impact of in-person school closures.
on substance use among young Canadians during and after the COVID-19 pandemic.

There is a body of research applying social network analysis to secure insights into substance use behavior among youth [335, 334, 107]. Although social network analysis can offer enormous insights into the social context of and influence on the use of drugs, reducing an individual to a node in a network limits the integration of personal characteristics [227]. While incorporating such representation of network structures, an agent-based modeling approach can more deeply analyze individual affiliative structures in the context of evolving and actively interacting agents with varying characteristics [166, 209].

To explore fundamental elements of substance use among youth, different agent-based models have been built [7, 8, 123, 195, 12, 260, 9, 95]. These models highlight the use of the computational modeling method as a possible way to explore the complex concept of substance use amongst youth. One little-explored approach to study the possible association between social influence and substance use amongst youth is through opinion dynamics computational models. Opinion dynamics computational models can highlight mechanisms underlying the convergence of behaviors and theoretical implications for imitator behaviors. There is a substantial body of literature on opinion dynamics models, with model formulations having been contributed from domains as varied as social psychology, statistical physics, mathematics, and computer science. These varying angles of contributions have led to a vast and diverse body of research [77, 135, 21]. Despite the breadth of past applications of opinion dynamics models, there are few computational modeling studies that employ the opinion dynamics model to study addictive behaviors [321, 235], and none of them devote particular attention towards how in-person school closures may affect youth nonmedical prescription opioid use.

Broadly, opinion formation models can be categorized into discrete and continuous models. Discrete models permit an agent to hold one of a finite set of opinions, whereas continuous models allow for a real-valued opinion [135]. Below, we informally characterize eight prominent subgroups in the opinion dynamics models within the literature [77], recognizing that the taxonomy employed here is not a canonical one and that other forms of classification of opinion dynamics models can be seen within the literature [135].

One of the earliest dichotomous discrete opinion dynamics models to simulate how people’s attitudes evolve over time is the voter model. Each individual inside an arbitrary network is selected randomly and adopts the state of a randomly chosen neighbor. Arrival at a consensus is the main feature of the voter model [76]. Many variants of the voter model have been examined, including a nonlinear formulation [66], alternative starting network configurations [65], the impacts of “zealots” carrying invariant beliefs [230], and those reflecting various co-evolutionary principles [210]. A second discrete model of opinion dynamics — the majority rule model—considers a set of agents who have discrete opinions and selects alternatives that enjoy majority support [188, 119]. Third, the Sznajd model provides a discrete model of opinion dynamics and implements a rule in which a pair of neighbors is randomly chosen to change their nearest neighbor’s opinion; if that pair of close neighbors agree, their nearest neighbors will eventually agree. By contrast, if the pair disagree, the opinion of the nearest neighbors remains unchanged, with no common opinion developing.
among their nearest neighbors [324, 325, 323]. Fourth, the bounded confidence model was developed by Deffuant et al. and consists of a stochastic model for the evolution of continuous-valued opinions within a finite group of peers [88]. Fifth, the relative agreement model is a variant of the bounded confidence model that uses individual uncertainty as the criterion for deciding whether two agents can interact; uncertainty, as well as opinion, can be modified by interactions within this model [89]. Sixth, the continuous opinions and discrete actions model describes a situation in which agents hold real-valued opinions yet may only express themselves in discrete terms [218]. Seventh, the social judgment-based opinion model shares certain features with the continuous opinions and discrete actions model with two alternative structures: one in which agents can express their opinion as a real number and another in which they are restricted to one of a set of discrete possibilities [111, 219]. A final class of opinion dynamics models are those employing the social impact theory model, which offers a discrete model of opinion dynamics based on social impact theory in psychology [198]. Social impact theory associates each agent with three variables—a level of persuasiveness, a level of supportiveness, and a binary opinion. The model further presents a set of formulæ to characterize the total impact on each agent based on the number, strength, and immediacy of its neighbors [247]. This work employs this final class of opinion dynamics models as an established theory of clear relevance to study the impact on youth drug use of direct (in-person) peer influences at school and indirect perceived norms from the socio-cultural environment.

The COVID-19 pandemic has had a profound impact on the lives of people around the world, including youth. In particular, the closure of in-person schools has raised questions about the potential impact on nonmedical prescription opioid use among youth. The current study centers on the question of how in-person school closures during and after the COVID-19 pandemic affect nonmedical prescription opioid use among youth, and what measures can be taken to alleviate any potential risks or improve the situation. The findings of this research can be utilized to develop policies and interventions aimed at decreasing the risk of nonmedical prescription opioid use among youth during and after in-person school closures. This study is one of the first to investigate the impact of in-person school closures on nonmedical prescription opioid use among youth during and after the COVID-19 pandemic in Canada. To support this investigation, this work employed an agent-based model formulated based on the social impact model of opinion formation [64, 158], and was calibrated to reflect data from the Ontario Student Drug Use and Health Survey (OSDUHS) [44, 45].

The remainder of this paper is organized as follows: Section 2 describes the model, including the agent-based formulation and the social impact theory implementation, cellular automata spatial structure, and the experimental design. Section 3 elucidates the results. Section 4 includes the corresponding discussion and concludes the paper.
3.2 Materials and Methods

Within this work, the influences of peers, families, and socio-cultural environment on nonmedical prescription opioid use among youth are investigated using an agent-based model operating within a spatial grid-based network structure in accordance with cellular automata (CA) principles. The data on the prevalence of nonmedical prescription opioid use among youth, as well as the frequency and sources of use reported in the Ontario Student Drug Use and Health Survey (OSDUHS) [44, 45], were used to parameterize and calibrate the agent-based model. The selection of the most appropriate agent-based modeling toolkit for this project was based on a variety of factors, including the programming experience and abilities of the individuals involved, the activity of the toolkit’s community and the availability of specialized resources, the scalability and adaptability of the platform, and the built-in visualization options. Two separate reports [40, 245] evaluated various agent-based modeling toolkits against different criteria and offered recommendations based on specific needs. For this study, the model was created using simulation software AnyLogic Version 8.8.1 [52, 53] and the model was run for a time horizon from 2017 to 2025.

The design of the agent-based model drew on the social impact model of opinion formation [64, 158]. The agent-based model was created, parameterized, calibrated, and used to investigate the prevalence of nonmedical prescription opioid use among youth, their prescription opioids resources, and the frequency of nonmedical prescription opioid use within the past year when varying peer influence, youth exposure to prescription opioids at home, and the influence of the socio-cultural environment. To support this investigation, the peer network context, families, and the socio-cultural environment shaping nonmedical prescription opioid use in youth were captured within a three-level CA context (corresponding to peers, families, and the socio-cultural environment), where each youth’s nonmedical prescription opioid use evolved according to the social impact theory of opinion formation.

3.2.1 Agent-Based Modeling

The use of agent-based modeling in this study supports the analysis of changes in the prevalence of nonmedical prescription opioid use among youth and the characterization of the effects of their peers, families, and socio-cultural environment. Hence, the model features three type of agents: youth, family, and socio-cultural environment. Youth behavior is governed by three different state charts depicted in Figure 3.2. These state charts collectively characterize the possible state-space for a single youth and the events that lead to transitions from one state to another.

The logic for transitions between states within the Youth Drug Use Opinion Evidence state chart was informed by social impact theory. At the topmost level, the Youth Drug Use state chart characterizes whether the individual currently uses nonmedical pre-scription opioids. Youth who are not currently using nonmedical prescription opioids are divided into two groups: youth who have never used nonmedical prescription opioids and youth who previously used but have since quit by electing not to use nonmedical prescription opioids.
Figure 3.2: Youth state charts - Youth Drug Use Opinion Evidence state chart at the top middle, Frequency of Drug Use in the past year state chart at the bottom left, and Drug Sources state chart at the bottom right.
when the opportunity arose. Youth who currently use nonmedical prescription opioids are also divided into
two groups: youth who are within their initial period of nonmedical prescription opioids use and youth who
relapsed after previously quitting.

The Frequency of Drug Use in the past year state chart represents the number of times that youth used
nonmedical prescription opioids during the past year, and it is updated as time passes and as youth use
nonmedical prescription opioids.

The Drug Sources state chart depicts two important sources for the most recent prescription opioids use
for youth: family and friends. Youth are considered to have a possible opportunity to obtain opioids from
family when their family includes at least one person with an opioid prescription. In the absence of a family
source, youth can seek available prescription opioids amongst their close friends (considered to be those
within their range 1 Moore neighborhood; see below); based on a probability, youth can obtain prescription
opioids from friends who are themselves nonmedical prescription opioid users. The unspecified state reflects
other sources of opioids.

Each youth is associated with a family, as represented by a family agent. Each such family agent has a
family size parameter, which is drawn from a Poisson distribution to represent the empirical data that the
average family size in Canada was 2.9 in 2019 [316]. The probability of filling an opioid prescription per week
for each family member previously without an opioid prescription and the per week probability of ending
opioid prescription treatment for each family member with prescription opioids are calibrated to represent
the 12.7% of Canadians who reported having used opioids pain relief medications in 2018 [63]. If a member
of any family has been prescribed an opioid, a child in the family might be exposed to prescription opioids,
with the level of exposure differing between families. The child exposure to opioids parameter is calibrated
to represent the 49.3% of Ontario youth who reported using nonmedical prescription opioids, obtaining them
from a parent, sibling, or someone else with whom they live [44, 45].

The socio-cultural environment for contemporary youth is made up of neighborhoods, recreation areas,
social events, and other forces that affect a youth’s basic values, perceptions, and preferences. Within the
model, a socio-cultural environment agent is implemented to reflect the idea that youth prescription opioid
use is particularly high in some specific demographics [299]. Part of the socio-cultural environment within
the model is therefore assumed to have some degree of bearing on the valence of a youth’s attitude towards
drug use.

### 3.2.2 Cellular Automata for Spatially Localized Networks

This model uses a three-level spatial grid-based network structure to capture the social context of each youth.
All youth are randomly and injectively placed into individual cells (patches) in the cellular automata located
in the global environment. The three-level grid containing the youth, family, and socio-cultural environment
is a square containing 100 columns and 100 rows. Each patch corresponds to the youth at CA level one (as
depicted in Figure 3.3a), the youth’s family at CA level two (as depicted in Figure 3.3b), and the youth’s
socio-cultural environment at CA level three (as depicted in Figure 3.3c).

![Three-level cellular automata](image)

**Figure 3.3:** Three-level cellular automata (a) Each patch presents a youth. Colors distinguish youth who are absent nonmedical prescription opioid use experience in the past year (yellow) and with nonmedical prescription opioid use experience in that interval (red). (b) Each patch represents family. Corresponding colors for a family with at least one member with current prescribed opioids and family without any prescribed opioids are pink and ivory, respectively. (c) Socio-cultural environment, in which the black areas represent a positive perspective toward drug use and gradations towards white represent successively more negative attitudes towards drug use.

This implantation provides a spatially explicit, grid-based network structure for the youth, who remain immobile throughout the simulation. The lack of spatial mobility reflects the fact that many youths exhibited high conservation in their social networks and interaction patterns during and immediately after the pandemic, partly because of the fact that such networks reflect the composition of the family and socio-cultural environment in which the youth is nested [56]. Social network density for youth and their peers at CA level one is operationalized by considering Moore neighborhoods with different diameters (ranges) as shown in Figure 3.4.

### 3.2.3 Social Impact Model of Opinion Formation

The model characterizes how youths’ nonmedical use of prescription opioids might be governed by environmental influences, availability of prescription opioids at home, and the actions of their peers following a discrete opinion model based on social impact theory. The model consists of 10,000 youths and their corresponding family and socio-cultural environment. Each youth is considered to have one of two opposite opinions on nonmedical prescription opioid use, according to whether they currently nonmedically use prescription opioids. The presence or absence of nonmedical prescription drug use is assumed to be dictated entirely by the attitude (opinion) of the youth with respect to drug use.

In accordance with social impact theory, each youth is characterized by two independent parameters
Figure 3.4: Moore neighborhood with different ranges from left to right: $r = 0$, $r = 1$, $r = 2$, and $r = 3$.

called persuasiveness and supportiveness. The strength of persuasiveness is the ability to persuade another youth with a discordant drug use attitude to change their current attitude. The strength of supportiveness characterizes the ability to support another youth with an identical drug use attitude to persist in their current attitude [247].

Following the literature [247, 214], the values of the persuasiveness and supportiveness attributes are assigned as random real-number values uniformly drawn between 0 and 100; when youth flip to an alternative attitude and associated behavior, their parameters for persuasiveness and supportiveness are independently drawn from the same distribution.

Youth experience a net impact from interactions with the socio-cultural environment, family, and peers. Employing a formulation drawn from the opinion dynamics literature [247, 214], the model characterizes the quantitative value of that impact $I_i$ for an agent $i$ at each drug use occasion with the equation shown in Equation (1).

$$I_i = \left( \sum_{j=1}^{N} \frac{p_j}{d_{ij}^a} (1 - o_i o_j) \right) - \left( \sum_{j=1}^{N} \frac{s_j}{d_{ij}^a} (1 + o_i o_j) \right) - o_i E_i - o_i M_i$$  \hspace{1cm} (Eq. 3.1)

where $j$ denotes another agent influencing agent $i$, and $o_i$ and $o_j$ denote the dichotomous ($\pm 1$) opinion values of agents $i$ and $j$, respectively, towards opioid use, where $-1$ indicates an attitude disfavoring opioid use and $+1$ indicates an attitude in favor of opioid use.

$p_j$ and $s_j$ denote the persuasiveness and supportiveness of agent $j$, respectively. In accordance with a gravity model formulation, $d_{ij}$ represents the Euclidean distance between youth $i$ and $j$, and $a$ defines the speed of drop-off of influence with distance. The current model considers peers at Moore neighborhoods with three different levels of influence on nonmedical opioids use for youth; therefore, $d$ is equal to the minimum Moore neighborhood radius with which agents $i$ and $j$ are connected ($\text{max} = 3$). For a given agent $i$, an agent $j$ lying outside the distance of 3 Moore neighborhoods surrounding agent $i$ is assumed to exert zero
influence on agent \( i \) (that is, \( \frac{p_j}{d_{ij}} \) and \( \frac{s_j}{d_{ija}} \) are considered to be 0). Following the literature \cite{247, 214} and consistent with calibrated results of the model, \( a \) is considered equal to 2.

The peer impact on youth \( i \) is calculated as the difference between the collective impact of the interacting youth exerting influence on youth \( i \) to change opinion (characterized by the first bracketed term of Equation (1)) and the collective impact of peers exerting influence to maintain youth \( i \)'s current opinion (the second bracketed term of Equation (1)).

\( E_i \) is a so-called socio-cultural environment pro-drug influence parameter reflecting the level of promotion of drug use by youth \( i \)'s neighborhoods, recreation areas, social events, and other forces (a value greater than 0 when there is a pro-drug influence and equal to 0 for areas without pro-drug influence). \( M_i \) is a child’s exposure to opioids at home parameter (family influence), reflecting the level of unsafe opioid storage practices by the youth’s family (a value greater than 0 when there is some opioid storage by the youth’s family and equal to 0 for youth \( i \) in a family without prescription opioids).

If the overall impact from interacting with peers, families, and the socio-cultural environment for a youth who is absent any nonmedical prescription opioids experience as characterized by Equation (1) is greater than 0, then the current youth will immediately initiate nonmedical prescription opioids use. Equation (1) individually governs initiation behavior in youth who are absent nonmedical prescription opioid use experience, as they do not have any acute withdrawal symptoms for opioids prior to any experience.

After initial experience with nonmedical prescription opioid use, the behavior of youth continues to be influenced by peers, families, and the socio-cultural environment; however, another key factor also arises at this point: the severity of acute withdrawal. This factor can serve to either reinforce or discourage youth drug use \cite{7}.

Past research has suggested that the temporal evolution of the severity of acute withdrawal symptoms for opioid drugs can be characterized by a lognormal function of days from the last dose \cite{200}. We employed a lognormal function where scale parameter \( \mu \) ranged between 0 and 1 and shape parameter \( \sigma \) ranged between \( 1 \times 10^{(-3)} \) to \( 1.5 \times 10^{(-3)} \).

The attitude of youth with nonmedical prescription opioid use experience may change in each drug use situation according to Equation (2).

\[
o_i(t + 1) = \begin{cases} 
  o_i(t) & \text{with probability } \frac{\exp\left(\frac{T_i}{\sigma}\right)}{\exp\left(\frac{T_i}{\mu}\right) + \exp\left(\frac{T_i}{\sigma}\right)}, \\
  -o_i(t) & \text{with probability } \frac{\exp\left(\frac{T_i}{\mu}\right)}{\exp\left(\frac{T_i}{\mu}\right) + \exp\left(\frac{T_i}{\sigma}\right)} 
\end{cases} \quad (Eq. 3.2)
\]

The parameter \( T_i \) represents the severity of acute withdrawal at the current time, and may be interpreted as a personalized parameter to show randomness in the behavior of youth, who may reject peers, families, and the socio-cultural environment’s impact about nonmedical prescription opioid use and elect to quit or relapse. Although the impact \( I_i \) is a deterministic endogenous parameter that represents a propensity to change—that is, it causes youths who are absent nonmedical prescription opioid experience to initiate opioid use.
use (when the total impact is greater than 0)—any youth with experience of nonmedical prescription opioid use may quit or relapse based on the probability calculated within Equation (2). A higher value of \( I_i \) indicates a greater likelihood of changing behavior within Equation (2). Equation (2) is a particular case of the system considered in the literature [50, 157].

3.2.4 In-Person School Closures Implementation Due to the COVID-19 Pandemic

The model characterizes in-person school closures associated with the COVID-19 pandemic as a change in the range of the Moore neighborhood mediating inter-youth interaction starting on 14 March 2020. Specifically, mass in-person school closures are implemented as a Moore neighborhood of range 0 (which has the effect of eliminating the spread of direct—in person—influence between youth) and in the case of the Ontario school closure timeline, the Moore neighborhood range differs for mass closure, partial opening, and phased opening.

3.2.5 Parametrization, Calibration, and Validation

While the agent-based model presented in this study is a stylized one, it drew heavily on the Ontario Student Drug Use and Health Survey (OSDUHS) [44, 45] to provide data to characterize dynamics of nonmedical prescription opioid use among youth in Canada. The baseline empirically grounded model reflects nonmedical prescription opioids use among students in Grades 7–12 from 2017 to 2021 based on OSDUHS [44, 45] and projected until the end of 2025.

Ontario mass in-person school closures were characterized by imposing a Moore neighborhood of range 0 in any phases of the lockdown. The first school closure period was from 14 March 2020 to 8 September 2020, then from 20 December 2020 to 8 January 2021, and finally from 12 April 2021 to 17 January 2022 [121, 41]. The period of phased reopening was characterized as imposing a Moore neighborhood of range 2 from 8 September 2020 to 21 September 2020, with partial reopening characterized as a Moore neighborhood of range 1 from 8 January 2021 to 1 February 2021, and as a Moore neighborhood of range 2 from 2 February 2021 to 16 February 2021 to reflect the transition from the mass school closure to full reopening. Finally, the full reopening of Ontario schools was characterized as a Moore neighborhood of range 3.

The model was calibrated so as to match model output against the time-series of the prevalence of youth with nonmedical prescription opioid use, and the time-series of the prevalence of youth using nonmedical prescription opioids frequently (six times or more over the past year) targets from 2017 to 2019 at 2-year intervals and data points of the prevalence of youth using nonmedical prescription opioids obtained from different resources (including families, friends, and unspecified resources) in 2019. During the calibration process, we varied the following set of model parameters by hand until the model outputs approximated empirical data.

Several model parameters were calibrated against the prevalence of youth with nonmedical prescription opioid use and the prevalence of youth using nonmedical prescription opioids obtained from families. Youth
exposure to prescription opioids at home was calibrated against the prevalence of youth with nonmedical prescription opioid use and the prevalence of youth using nonmedical prescription opioids obtained from families. The severity of acute withdrawal from nonmedical opioid use was calibrated against the prevalence of youth with nonmedical prescription opioid use. The percentage of the socio-cultural environment with a positive drug use view and the level of drug promotion inside the drug-positive socio-cultural environment were calibrated against the prevalence of youth with nonmedical prescription opioid use. The probability that peers share drugs with peers who request it was calibrated against the prevalence of youth using nonmedical prescription opioids obtained from families. The rate of encountering drug use situations for youth consisted of an initial amount and a coefficient to reflect the current socialization level, and both were calibrated against the prevalence of youth with nonmedical prescription opioid use. The rate of opioid prescription for each family member without prescription opioids and the probability that the duration of the opioid prescription ends for each family member was calibrated to accord with the prevalence of Canadians with an opioid prescription. See Table 3.1 for more details on parameter values and references.

Finally, to ensure the reliability, validity, and robustness of the current model, a comprehensive validation process was conducted in three phases [79, 287]. The first phase, verification, evaluates the correctness of the model by comparing the model’s assumptions to the code logic. The second phase, validation, assesses the accuracy of the model’s emergent behavior by comparing it to external criteria such as real-world data or expert knowledge. The final phase, sensitivity analysis, examines how variations in model assumptions impact the model’s outcomes. The model demonstrates a visually good fit between the observed and model-predicted prevalence of youth with a nonmedical prescription opioid in 2021 during the COVID-19-related in-person school closures.

3.2.6 Scenarios

To investigate the impact of in-person school closures on nonmedical prescription opioid use among youth, two sets of scenarios were examined. The first set of scenarios examined outcomes from 6, 12, 18, and 24 months of mass in-person school closures followed by partial opening, phased opening, or full opening (i.e., characterizing using different Moore neighborhood ranges) after removing the mass in-person school closures order. For the first set of scenarios, an ensemble of 30 realizations was conducted to secure statistical confidence in results despite stochastic variability.

The second set of scenarios sought to examine the impact of the Ontario school closure timeline and further applied the intervention of reducing youth exposure to prescription opioids at home by 20%, 50%, and 80% at three different time points, considered singly. For the second set of scenarios, an ensemble of 100 realizations was conducted. Furthermore, to generate outcomes of interest that are compatible with the empirical data for the baseline, each simulation employed a 3-year burn-in period for the model. Following the burn-in period, the model was run for a time horizon from 2017 to 2025. Outcomes of interest are plotted daily to see the pattern of changes and recorded yearly to compare with the baseline.
3.3 Results

This section describes the results of model simulations. The Monte Carlo simulation of the model utilized different realizations to generate a sample of potential outcomes, given a set of inputs and assumptions. Each realization represented a single simulation of the system, utilizing a randomly generated set of inputs. By conducting multiple realizations and introducing randomness in the input parameters, the simulation aimed to gain a deeper understanding of the uncertainty of the results. The results are divided into three subsections, starting with the model-generated prevalence of youth with nonmedical prescription opioid use in the past year for different durations of in-person school closures, followed by a simulation of the model using the Ontario school closure timeline without any intervention. Finally, the impact of safe storage of prescription opioids at home on the prevalence of youth engaged in nonmedical prescription opioid use on the result of the model using the Ontario school closure timeline is explored.

3.3.1 Results of the Simulation for the Prevalence of Youth with Nonmedical Prescription Opioid Use in the Past Year for Different In-Person School Closure Durations

Figure 3.5 illustrates the model-generated prevalence of youth with nonmedical prescription opioid use in the past year for the different durations of in-person school closures. There is a small increase in the prevalence of drug use for the first six months of in-person school closures. Following this initial increase in prevalence, scenarios exhibit a decline to a steady level for the next six months of in-person school closures. Following that—for sufficiently long durations of in-person school closures—a plateau persists until the end of the in-person school closures. The prevalence of youth with nonmedical prescription opioid use significantly increases after the lifting of the in-person school closures, regardless of its duration. Nevertheless, the appearance of the increase remained consistent across different levels of in-person socialization following the lifting of in-person school closures, supporting the robustness of this conclusion (See Figures 3.8 and 3.9).

3.3.2 Simulation of the Model Using Ontario School Closure Timeline

Figure 3.6 represents the model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year based on the Ontario school closure timeline. Figure 3.6 also demonstrates a visually good fit between the observed and model-generated prevalence of youth with nonmedical prescription opioids, persisting even in the middle of in-person school closures in 2021. After the first school closure came into effect on 14 March 2020, the model-generated prevalence of youth exhibiting nonmedical prescription opioid use shows an increasing trend. The increase continues through the year as schooling experiences were more differentiated across Ontario with the different possible levels of socialization for youth. However, as the second mass in-person school closures due to the COVID-19 pandemic lasted for more than six months, the
model-generated prevalence of drug use shows a downward shift. The model-generated prevalence of youth exhibiting nonmedical prescription opioid use increases after the lifting of the in-person school closures. Further, we used the model to estimate the overall impact of in-person school closures through the COVID-19 pandemic on youth opioid use by comparing the model-generated prevalence of drug use in 2025, with and without in-person school closures due to the COVID-19 pandemic. The model-generated prevalence of youth exhibiting nonmedical prescription opioid use could show a significant increase (of +195%) in 2025 as a consequence of in-person school closures. Furthermore, the distributions of simulation outputs and the coefficient of variation remain relatively stable under different population sizes (See Figure 3.10).

### 3.3.3 Impact of Safely Storing Prescription Opioids at Home on the Result of the Model Using the Ontario School Closure Timeline

Figure 3.7 illustrates the impact of safely storing prescription opioids at home on the prevalence of youth with nonmedical prescription opioid use in the past year. Specifically, it shows the impacts when youth
Figure 3.6: Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year based on Ontario school closure timeline. The blue dots show the empirical data and the two vertical black arrows represent the start and end of the Ontario school closure timeline.

exposure to prescription opioids at home is reduced by 20%. Figure 3.7b illustrates a scenario in which the intervention of safely storing prescription opioids with a decrease of 20% in youth exposure to prescription opioids at home was implemented in 2017. Figure 3.7c depicts the effects of this intervention when it was implemented at the start of the COVID-19-related in-person school closures, while Figure 3.7d depicts the effects of the intervention of securely storing prescription opioids when it was implemented at the start of the 2022–2023 academic year. Cases in which this intervention was implemented before or early in the COVID-19-related in-person school closures slightly mitigate the extent of the increase in prevalence of drug use after the lifting of in-person school closures (Figure 3.7b,c). However, even a delayed implementation of safely storing prescription opioids—where such precautions are introduced after the lifting of the COVID-19-related in-person school closures—has also achieved a modest reduction in the peak in the prevalence of youth with nonmedical prescription opioid use (Figure 3.7d).

Decreasing youth exposure to prescription opioids by 20% would reduce the prevalence of youth with nonmedical prescription opioid use after the lifting of the COVID-19-related in-person school closures by 27% and 28% in 2025 relative to the baseline, depending on whether the intervention was implemented before or at
the beginning of the COVID-19-related in-person school closures, respectively. However, late implementation of the intervention at the start of the 2022–2023 academic year would also reduce the prevalence of youth with nonmedical prescription opioid use in 2025 by 9%, relative to the result of the model using the Ontario school closure timeline without any intervention.

The results of the model also indicate that decreasing youth exposure to prescription opioids by 50% can lead to a significant reduction in the prevalence of nonmedical prescription opioid use among youth after the lifting of the COVID-19-related in-person school closures. Specifically, the prevalence of youth with nonmedical prescription opioid use in 2025 would be reduced by 58% and 56%, depending on whether the intervention was implemented before or at the beginning of the COVID-19-related in-person school closures, respectively. With a late implementation at the start of the 2022–2023 academic year, the prevalence of youth with nonmedical prescription opioid use in 2025 would still be reduced by 19% in comparison to the model using the Ontario school closure timeline without any intervention (See Figure 3.11).

Finally, a significant decrease in youth exposure to prescription opioids by 80% could greatly reduce the prevalence of nonmedical prescription opioid use among youth following the lifting of the COVID-19-related in-person school closures. The prevalence of youth with nonmedical prescription opioid use in 2025 could be lowered by 68% and 66% if the intervention was implemented prior to or at the beginning of the COVID-19-related in-person school closures, respectively. Even with a delayed implementation at the start of the 2022–2023 academic year, the prevalence of youth with nonmedical prescription opioid use in 2025 could still be reduced by 21% compared to the model using the Ontario school closure timeline without any intervention (See Figure 3.12).

3.4 Discussion

This simulation demonstrates that public health orders mandating in-person school closures may have had direct and indirect effects on youth opioid use during and after school closure. Limited in-person social interaction changes the circumstances surrounding youth, resulting in unintended consequences on risk factors for opioid use. The simulation illustrates that the pervasiveness of unsafely stored opioids in homes and limited in-person social interaction with anti-drug peers could facilitate the initiation of opioid use among youth. However, decreasing social events for recreational drug use, the absence of peers who might encourage taking certain risks [22], and the negative effect of withdrawal symptoms limit the increase of opioid use further during in-person school closures. The lifting of in-person school closures may lead to a high increase in the prevalence of youth engaged in nonmedical prescription opioid use. The “rebound” effect on the prevalence of nonmedical prescription opioid use after in-person school closures end could occur for several reasons. One possible explanation is that when in-person school closures end, youths may be more likely to come into contact with peers who use drugs. These social networks can play an important role in shaping youth drug use behaviors. The increased socialization that occurs when school is in person can expose young people to
Figure 3.7: Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year for the baseline scenario (a) and after applying safe storage intervention with a decrease of 20% in youth exposure to prescription opioids at home beginning at different time points (b–d). The two vertical black arrows represent the start and end of the Ontario school closure timeline. (a) Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year for the baseline scenario. (b) Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year after applying safe storage in 2017. (c) Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year after applying safe storage at the beginning of the general COVID-19-related in-person school closures on 14 March 2020. (d) Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year after applying safe storage at the start of the 2022–2023 academic year.
a higher risk of peer pressure and influence, which could lead to an increase in drug use. The literature also argues the plausibility that ongoing effects of the COVID-19 pandemic in North America will place youth at a greater risk for nonmedical prescription opioid use [171, 74, 257]. Factors outside the scope of the model may have influenced such effects in either direction. For example, while family members staying home from work may have restricted youth access to opioids in some households, in some settings, the consequences of concurrent parental unemployment and spending more time at home and witnessing possible elevated levels of family member substance use [136] may put youth at a higher risk for opioid use.

The simulation outcomes demonstrate that interventions that decrease youth exposure to prescription opioids in the home context could constitute an effective intervention pathway to mitigate what could be a significant increase in youth opioid use following the lifting of in-person school closures. Interventions targeting associated risk factors for youth exposure to prescription opioids at home can be beneficial whenever they come into effect, whether before or during in-person school closures; while the benefits secured by intervention at those times are particularly pronounced, later implementations will also help mitigate what could constitute a significant increase in youth opioid use.

The findings from this study should be interpreted within the context of the following limitations. First, the current approach focuses specifically on the in-person peer socialization component of the peer influence process; this work therefore does not consider either peer selection or online peer socialization, which may influence regular substance use among youth [228, 161]. Instead, our goal was to identify the extent to which lack of in-person peer socialization as a result of in-person school closures could plausibly influence nonmedical opioid use among youth. Second, research indicates that youth consumption of prescription opioids may be mediated by anxiety and hopelessness [239], as contributed to by the adverse psychological impacts on youth from the pandemic compounded by in-person school closures and isolation from peers. Since this study focused on the sociological aspect of substance use in particular, future research could study psychological factors which may have a reinforcing effect on youth drug use. Third, the current modeling analysis does not explicitly track the effect of opioid tolerance and possible overdoses on later opioid use among youth. Fourth, the current level of model abstraction filtered out some less-essential details for youth within the model, such as youth siblings, youth year in school, and disconnection from peers after school. Finally, exploring alternative network structures and theories of opinion dynamics among youth in future agent-based modeling studies may be worthwhile. Of particular note, more extensive national data on youth opioid use would especially inform the model parameterization and assumptions, support testing the plausibility of model baseline scenario outcomes, and support critical evaluation of the current conclusions.

Despite these limitations, identifying a potential increase in the prevalence of youth with nonmedical prescription opioid use after the lifting of in-person school closures suggests the importance of effective opioid surveillance, and awareness and availability of naloxone and treatment options to prevent serious medical outcomes and death in this vulnerable population. Furthermore, efforts to encourage new opioid packaging, such as personalized pill dispensers, may lower the accessibility of incompletely dispensed prescription opioids.
It should be noted that a disruption to the supply of opioids from home should be combined with supporting and promoting awareness of the risks of opioid abuse amongst youth.
Figure 3.8: Model-generated prevalence of youth with nonmedical prescription opioid use in the past year for the different durations of in-person school closures (a–d). The model predicted the prevalence of youth with nonmedical prescription opioid use in the past year for (a) 6-month in-person school closures, (b) 12-month in-person school closures, (c) 18-month in-person school closures, and (d) 24-month in-person school closures. In-person socialization following the lifting of in-person school closures is characterized as a Moore neighborhood of range 1. The two vertical arrows represent the start and end of the in-person school closures for each panel, respectively.
Figure 3.9: Model-generated prevalence of youth with nonmedical prescription opioid use in the past year for the different durations of in-person school closures (a–d). The model predicted the prevalence of youth with nonmedical prescription opioid use in the past year for (a) 6-month in-person school closures, (b) 12-month in-person school closures, (c) 18-month in-person school closures, and (d) 24-month in-person school closures. In-person socialization following the lifting of in-person school closures is characterized as a Moore neighborhood of range 2. The two vertical arrows represent the start and end of the in-person school closures for each panel, respectively.

Figure 3.10: Model-generated prevalence of youth with nonmedical prescription opioid use in the past year (left-hand side) and coefficient of variation for simulation means and standard deviation in 2025 (right-hand side) of the baseline scenario under different population sizes.
Figure 3.11: Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year for the baseline scenario (a) and after applying safe storage intervention with a decrease of 50% in youth exposure to prescription opioids at home beginning at different time points (b–d). The two vertical black arrows represent the start and end of the Ontario school closure timeline. (a) Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year for the baseline scenario. (b) Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year after applying safe storage in 2017. (c) Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year after applying safe storage at the beginning of the general COVID-19-related in-person school closures on 14 March 2020. (d) Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year after applying safe storage at the start of the 2022–2023 academic year.
Figure 3.12: Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year for the baseline scenario (a) and after applying safe storage intervention with a decrease of 80% in youth exposure to prescription opioids at home beginning at different time points (b–d). The two vertical black arrows represent the start and end of the Ontario school closure timeline. (a) Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year for the baseline scenario. (b) Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year after applying safe storage in 2017. (c) Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year after applying safe storage at the beginning of the general COVID-19-related in-person school closures on 14 March 2020. (d) Model-generated prevalence of youth exhibiting nonmedical prescription opioid use in the past year after applying safe storage at the start of the 2022–2023 academic year.
Table 3.1: Parameters, values, and references

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Chapter 4

Opioid-related harms and care impacts of conventional and AI-based prescription management strategies: Insights from leveraging agent-based modeling and machine-learning

Abstract: Like its counterpart to the south, Canada ranks among the top five countries with the highest rates of opioid prescriptions. With many suffering opioid use disorder first having encountered opioids via prescription routes, practitioners and health systems have an enduring need to identify and effectively respond to problematic opioid prescription use. There are strong challenges to successfully addressing this need: Importantly, the patterns of prescription fulfillment that signal opioid abuse can be subtle and difficult to recognize, and overzealous enforcement can deprive those with legitimate pain management needs appropriate care. Moreover, injudicious responses risk shifting those suffering early-stage abuse of prescribed opioids to illicitly sourced street alternatives, whose varying dosage, availability, and risk of adulteration can pose grave health risks. This study employs dynamic modeling and simulation to evaluate the effectiveness of prescription regimes employing machine learning monitoring programs to identify patients who are at risk of opioid abuse while being treated with prescribed opioids. To this end, an agent-based model was developed and implemented to examine the effect of reduced prescribing and prescription drug monitoring programs on overdose and escalation to street opioids among patients, and on the legitimacy of fulfillments of opioid prescriptions over a five-year time horizon. A study released by the Canadian Institute for Health Information was used to estimate parameter values and assist in the validation of the existing agent-based model. The model estimates that lowering prescription doses exerted the most favorable impact on the outcome of interest over five years with a minimum burden on patients with a legitimate need for pharmaceutical opioids. The accurate conclusion about the impact of public health interventions requires a comprehensive set of outcomes to test their multi-dimensional effects, as utilized in this research. Finally, combining machine learning and agent-based modeling can provide significant advantages, particularly when using the latter to gain insights into the long-term effects and dynamic circumstances of the former.
4.1 Introduction

The risks associated with psychoactive prescription medicines — particularly opioids — are significant public health and patient safety issues [27, 114, 160, 170], still Canada is among the top five countries with the highest rate of opioid prescriptions for the last fifteen years [122, 155]. Some patients who were prescribed opioids have sometimes resorted to non-medical opioid use or illicit drug supply due to various factors such as inadequate pain management, lack of access to alternative treatments, mental health issues, and addiction vulnerability [124, 217]. In 2017, eleven lives were lost each day owing to opioid overdoses in Canada, with 3,658 opioid-related deaths reported in 2019 [165, 112]. During the COVID-19 pandemic, this problem has become particularly acute, with sharp rises in opioid overdose death rates [112, 17] and destabilizing effects in prescription opioids [132]. Undeniably, the opioid crisis continues unmitigated in Canada [246], therefore ensuring the safety of opioid use, and adequate access to pain management should be among the top priorities for the healthcare system.

In recent years, a variety of policy interventions have been suggested to restrain medical opioid dispensing [237, 264], however, there are discrepant developments of decreasing opioid availability and increasing opioid mortality [175, 339, 113]. Contradictions inherent in these interventions call for a systems science approach [168] to consider broader structural conditions contributing to the issue.

Systems science offers more holistic tools and framework for improving understanding and decision-making regarding complex problems. Systems science methods enhance the capacity to reason about complex system behavior in systems marked by entangling of factors, feedbacks, path-dependence, delays and non-linearities, local contextual dependence, and distinct emergent behavior at different scales [205] — characteristics that are each notable features of the opioid crisis. Dynamic modeling within systems science supports alternative mechanisms for characterizing the structure of complex systems, which can aid in identifying key drivers that contribute to the emergence and persistence of complex phenomena, such as opioid use disorder [143, 231]. Systems science and the dynamic simulation models can be used to explore the complex nature of the opioid crisis and study the effect of changes to the system with minimal costs, risks, and time [167].

A set of literature reviews [232, 298, 35, 302] summarizes present existing research on implemented dynamic models for prescription opioid use and harms. While dynamic modeling and simulation have been employed to study different aspects of medical opioid dispensing, they have not taken into consideration the effectiveness of prescription regimes at the individual level, in general, or in the specific Canadian context that forms the focus of this work.

An agent-based model methodology can readily capture population heterogeneity and facilitate the study of a wide variety of the individual-level factors and their contribution to whole system behavior by simulating nature's evolution in opioid prescribing practices, based on a set of specified rules. In comparison with previous dynamic modeling approaches that focus at an aggregate level, the individual-level characterization that is the hallmark of agent-based modeling supports capturing the effects of pro-social companionship and
adverse social networks, feedback, and history dependence at an individual level — such as those associated with the development of tolerance and escalation of dosage levels and ensuring physiological dependence, stigmatization and the impact of adverse childhood experiences — widespread heterogeneity, as well as the effects of local context on a situated agent. With the application of agent-based modeling, new insight from a complex interaction of a whole system will often emerge which was not seen before [49, 125, 199]. Within the prescription context of the opioid use and misuse examined here, the utilization of an agent-based model allows the computer to evaluate different scenarios results regarding altering prescribing practices, which can be examined and optimized with lower resources and cost than would be required for human trials [356]. This paves the way for more exploratory use of the model as the source of the observed data and incorporation of a hidden Markov model (HMM) as a simulation model enhancement to implement a prescription drug monitoring program (PDMP) [281]. A simple PDMP designed to prevent diversion and misuse of controlled substances by identification of possible “doctor-pharmacy shoppers” patterns (i.e., overlapping opioid prescriptions or obtaining multiple prescriptions from different prescribers and pharmacies) [6]. However, an HMM-aided PDMP aims to monitor the legitimacy of prescriptions by leveraging agent-based modeling and machine learning algorithms to identify potential cases of opioid overuse among patients.

A hidden Markov model [273] as a machine learning method has been used to capture hidden information from a sequence of observations over time. While there are various probabilistic sequence classification methods available [346, 25, 220], the HMM is specifically chosen over other approaches for this study due to its strengths in handling sequential data, capturing hidden dynamics underlying the observed data, representing discrete hidden states, and modeling transitions between such hidden states. Furthermore, the HMM's solid mathematical foundation, satisfactory computational performance, and ability to provide a clear representation of the underlying model enable more meaningful interpretation of outcomes, particularly in the context of health policy studies [213, 296].

To employ an HMM, acquiring intensive longitudinal data is of utmost importance [273]. A detailed set of data is utilized for estimating the probability of a sequence of observations, decoding the most likely sequence of hidden states underlying such a sequence, and training the HMM parameters based on those observations. An appropriate agent-based modeling framework has the potential to generate high-quality data specifically for these purposes [183, 57]. In this study, an HMM-aided PDMP is implemented in the agent-based model [105] to investigate whether the HMM could improve prescription drug monitoring programs to detect these unobserved legitimate states for any new opioid prescription filled by each patient and further study the consequence of the HMM-aided PDMP intervention.

The goal of the study is to emphasize the significance of utilizing dynamic modeling and simulation techniques with the integration of machine learning algorithms to investigate opioid use disorder among patients who have been prescribed opioids. Utilizing an agent-based model is essential to serve as a basis for an HMM-aided PDMP and explore possible interventions while assessing any unforeseen consequences of different prescription regimes. Accordingly, this paper consists of the following sections. Section 2 presents
the research methodology and provides an overview of the conceptual model, the agent-based model details, the HMM-aided PDMP implementation, and outlines different policy interventions, section 3 discusses the different policy interventions results, and section 4 brings the overall conclusions of this study along with policy suggestions.

4.2 Research Methodology

In considering the complex nature of the opioid crisis [340, 202] and data gaps in this area [43, 169], it is evident that a conceptual model can facilitate developing an accurate and useful computational simulation model to support decision-making in the context of opioid therapy in the healthcare system [276].

4.2.1 Conceptual Model for Opioid Therapy Agent-Based Model

The opioid crisis remains a significant public health challenge in Canada [246]. Canada ranks among the countries with the highest per capita consumption of prescription opioids, with an average amount consumed per person that is among the highest in the world [46]. Prescription opioids are of particular concern, due to potential harms associated with them, such as overdose and addiction [265]. An estimated 8 to 12 percent of patients who were prescribed these medications developed dependence and started obtaining additional prescription opioids from different means such as overlapping opioid prescriptions, feigning symptoms of pain, or borrowing from other patients [124, 217]. The quest to use escalating quantities may shift patients to street opioids [71]. Potential shifts in opioid utilization and provision may lead to a move towards stronger illicit resources, beginning with heroin and possibly escalating to fentanyl [184, 38], to the extent that, the prevalence of synthetic opioids like fentanyl in street opioids is responsible for 80% of all opioid-related deaths recorded in Canada in 2021 [112].

The nature of opioid use and outcomes includes many entangled components, rendering evaluation of the public health impact of any changes in opioid prescribed practicing is extremely challenging. Particularly notable are challenges associated with balancing the provision of pain relief for those with acute, chronic or transient pain, the desire to minimize the development of high levels of tolerance and physical dependency amongst those on prescription opioids, and the need to prevent individuals whose dosing is restrained in this way from switching to or supplementing their use with illegitimate requests for prescription or street supplied opioids [278, 322].

Having stated the foregoing, Figure 4.1 represents a causal loop diagram for opioid therapy agent-based model. This causal loop diagram shows the boundary of the model in terms of its breadth and highlights two reinforcing feedback loops and one balancing feedback loop in the current study scope. The researchers benefited from published literature, and expert opinion in the development of this framework and consistent with the understanding gained through interaction with those with lived experience in this area.

As illustrated in Figure 4.1, the causal loop diagram assumes that a proportion of the population is
Figure 4.1: Causal loop diagram for the opioid prescription practicing consequence. This causal loop diagram consists of variables connected by arrows showing causal influence, with each relationship being positive (e.g., an increase in “Receiving opioid therapy” leads to an increase in “Overusing prescription opioids” compared to the value it otherwise would have held, ceteris paribus) or negative (e.g., an increase in “Borrowing prescription opioids from others” leads to a decrease in “Available surplus prescription opioid” compared to the value it otherwise would have held). Closed loops denote feedback, which is either reinforcing (R1 and R2) or balancing (B1). A switch to a supply of street opioids represents a situation where prescription-related factors may no longer apply.

misusing their prescription after the loss of adherence to opioid therapy, either by underusing or overusing opioids. A fraction of these people who start underusing might keep a portion of surplus opioids in their medication cabinet, ready to share with others. Another fraction of these people who start overusing might experience drug tolerance, which means over time the dose must be increased to achieve the same effect [101]. Therefore, they might engage in a few common mechanisms to obtain illegitimate prescriptions such as requesting frequent refills of opioid prescriptions, feigning symptoms of pain, prescription forgery, and fraudulent telephone calls to pharmacies. These mechanisms are implemented in the model through the inclusion of either at least one day of overlapping opioid prescriptions or the procurement of new opioid prescriptions illicitly. The process creates the first reinforcing loop. Overusing patients who do not attempt to obtain illegitimate prescriptions seek surplus prescriptions acquired from others to address increasing required doses. The process creates the second reinforcing loop. As patients demand surplus opioid prescriptions, the
overall source of surplus opioid prescriptions decreases. Because of this balancing feedback loop, patients might shift to street opioids to address their needs.

Furthermore, the following statements describe the boundary of the model in terms of the depth of detail that was implemented for each person within the scope of the model. The model includes a population of 50,000 individuals, each characterized by two properties: opioid prescription dose and duration of treatment. Each individual has one type of social connection network and the possible final states for an individual are either entering street opioid use or showing the signs of overdose.

4.2.2 Agent-Based Model and Simulation

Designing a detailed conceptual model paved the way for developing and implementing a more detailed computational simulation model. As a result, an agent-based model was developed and implemented to examine the potential impact of reducing opioid prescription does and treatment durations, a simple PDMP and an HMM-aided PDMP on potentially important outcomes of interest such as medical and nonmedical overdose, individuals who escalate to street opioids, legitimate, illegitimate, and total filled opioid prescriptions over a five-year time horizon which spans from 2013 to 2018. This time interval is consistent with the time period reported in the literature and does not include any temporary alterations in the opioid prescription practice that may have occurred during the COVID-19 pandemic. The agent-based model was developed using the simulation software AnyLogic version 8.8.1 [53] which is a simulation tool that performs the major types of systems science simulations [52]. The model time unit is one day, and the model operates in continuous time. The model is initialized after a five-year burn-in period. After this five-year burn-in period, patients exhibit different histories states of use of prescribed opioids and resulting differences in adherence to opioid treatment. Therefore, the model started to show a meaningful and constant pattern after a five-year burn-in period, and any calibration or experimentation is run after that period.

4.2.2.1 Agent-Based Model Structure and Agent-Characteristics

The agent-based model presented in this study characterizes the dynamics of opioid prescribing in Canada and can be used to evaluate different intervention responses to reduce harms associated with prescription opioid use. There is only one type of agent in this model: person. The dynamic of opioid prescribing for each person is captured via two state charts: the opioid prescribing state chart (depicted in Figure 4.3) and the medication adherence state chart (depicted in Figure 4.4).

At the topmost level, the opioid prescribing state chart (depicted in Figure 4.3) characterizes whether the individual was or was not in opioid therapy in the past year. In the opioid therapy state, based on the patient’s duration of the prescription, that patient is further characterized as to whether they are on short-term therapy or long-term therapy. People in the not in opioid therapy state transition into opioid therapy based on two different prescription initiation rates specified for new or established patients, respectively. These rates were determined based on the calibration experiment. To enter the opioid therapy state, firstly
patients seek their prescriptions in one eponymous state and, upon receiving such prescriptions move to the opioid therapy state. Another thing that occurs in the seeking prescription state is the HMM-aided PDMP which classify requests for an opioid prescription to legitimate or illegitimate ones and therefore stop the person with an illegitimate opioid prescription from entering the opioid therapy state. Further information about the implantation of the HMM-aided PDMP is provided in section 2.3.

As patients initiate opioid therapy, a new opioid prescription dose and a new anticipated treatment length will be assigned to each patient based on custom distributions parameterized from CIHI data [61]. Absent developing opioid overuse, all patients exit opioid therapy following the length of treatment based on timeout transitions.

Losing adherence to opioid treatment is implemented using the medication adherence state chart (depicted in Figure 4.4), where people are divided into two groups via a binary representation of adherence to opioid treatment. When patients receive an opioid prescription, they move to an adherence state. An internal timeout transition in adherence state calculates the remaining total prescription opioid dosage in case of loss of adherence. As time passes, each person might lose adherence based on a geometric growth function implemented inside an external timeout transition and move to a non-adherence state. Then patients are divided into two main groups in non-adherence state, which are underuse prescribed opioids or overuse prescribed opioids. This division is based on a possibility portion driven from literature. In the underuse state, each patient decides to store a portion of surplus prescribed opioids or dispose of them. After the initial treatment length finishes for the person in underuse state, a transition fires, and the patients exit the underuse state and enter the free opioid state.

If a patient enters the overuse state after losing adherence to opioid treatment, the patient requires higher doses compared to the initial prescribed dose which is calculated using a geometric growth function implemented within internal timeout transition. Another internal timeout transition calculates the remaining opioid dose and as the current available opioid prescription finishes, a transition fires, therefore patients start looking for other resources of available opioid prescription.

A portion of patients start to look for the possibility of obtaining illegitimate prescriptions. If any of the mechanisms for obtaining illegitimate prescriptions is successful, a transition fires and patients move to the taking prescription opioids state. Some patients are not successful to obtain illegitimate prescriptions, as well as other patients who do not try obtaining illegitimate prescriptions, start to investigate their network for others with surplus prescription opioids implemented inside a timeout transition. If a patient obtains prescription opioids from others that meet the patient's needs in terms of the required opioid doses, a transition fires and moves the patient to the taking prescription opioids state.

Any successful obtaining of prescription opioids keeps patients in the overuse state while using prescription opioids. Patients who fail to obtain prescription opioids move to the seeking street opioids state. A small portion of patients in the overuse state might stop using opioids and seek out of this state because of self-caring or treatment, based on a rate transition.
Patients at any state of opioid therapy have a transition to an overdose state governed by a hazard-rate based on the annual overdose rate considering recent opioid dose. The cumulative count of medical overdoses is calculated as the cumulative count of overdoses that occurred for patients in the adherence state. The cumulative count of nonmedical overdoses is calculated as the cumulative count of overdoses that occurred for patients in the non-adherence state which implies patients take a dosage other than the medically recommended one. (Note that other assumptions in translation from the real world into the opioid therapy agent-based model are provided in the Table 4.1).

**Table 4.1: List of assumptions for opioid therapy agent-based model**

<table>
<thead>
<tr>
<th>Assumption and Simplification</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>The simulation model follows a population cohort.</td>
<td>Model run time is short (5 years burn-in and 5 years results analysis)</td>
</tr>
<tr>
<td>Reference data is for three Canadian provinces cumulatively (Ontario, Saskatchewan, and British Columbia).</td>
<td>Currently available data for the individual cities are limited, therefore the patterns of results are studied for these three provinces cumulatively as well.</td>
</tr>
<tr>
<td>As time passes, patients in opioid therapy are more likely to lapse in adherence to opioid treatment</td>
<td>Based on the related literature [103, 297], the loss of adherence coefficient is calibrated to the reference data (see Table 4.2)</td>
</tr>
<tr>
<td>After entering an overuse state, the need for the opioid dose increases exponentially over time.</td>
<td>Based on the related literature [187, 236], the opioid dose accretion coefficient is calibrated to the reference data (see Table 4.2)</td>
</tr>
<tr>
<td>Misusing opioid behavior is divided into two mutually exclusive situations: overuse or underuse.</td>
<td>If overuse behavior is dominant, patients will not have any surplus opioid for sharing</td>
</tr>
<tr>
<td>Illegitimate prescription requests are identified by pharmacists at pharmacies.</td>
<td>The Prescription Drug Monitoring Program (PDMP) was initially implemented at pharmacies and used by Pharmacists [314].</td>
</tr>
<tr>
<td>If patients in an overuse state try to obtain surplus opioids from others, they will get all available surplus opioids.</td>
<td>Outcomes of the simulation model are not sensitive to this simplifying assumption.</td>
</tr>
<tr>
<td>Patients in the underuse state store different portion of their surplus opioids.</td>
<td>Outcomes of the simulation model are not sensitive to this simplifying assumption.</td>
</tr>
</tbody>
</table>

### 4.2.2.2 Population and Network

Agents were placed into a modeled environment of 50,000 persons and the model incorporated a cohort population. The interaction of people in the model is essential when patients start to look for surplus opioids.
through their connections. These interactions make use of a social network; for this purpose, the population was associated with an Erdos-Renyi network [109]. Thus, people are connected randomly with a given average number of connections per person. Within the model, 60% of individuals know 5 or more people which aligns with the existing literature [173, 249] (see Figure 4.5). The network connections for each individual are set at the initialization of the model and remain invariant throughout the simulation.

4.2.2.3 Parameterization

A study released by the Canadian Institute for Health Information (CIHI) [61] provided the custom distribution of prescribed dose and duration for new and established patient prescribed opioids within Canada. This study was used, together with information from a review of the literature on adherence with opioid therapy to estimate parameter values needed for building the agent-based model. Information to estimate the occurrence of other relevant behaviors such as opioid overuse, and overdose possibility was obtained from relevant literature which the reported data should be adjusted for smoking, depression, pain site, age, and gender. Table 4.2 summarizes the parameters and their sources. The assumed parameters are derived from the literature review, and the researcher’s judgment, domain expertise, and assumptions made about the underlying system. Furthermore, the coefficient of variation across different population sizes remains less than 10% for all outcomes, except for nonmedical overdoses, which remain less than 15%. This observation suggests that variations in the current population size have minimal impact on the overall outcome.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Values</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population size (Persons)</td>
<td>Population size at the model’s initialization.</td>
<td>50000</td>
<td>Assumed</td>
</tr>
<tr>
<td>Duration of use for people starting opioids</td>
<td>Represents prescription opioid use duration for people without opioid therapy in the past year</td>
<td>Custom Distribution (Maximum time is calibrated to give rise to the proportion of people prescribed opioids who were on long-term therapy)</td>
<td>Parametrized CIHI [61]</td>
</tr>
<tr>
<td>Doses being prescribed to people starting opioids (by average MMEs daily)</td>
<td>Represents prescription opioid use doses for people without opioid therapy in the past year</td>
<td>Custom Distribution</td>
<td>Parametrized CIHI [61]</td>
</tr>
<tr>
<td>Duration of use for established patients</td>
<td>Represents prescription opioid use duration for people with opioid therapy in the past year</td>
<td>Custom Distribution (Maximum time is calibrated to show proportion of people prescribed opioids who were on long-term therapy)</td>
<td>Assumed based on CIHI [61]</td>
</tr>
<tr>
<td>Doses being prescribed to patients on long term therapy (by average MMEs daily)</td>
<td>Represents prescription opioid use doses for patients with current prescription opioid use duration more than 90 days</td>
<td>Custom Distribution</td>
<td>Parametrized CIHI [61]</td>
</tr>
<tr>
<td>Doses being prescribed to established patients on short term therapy (by average MMEs daily)</td>
<td>Represents prescription opioid use doses for people with opioid therapy in the past year and current prescription opioid use duration less than 90 days</td>
<td>Custom Distribution</td>
<td>Assumed based on CIHI [61]</td>
</tr>
<tr>
<td>Parameter</td>
<td>Description</td>
<td>Values</td>
<td>References</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>Opioid prescription rate for new patients (1/Week)</td>
<td>Represents rate per week of new patients prescribed opioid.</td>
<td>0.0005</td>
<td>Calibrated to CIHI [61]</td>
</tr>
<tr>
<td>Opioid prescription rate for established patients (1/Week)</td>
<td>Represents rate per week of established patients prescribed opioid.</td>
<td>0.06</td>
<td>Calibrated to CIHI [61]</td>
</tr>
<tr>
<td>Initial amount of nonadherence rate (1/Week)</td>
<td>Represents initial rate per week of loss of adherence to opioid treatment.</td>
<td>0.0335</td>
<td>Parametrized [225]</td>
</tr>
<tr>
<td>Loss of adherence coefficient</td>
<td>Represents growth rate per week for nonadherence rate</td>
<td>0.035</td>
<td>Calibrated to [344]</td>
</tr>
<tr>
<td>Probability overuse opioid after the loss of adherence</td>
<td>Probability that a patient starts overusing prescription opioids after the loss of adherence</td>
<td>0.235</td>
<td>Parametrized [279]</td>
</tr>
<tr>
<td>Opioid dose accretion coefficient</td>
<td>Represents growth rate per week of required opioid doses for patients in the overuse state</td>
<td>0.0008</td>
<td>Calibrated to [344]</td>
</tr>
<tr>
<td>Self-care-treatment rate (1/Week)</td>
<td>Represents rate per week of stopping overusing opioid due to self-care or treatment</td>
<td>0.06</td>
<td>Calibrated to [344]</td>
</tr>
<tr>
<td>Probability attempting to obtain illegitimate prescriptions when in overuse state</td>
<td>Probability that a patient in an overuse state attempt to obtain illegitimate prescriptions</td>
<td>0.5</td>
<td>Assumed</td>
</tr>
<tr>
<td>Parameter</td>
<td>Description</td>
<td>Values</td>
<td>References</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------</td>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>Transition rate to street opioid for patients who misuse prescription opioids with no access to prescription opioids (1/Week)</td>
<td>Represents rate per week of transition to street opioid for patients who misuse prescription and cannot obtain prescription opioids</td>
<td>0.4</td>
<td>Calibrated to [344]</td>
</tr>
<tr>
<td>Probability of dispose of all surplus opioid</td>
<td>Probability that a patient in the underuse state disposes of all surplus opioid</td>
<td>Between 0.05 and 0.25</td>
<td>Parametrized [194]</td>
</tr>
<tr>
<td>Available surplus of prescription opioids</td>
<td>The portion of prescription opioids which have been stored by each patient in underuse state</td>
<td>Between 1 and 1/3</td>
<td>Assumed</td>
</tr>
<tr>
<td>Overdose rate based on recent opioid doses (1/Year)</td>
<td>Represents rate per year of overdose occurrence for patients currently using opioids</td>
<td>Custom Distribution</td>
<td>Parametrized [102]</td>
</tr>
</tbody>
</table>

### 4.2.2.4 Sensitivity Analyses, Calibration, and Validation of the Model

Sensitivity analyses were conducted to identify sensitive parameters in which the model outcome was affected by changes in them. Thus, the calibration was performed on these sensitive parameters to find their values which best replicated the reported data in the literature. During the calibration process, we varied a set of model parameters by hand until the model outputs approximated empirical data (see Table 4.3 and Table 4.4). The total percentage of people prescribed opioids in Table 4.3 for three Canadian provinces was computed by multiplying the individual percentages of the parameter in each province by their respective total population. After summing these values, the total parameter value was divided by the total population across all three provinces and multiplied by 100 to obtain the total percentage of people prescribed opioids.
**Table 4.3: List of parameters used in opioid therapy agent-based model calibration and validation**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion (%) of the study population starting opioids without being prescribed opioids in the past year</td>
<td>From 9.5% in 2013 to 8.1% in 2018</td>
<td>Based on CIHI [61]</td>
</tr>
<tr>
<td>Proportion (%) of people prescribed opioids</td>
<td>From 14.26% in 2013 to 12.32% in 2018</td>
<td>Calculated based on CIHI [61]</td>
</tr>
<tr>
<td>Proportion (%) of people prescribed opioids who were on long-term therapy</td>
<td>From 19.8% in 2013 to 17.6% in 2018</td>
<td>Based on CIHI [61]</td>
</tr>
<tr>
<td>Prevalence of successful opioid doctor shopping as the behavior of visiting different prescribers and/or pharmacies to obtain opioids</td>
<td>Between 0.2% to 4%</td>
<td>Based on [176]</td>
</tr>
<tr>
<td>Proportion (%) of patients prescribed opioids misuse them</td>
<td>Between 21% to 29%</td>
<td>Based on [344]</td>
</tr>
<tr>
<td>Proportion (%) of patients who use opioids and develop opioid use disorder</td>
<td>Between 8% to 12%</td>
<td>Based on [344]</td>
</tr>
<tr>
<td>Proportion (%) of patients who misuse prescription opioids transition to heroin</td>
<td>Between 4% to 6%</td>
<td>Based on [344]</td>
</tr>
</tbody>
</table>
**Table 4.4:** List of the parameters that are calibrated and the corresponding empirical data used for the calibration process

<table>
<thead>
<tr>
<th>Parameters which are calibrated</th>
<th>Data against which calibration occurs (see Table 4.3 for references)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid prescription rate for new patients (1/Week)</td>
<td>Proportion (%) of the study population starting opioids and Proportion (%) of people prescribed opioids</td>
</tr>
<tr>
<td>Opioid prescription rate for established patients (1/Week)</td>
<td>Proportion (%) of the study population starting opioids and Proportion (%) of people prescribed opioids</td>
</tr>
<tr>
<td>Loss of adherence coefficient</td>
<td>Proportion (%) of patients prescribed opioids misuse them</td>
</tr>
<tr>
<td>Opioid dose accretion coefficient</td>
<td>Proportion (%) of patients who use opioids and develop opioid use disorder</td>
</tr>
<tr>
<td>Self-care-treatment rate (1/Week)</td>
<td>Proportion (%) of patients using an opioid develop an excessive opioid use</td>
</tr>
<tr>
<td>Maximum time of duration of use for people starting opioid</td>
<td>Proportion (%) of people prescribed opioids who were on long-term therapy and Proportion (%) of the study population starting opioids and Proportion (%) of people prescribed opioids</td>
</tr>
<tr>
<td>Maximum time of duration of use for established patients</td>
<td>Proportion (%) of people prescribed opioids who were on long-term therapy and Proportion (%) of the study population starting opioids and Proportion (%) of people prescribed opioids</td>
</tr>
<tr>
<td>Transition rate to street opioid for patients who misuse prescription opioids with no access to prescription opioids</td>
<td>Proportion (%) of patients who misuse prescription opioids transition to heroin and Prevalence of successful opioid doctor shopping</td>
</tr>
</tbody>
</table>

Furthermore, seven outcomes were utilized to validate the outcomes of the agent-based model over a five-year time horizon against empirical data reported by CIHI [61] or in the related literature including the proportion of people starting opioids without being prescribed opioids in the past year and the proportion of patients on opioid therapy (see Figure 4.6), the proportion of patients prescribed opioids who either underuse or overuse them, and the proportion of patients who develop an opioid use disorder after being prescribed opioids and subsequently overuse them (see Figure 4.7), the proportion of patients on long term opioid therapy and the proportion of patients who overuse prescription opioids transition to street opioids (see Figure 4.8) and the prevalence of illegitimate opioid prescriptions (see Figure 4.9).

At that point, a set of requirements to establish the model’s credibility and validity was met, and the
model is deemed suitable as a source of observed data to train the HMM-aided PDMP and it also explores different policies targeting the reduction of prescription opioid misuse.

4.2.3 Prescription Drug Monitoring Program Implementation using Two-State Hidden Markov Model

One of the most challenging tasks for any practitioner is to assess the legitimacy\(^1\) of prescriptions [294] for controlled substances [268]. In the implemented model, as different studies of the prescription opioid use have found [187, 236, 347], some patients are more likely to seek additional prescription opioids due to building tolerance. They may try to fulfill their need through different pathways such as obtaining extra opioid prescriptions [354]. In this case prescription opioids are no longer safe and effective in treating the patient’s medical condition and potentially used for illegitimate purposes. Moreover, there is always some chance for these people to stop seeking additional prescription opioids based on self-care or treatment [78]. Therefore, considering the ultimate goal of a prescription drug monitoring program to facilitate the fulfillment of legitimate prescriptions while preventing illegitimate ones, it is justifiable to incorporate two unobserved states, namely "Legitimate" and "Illegitimate," for each new opioid prescription, which rely on the patient's present state of adherence and are not directly observable to practitioners.

Due to challenges in obtaining integrated longitudinal data of patients undergoing opioid prescription treatment, the training data for the HMM was produced by running the above calibrated agent-based Monte Carlo simulation model with 10 realizations (each equipped with a different random seed) for 10 years. By employing random sampling techniques, the Monte Carlo simulation allows for the exploration of a wide range of possible scenarios and outcomes, facilitating a broad understanding of the system's behavior. The Monte Carlo simulation involved ensembles of 10 realizations each possessing a unique random seed, to help capture the inherent variability in the system and enhance the robustness of the analysis. The conceptual model assumes that patients initially adhere to opioid prescriptions. Therefore, the model is simulated for a duration of 10 years and the data from the entire period for each individual is retained to maintain the desired initial probability of starting from an adherence state, regardless of the fact that the HMM-aided PDMP can be utilized at any point in a patient’s opioid therapy trajectory. Therefore, by utilizing a Monte Carlo simulation with 10 realizations over a 10-year period and and drawing upon data from a limited subset of agents, a robust training dataset was generated for the HMM-aided PDMP. The validation dataset, on the other hand, was obtained by excluding the initial 5-year burn-in period and encompassing a considerable population of agents. Additionally, a Monte Carlo simulation with 100 realizations was conducted, introducing novel and previously unseen data for validation purposes. This approach facilitates the evaluation of the HMM-aided PDMP’s performance and its capacity to extend beyond the confines of the training data, thereby enhancing

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\(^1\) "Legitimate Medical Purpose means a therapeutic treatment regimen or program generally recognized and accepted in the field of medical science as being safe and effective in the diagnosis, treatment, correction or alleviation of the specific medical condition of the patient under all relevant circumstances." [164]
its reliability and effectiveness. To explore the receiver operating characteristic curve, the HMM threshold range was set between 0 and 1, with an incremental step of 0.1. However, when there is a significant jump between outcomes in the receiver operating characteristic and precision-recall curves, the incremental step was reduced to 0.01. This range allows for a comprehensive exploration of different threshold values and their impact on the classification of prescriptions as legitimate or illegitimate opioid prescriptions.

Throughout each such realization, data for any new opioid prescription claimed by each patient were reported, including opioid prescription date, opioid prescription duration, and opioid prescription dose. To extract the HMM’s parameters from the reported data; further observations — such as the cumulative count of opioid prescriptions for each patient, cumulative opioid doses, cumulative prescription duration, overlap for each prescription with the previous one, and the time interval between each prescription — also are calculated based on reported data.

An exploratory investigation of the longitudinal data of patients finds that the “Legitimate” state and “Illegitimate” state of the prescription correspond to two distinct categorical distributions for dichotomous prescription overlap and fraction of time in which the patient was not on opioid therapy. This difference raises opportunities for machine-learning based classification of a given prescription refill attempt on the basis of these patterns. The opioid prescription overlap as the observation input was split into a vector of two sub-features as overlapping prescription and non-overlapping prescription. Furthermore, using the lower extreme of the box plot (disregarding outliers) of the fraction of time which legitimate patients was not on opioid therapy, the fraction of time which any patient was not on opioid therapy also was split into a vector of two sub-features less than and equal to the lower extreme and higher than the lower extreme. Finally, as a combination of these two separate categorical distributions, four observations for each state are defined. Using a package in R named ‘mHMMbayes’ [2], the HMM parameters were estimated as depicted in Figure 4.2. The complete mathematical description of HMM algorithms and equations can be referenced in [82], while discussion of the well-documented R package mHMMbayes can be found in [105, 1, 3, 128]. In brief, the R package mHMMbayes fits the model by employing a hybrid Metropolis within Gibbs Markov Chain Monte Carlo algorithm. This approach extends the traditional HMM implementation by incorporating Bayesian estimation techniques [292]. Therefore, longitudinal data of various agents was studied using a multilevel HMM simultaneously, in which the aggregated level model was trained on agent level data with one overall categorical distribution [3].

Finally, the forward-backward algorithm was implemented in the agent-based model to compute the posterior marginals of two hidden state variables for any new prescription presented by a patient, given a sequence of previous observations of the patient’s prescription at the seeking prescription state. Then, based on HMM assumed thresholds, the prescription is classified as legitimate or illegitimate opioid prescription. Illegitimate requests for opioid prescription cannot be filled, therefore the person stops from entering the opioid therapy state in the opioid prescribing state chart.

For each HMM threshold set between 0 to one, with incremental step equal to 0.1 (in certain circum-

65
Figure 4.2: Graphical representation of the HMM-aided PDMP. This HMM-aided PDMP consists of initial state probabilities (represented by black arrows), hidden states (represented by circles), transition probabilities (represented by blue arrows), observations (represented by squares) and emission probabilities (represented by brown arrows).

stances, in 0.01: see above), a Monte Carlo simulation for 10 years with 100 runs and a random seed was conducted. After 5-years burn-in period for the model, the HMM-aided PDMP started to classify each prescription as legitimate or illegitimate opioid prescription and key metrics such as the cumulative number of correctly and incorrectly predicted positive cases, as well as the total positive cases and the total negative cases of illegitimate opioid prescription over 5 years, were reported. The initial analysis of these outcomes highlights the HMM-aided PDMP is an imbalanced classification problem. Therefore, the HMM-aided PDMP performance with different HMM thresholds was evaluated via different metrics such as sensitivity (recall), specificity, concordance probability, accuracy, and F1 Score. False negatives represent cases where the HMM-aided PDMP fails to identify illegitimate prescription refills, and mistakenly classifying them as legitimate. These instances pose a concern as they indicate missed opportunities to detect and intervene in potentially harmful situations. True positives refer to the correct identification of illegitimate prescription refills by the HMM-aided PDMP. These instances demonstrate the HMM-aided PDMP’s ability to accurately detect and flag suspicious behavior, aiding in preventing the misuse of prescription drugs. Minimizing false negatives and maximizing true positives are essential to ensure the effectiveness of the HMM-aided PDMP in accurately detecting illicit activities. Furthermore, false positives refer to cases where the HMM-aided PDMP incorrectly identifies legitimate prescription refills as illegitimate. These instances can lead to unnecessary interventions or delays for patients who legitimately require the prescribed medications. True negatives represent cases where the HMM-aided PDMP correctly identifies legitimate prescription refills. Minimizing false positives
and maximizing true negatives are essential in ensuring that legitimate patients receive the medications they need without unnecessary interventions or delays. Sensitivity (i.e., recall) measures the HMM-aided PDMP's ability to correctly identify true positives, that is, accurately detecting illegitimate prescription refills. A high sensitivity indicates that the HMM-aided PDMP has a strong capacity to capture instances of illicit activity, minimizing the risk of false negatives. Specificity evaluates the HMM-aided PDMP's ability to correctly identify true negatives, referring to the accurate identification of legitimate prescription refills. A high specificity implies that the HMM-aided PDMP can effectively distinguish between legitimate and illegitimate cases, reducing the occurrence of false positives. Accuracy reflects how well the HMM-aided PDMP performs in correctly classifying both legitimate and illegitimate prescription refills. It considers the combined impact of true positives, true negatives, false positives, and false negatives. A higher accuracy indicates that the HMM-aided PDMP is making more correct predictions overall. Concordance probability measures the probability that the HMM-aided PDMP will rank a randomly chosen illegitimate refill higher than a randomly chosen legitimate refill. A high concordance probability indicates a strong discriminatory power of the HMM-aided PDMP, where it can effectively differentiate between the two classes. While the concordance probability focuses on the model's overall discriminatory power, the F1 score considers the trade-off between precision and recall, and also providing insight into the HMM-aided PDMP's overall performance. The F1 score is particularly valuable in scenarios involving imbalanced datasets, as is the case in this study where the emphasis lies on accurately rejecting illegitimate prescription fillings while ensuring legitimate prescriptions are filled. To provide additional information regarding precision, it can be stated that precision indicates the HMM-aided PDMP's ability to accurately classify true positives while minimizing false positives. A high precision score implies that when the HMM-aided PDMP flags a refill as illegitimate, it is highly likely to be correct.

4.2.4 Interventions

To study the potential impact of reducing opioid prescription doses and treatment durations, a simple PDMP and the HMM-aided PDMP on outcomes of interest, different interventions were examined. These interventions involved:

1. Reducing opioid prescription dose from baseline by 5%, 10%, 15%, 20%, and 25%.

2. Reducing treatment duration from baseline by 5%, 10%, 15%, 20%, and 25%.

3. Applying a simple PDMP that prevents filling overlapped opioid prescriptions.

4. Applying the HMM-aided PDMP with four different HMM thresholds (i.e., 0.20, 0.30, 0.40, and 0.50) demonstrated a high F1 score, a high concordance probability, and a low false positive rate.

5. Combinations of dual reductions in prescription doses by 5%, 10%, 15%, 20%, and 25%, and treatment duration by 5%, 10%, 15%, 20%, and 25%.
<table>
<thead>
<tr>
<th>HMM Threshold</th>
<th>True Positive</th>
<th>Total Positive</th>
<th>False Positive</th>
<th>Total Negative</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Concordance Probability</th>
<th>Accuracy</th>
<th>F1 Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4567.91</td>
<td>4567.91</td>
<td>425839.52</td>
<td>425839.52</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.01061299</td>
<td>0.02100308</td>
</tr>
<tr>
<td>0.1</td>
<td>9554.81</td>
<td>10445.48</td>
<td>329472.29</td>
<td>399859.64</td>
<td>0.91473154</td>
<td>0.17603014</td>
<td>0.16102032</td>
<td>0.19483588</td>
<td>0.05468131</td>
</tr>
<tr>
<td>0.2</td>
<td>9190.85</td>
<td>14834.8</td>
<td>2355.83</td>
<td>315098.89</td>
<td>0.61954661</td>
<td>0.99252352</td>
<td>0.61491458</td>
<td>0.97575337</td>
<td>0.69676531</td>
</tr>
<tr>
<td>0.3</td>
<td>8895.44</td>
<td>14642.23</td>
<td>994.39</td>
<td>314822.43</td>
<td>0.60751948</td>
<td>0.99684143</td>
<td>0.60560059</td>
<td>0.97953899</td>
<td>0.72520938</td>
</tr>
<tr>
<td>0.4</td>
<td>8629.62</td>
<td>14396.04</td>
<td>232.96</td>
<td>314387.12</td>
<td>0.59944401</td>
<td>0.999259</td>
<td>0.59899983</td>
<td>0.98175278</td>
<td>0.74205778</td>
</tr>
<tr>
<td>0.5</td>
<td>8416.59</td>
<td>14307.3</td>
<td>107.4</td>
<td>314790.2</td>
<td>0.58827242</td>
<td>0.99965882</td>
<td>0.58807171</td>
<td>0.98177406</td>
<td>0.73728554</td>
</tr>
<tr>
<td>0.6</td>
<td>5687.29</td>
<td>12120.58</td>
<td>63.73</td>
<td>314857.54</td>
<td>0.4692259</td>
<td>0.99979759</td>
<td>0.46913092</td>
<td>0.98013011</td>
<td>0.6364612</td>
</tr>
<tr>
<td>0.7</td>
<td>5816.65</td>
<td>12476.96</td>
<td>32.5</td>
<td>315085.16</td>
<td>0.46619128</td>
<td>0.99989685</td>
<td>0.4661432</td>
<td>0.97956781</td>
<td>0.63479375</td>
</tr>
<tr>
<td>0.8</td>
<td>4393.35</td>
<td>11508.36</td>
<td>18.97</td>
<td>315487.51</td>
<td>0.38175292</td>
<td>0.99993987</td>
<td>0.38172996</td>
<td>0.97818327</td>
<td>0.55190482</td>
</tr>
<tr>
<td>0.9</td>
<td>2989.35</td>
<td>10514.57</td>
<td>8.71</td>
<td>315671.97</td>
<td>0.28430549</td>
<td>0.99997241</td>
<td>0.28429765</td>
<td>0.976903</td>
<td>0.44245273</td>
</tr>
<tr>
<td>1</td>
<td>18.31</td>
<td>10202.11</td>
<td>0.21</td>
<td>316276.42</td>
<td>0.00179473</td>
<td>0.99999934</td>
<td>0.00179473</td>
<td>0.96880649</td>
<td>0.00358295</td>
</tr>
</tbody>
</table>

Table 4.5: List of machine learning metrics for HMM-aided PDMP with different HMM thresholds
6. Combinations of any of the above interventions in which particularly strong benefits occurred when considered in isolation.

For each intervention or combined interventions, a Monte Carlo simulation with 100 realizations was conducted to ensure that a broad set of values for parameters treated as random variables was drawn from distributions. To accommodate transients associated with the initial state, each simulation employed a 5-year burn-in period for the model. Following the burn-in period, the model was run for a time horizon of 5 more years to track outcomes of interest for each run. Finally, the result section reported percentage change of medical and nonmedical pharmaceutical opioid use-related overdoses, percentage change of street opioid initiation, and percentage change of legitimate, illegitimate, and total filled opioid prescription from the baseline over five years for each intervention or selected combined interventions. These outcomes were compared across interventions to identify the most effective intervention for reducing the harms associated with prescription opioid use.

4.3 Results

The baseline scenario yields approximately 326500 opioid prescription fills with 3% illegitimate requests for prescription over five years. Meanwhile, 18% of patients prescribed opioids in the model misuse them at any given time, and 4% of patients who misuse prescription opioids eventually transition to street opioids. The total number of opioid overdoses is approximately 200 over five years, which implies the prevalence of overdose among patients treated with prescribed opioids is 0.03%.

4.3.1 Single Interventions

4.3.1.1 Lowering Prescription Doses

Table 4.6 shows the results of lowering prescription doses for the five-year outcomes of interest. Over five years, lowering prescription doses by 5% would provide a 0.25% reduction in medical overdose; with a 15% and 25% reduction in dose, the effect changes to 5.32% reduction and 11.41% reduction in medical overdoses, respectively.

Lowering prescription doses has also a favorable effect on nonmedical overdoses. Over five years, lowering prescription doses by 5% would provide a 1.27% reduction in nonmedical overdose: with a 15% and 25% reduction, the impact changes to 5.02% reduction and 12.17% reduction in such overdoses.

Lowering prescription doses slightly decreases the total number of individuals who escalate to heroin over five years (by a 1.65% decrease and 3.85% decrease in such escalation for a 15% and 25% dose reduction, respectively). Moreover, lowering prescription doses would have a modest effect on reducing the total number of filled opioid prescriptions, yielding a reduction by 0.05% and 0.30% for a 15% and 25% lowered dose, respectively, over five years. It further secures a reduction in illegitimate opioid prescriptions (reducing such
<table>
<thead>
<tr>
<th>Policy</th>
<th>Medical overdoses (%)</th>
<th>Nonmedical overdoses (%)</th>
<th>Shift to street opioid use (%)</th>
<th>Legitimate opioid prescriptions (%)</th>
<th>Illegitimate opioid prescriptions (%)</th>
<th>Total filled opioid prescriptions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced prescription dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction by 5%</td>
<td>-0.25%</td>
<td>-1.27%</td>
<td>-0.90%</td>
<td>-0.04%</td>
<td>-3.07%</td>
<td>-0.13%</td>
</tr>
<tr>
<td>Reduction by 10%</td>
<td>-3.12%</td>
<td>-5.29%</td>
<td>-0.52%</td>
<td>-0.12%</td>
<td>-2.95%</td>
<td>-0.21%</td>
</tr>
<tr>
<td>Reduction by 15%</td>
<td>-5.32%</td>
<td>-5.02%</td>
<td>-1.65%</td>
<td>+0.03%</td>
<td>-2.61%</td>
<td>-0.05%</td>
</tr>
<tr>
<td>Reduction by 20%</td>
<td>-8.60%</td>
<td>-9.45%</td>
<td>-3.62%</td>
<td>-0.04%</td>
<td>-4.57%</td>
<td>-0.18%</td>
</tr>
<tr>
<td>Reduction by 25%</td>
<td>-11.41%</td>
<td>-12.17%</td>
<td>-3.85%</td>
<td>-0.09%</td>
<td>-6.86%</td>
<td>-0.30%</td>
</tr>
<tr>
<td>Reduced treatment duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction by 5%</td>
<td>-2.21%</td>
<td>-6.83%</td>
<td>+2.67%</td>
<td>+1.23%</td>
<td>+1.22%</td>
<td>+1.23%</td>
</tr>
<tr>
<td>Reduction by 10%</td>
<td>-5.88%</td>
<td>-9.85%</td>
<td>+3.13%</td>
<td>+2.48%</td>
<td>+4.48%</td>
<td>+2.54%</td>
</tr>
<tr>
<td>Reduction by 15%</td>
<td>-7.59%</td>
<td>-14.33%</td>
<td>+6.01%</td>
<td>+3.80%</td>
<td>+4.85%</td>
<td>+3.83%</td>
</tr>
<tr>
<td>Reduction by 20%</td>
<td>-13.00%</td>
<td>-19.75%</td>
<td>+6.38%</td>
<td>+5.14%</td>
<td>+7.88%</td>
<td>+5.23%</td>
</tr>
<tr>
<td>Reduction by 25%</td>
<td>-14.47%</td>
<td>-27.13%</td>
<td>+8.24%</td>
<td>+6.63%</td>
<td>+10.52%</td>
<td>+6.75%</td>
</tr>
</tbody>
</table>
prescriptions by 2.61% and 6.86% for a 15% and 25% lower dose, respectively, over five years). It is notable that such results exhibit an elasticity of effect, leading, for example, to a doubling of the reduction in dose more than doubling the benefits in certain outcomes of interest. Such effects suggest the value of a closer examination of the dependence of such results on dose changes.

4.3.1.2 Lowering Treatment Duration

Table 4.6 shows results of reductions in treatment duration on the five-year outcomes of interest. Lower treatment durations have a larger favorable impact on both medical and nonmedical overdoses over five years. Lowering treatment duration in the model by 15% yields a reduction in medical overdose and nonmedical overdose of 7.59% and 14.33%, respectively, over five years. Lowering treatment duration by 25% would provide a 14.47% reduction in medical overdose and 27.13% reduction in nonmedical overdose, respectively, over five years.

Such benefits must be counterbalanced with the fact that lowered treatment duration in the model imposes the worst outcome in terms of the total number of individuals who escalate to heroin over five years. Specifically, a 15% and 25% lower treatment duration in the model yields a 6.01% increase and 8.24% increase escalation to heroin over that half-decade, respectively.

A lowered treatment duration also results in an increase in the number of filled opioid prescriptions over five years, with a 3.83% increase and 6.75% increase in such filled prescriptions resulting from a 15% and 25% lowering in treatment duration, respectively, over five years. Reduced treatment duration also leads to a superlinear increase in illegitimate opioid prescriptions, by 4.85% and 10.52%, for a 15% and 25% lowering in treatment duration, respectively, over five years.

4.3.1.3 Prescription Drug Monitoring Program

In order to examine the effectiveness of the HMM-aided PDMP, the receiver operating characteristic (ROC) curve and associated area under the curve (AUC) for different HMM thresholds (see Figure 4.10), and the precision-recall curve and associated AUC for different HMM thresholds (see Figure 4.11) were calculated. Plausibly acceptable frequencies of positive and negative results of the HMM-aided PDMP across both ROC and the precision-recall curves can be achieved with HMM thresholds equal to 0.2, 0.3, 0.4, and 0.5. This set of HMM thresholds is located progressively closer to the upper left-hand corner in the ROC curve plot and the upper right-hand corner in the precision-recall curve plot that reflects the progressively greater discriminant capacity of the HMM-aided PDMP. Additionally, they exhibit a high F1 score, a high concordance probability, and a low false positive rate compared to other HMM thresholds (see Table 4.5). The corresponding AUCs serve as confirm that the HMM-aided PDMP has a suitable predictive ability to differentiate illegitimate prescription refills from legitimate prescription refills.

Table 4.7 shows results for a simple PDMP (i.e., blocking the acquisition of overlapping prescriptions) and the HMM-aided PDMP interventions. The simple PDMP has only a small effect on medical and nonmedical
overdose (yielding a 0.24% increase and 0.59% reduction, respectively). By contrast, the simple PDMP exerts a large reduction in illegitimate opioid prescriptions (41.89% over five years), leading to a massive number of individuals who cannot access opioid prescriptions and who therefore escalate to street opioids (resulting in an 101.97% increase over five years). While the HMM-aided PDMP shares only a small impact on medical overdose (by 0.63% increase and 0.24% increase for 0.2 and 0.4 HMM- threshold, respectively), the HMM-aided PDMP has a larger impact on nonmedical overdose (yielding a 2.11% reduction and 4.20% reduction for HMM-thresholds of 0.2 and 0.4, respectively). Compared to the Baseline, also the HMM-aided PDMP achieves notable decreases in illegitimate opioid prescriptions, with 0.2 and 0.4 HMM thresholds yielding reductions of 44.30% and 43.45%, respectively, over five years. However, the advantages of the HMM-aided PDMP are subject to a crucial side-effect shared with its simple PDMP counterpart: significant increases in the number of individuals who shift to street opioids. Specifically, the HMM-aided PDMP precipitates 105.43% and 94.97% increases in transitions to street options, for HMM thresholds of 0.2 and 0.4, respectively.

4.3.2 Combined Interventions

Supplementary Table 4.8 shows results for combinations of two interventions — Lowered prescription doses and lowered treatment duration — with different levels of reduction. The most favorable impact in reducing three outcomes of interest (cumulative count of medical and nonmedical overdoses and count of individuals who escalate to street opioids), was achieved by lowering treatment duration by 5% combined with lowering prescription dose by either 20% or 25%. Illegitimate opioid prescriptions also decreased with these combinations.
Table 4.7: Results for the simple PDMP intervention and HMM-aided PDMP interventions: Percentage change from the baseline over five years

<table>
<thead>
<tr>
<th>Policy</th>
<th>Medical overdoses (%)</th>
<th>Non-medical overdoses (%)</th>
<th>Shift to street opioid use (%)</th>
<th>Legitimate opioid prescriptions (%)</th>
<th>Illegitimate opioid prescriptions (%)</th>
<th>Total filled opioid prescriptions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDMP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple PDMP</td>
<td>+0.24%</td>
<td>-0.59%</td>
<td>+101.97%</td>
<td>-0.59%</td>
<td>-41.89%</td>
<td>-1.87%</td>
</tr>
<tr>
<td>HMM-aided PDMP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMM threshold: 0.20</td>
<td>+0.63%</td>
<td>-2.11%</td>
<td>+105.43%</td>
<td>-1.19%</td>
<td>-44.30%</td>
<td>-2.53%</td>
</tr>
<tr>
<td>HMM threshold: 0.30</td>
<td>+0.03%</td>
<td>-3.52%</td>
<td>+98.42%</td>
<td>-0.94%</td>
<td>-43.88%</td>
<td>-1.99%</td>
</tr>
<tr>
<td>HMM threshold: 0.40</td>
<td>+0.24%</td>
<td>-4.20%</td>
<td>+94.97%</td>
<td>-0.67%</td>
<td>-43.45%</td>
<td>-1.99%</td>
</tr>
<tr>
<td>HMM threshold: 0.50</td>
<td>-0.12%</td>
<td>-1.84%</td>
<td>+91.35%</td>
<td>-0.60%</td>
<td>-42.71%</td>
<td>-1.90%</td>
</tr>
</tbody>
</table>
Table 4.8: Results of combinations of dual reductions in prescription doses and treatment duration:
Percentage change from the baseline over five years

<table>
<thead>
<tr>
<th>Policy dual reductions</th>
<th>Medical overdoses (%)</th>
<th>Non-medical overdoses (%)</th>
<th>Shifts to street opioid use (%)</th>
<th>Legitimate opioid prescriptions (%)</th>
<th>Illegitimate opioid prescriptions (%)</th>
<th>Total filled opioid prescriptions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses by Doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% 5%</td>
<td>-3.95%</td>
<td>-7.72%</td>
<td>+1.81%</td>
<td>+1.15%</td>
<td>+0.54%</td>
<td>+1.14%</td>
</tr>
<tr>
<td>5% 10%</td>
<td>-4.71%</td>
<td>-9.74%</td>
<td>+0.71%</td>
<td>+1.13%</td>
<td>-1.86%</td>
<td>+1.04%</td>
</tr>
<tr>
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<td>-8.20%</td>
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Strong reductions in medical and nonmedical overdose would also be achieved with the combination of a
25% reduction in prescription dose with lowering treatment duration either by a 10% or 15%, however, this combination also leads individuals who escalate to street opioids to slightly increase.

Table 4.9 shows results for three interventions, each representing a combination of interventions in which particularly strong benefits occurred when considered in isolation. These combined interventions are 1) the combination of lowering prescription doses by 25% and the HMM-aided PDMP with threshold equal to 0.40, 2) the combinations of lowering treatment duration by 25% and the HMM-aided PDMP threshold equal to 0.40, 3) the combination of lowering treatment duration by 10%, lowering prescription doses by 20%, and the HMM-aided PDMP threshold equal to 0.40. In all three cases, intervention combinations are less beneficial than the lowering prescription doses or treatment durations by corresponding amounts in isolation and leading to nearly two times higher escalation to street opioids relative to the baseline.

### 4.4 Discussion

This work sought to secure both methodological and public health insights from use of a machine learning-equipped stylized agent-based simulation model characterizing dynamics associated with prescription opioid use, and risk of shifts to street-sourced opioids. While this work evaluated the accuracy extending from using the hidden Markov model to recognize individuals engaged in opioid seeking for legitimate needs, it did so in the broader context of a simulation model recognizing the risk that individuals flagged as engaged in doctor shopping would transition to street opioid use, and of overdoses. As an example of application of this framework, this work investigated the opioid overdose and street opioid escalation impacts of two policies targeting opioid prescription practices among patients prescribed pharmaceutical opioids.

The majority of the data utilized in this work was sourced and derived from a study published by the Canadian Institute for Health Information (CIHI) [61], a Canadian Federal institution that seeks to preserve public trust by placing foremost importance on ethical considerations and responsible data handling practices. In its commitment to the Canadian public, CIHI is committed to protecting patient privacy, ensuring data security, addressing biases in data collection and analysis, and promoting transparency and accountability [116]. Furthermore, we carefully documented and detailed the assumptions made during the simulation model’s development to ensure transparency and provide a clear understanding of the underlying principles. We additionally employed rigorous validation procedures to assess the simulation model’s performance and assess potential biases.

At a methodological level, findings suggest both the practicality and desirability of informing agent-based models using machine learning methods at an individual level. This work further demonstrated that the simple and computationally frugal approach of hidden Markov modeling can achieve favorable accuracy profiles, raising the potential for more heavily data-driven approaches to further boost both the accuracy of the classification and the public health gains from HMM-informed policies.

With respect to the example policies examined here, simulation model findings suggest that if used
Table 4.9: Results of combinations of HMM-aided PDMP, lowering in prescription doses and lowering in treatment duration: Percentage change from the baseline over five years

<table>
<thead>
<tr>
<th>Policy</th>
<th>Medical overdoses (%)</th>
<th>Nonmedical overdoses (%)</th>
<th>Shifts to street opioid use (%)</th>
<th>Legitimate opioid prescriptions (%)</th>
<th>Illegitimate opioid prescriptions (%)</th>
<th>Total filled opioid prescriptions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMM-aided PDMP threshold: 0.40 plus Lowering in prescription doses level 5 (25%)</td>
<td>-13.09%</td>
<td>-13.96%</td>
<td>+87.85%</td>
<td>-0.66%</td>
<td>-45.14%</td>
<td>-2.04%</td>
</tr>
<tr>
<td>HMM-aided PDMP threshold: 0.40 plus Lowering in treatment duration level 5 (25%)</td>
<td>-16.20%</td>
<td>-29.75%</td>
<td>+106.07%</td>
<td>+5.85%</td>
<td>-36.73%</td>
<td>+4.54%</td>
</tr>
<tr>
<td>HMM-aided PDMP threshold: 0.40 plus Lowering in treatment duration level 2 (10%) plus Lowering in prescription doses level 4 (20%)</td>
<td>-13.78%</td>
<td>-21.91%</td>
<td>+91.31%</td>
<td>+1.80%</td>
<td>-42.98%</td>
<td>+0.42%</td>
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</table>
aggressively to lower doses, lowering prescription doses could have the most favorable impact on the outcome of interest over five years while minimizing burden on patients with a legitimate need for pharmaceutical opioids.

Lowering treatment duration would introduce varying degrees of potential unintended consequences by escalating some patients who cannot access prescribed pharmaceutical opioids to street opioids. These unintended consequences vary widely across different types of intervention, especially with the PDMP. Both the simple PDMP and the HMM-aided PDMP readily reduced the number of illegitimate opioid prescriptions and decreased the supply of prescription opioids, but thereby caused some patients to shift to street opioid use.

Note that a combination of lowering in prescription doses and lowering in treatment duration did not perform much better than lowering prescription doses, considered alone, with the respect to all outcomes of interest. Moreover, the combination of the HMM-aided PDMP with other interventions presented above are only examples of the more than 100 possible combinations of strategies, and in the exploratory testing of other combinations of strategies, the adverse influence of the HMM-aided PDMP on escalation to the street opioids is always a pronounced dynamic.

The current study offers two primary findings. The first is that it is misleading to consider combined interventions to always provide a greater positive effect on the potential issue than any single policy. While the combined interventions exert a large positive impact on reducing both medical and nonmedical opioid overdose, when considered in terms of reducing the number of individuals who shift to street opioids, none of the combined interventions achieved more favorable outcomes than the single intervention of lowering in opioid dose by 25%. Ultimately, it is essential to create a comprehensive set of outcomes to test the multi-dimensional effect of suggested interventions.

The second major finding is the strong benefits conferred by jointly conducting machine learning and agent-based modeling when using the latter to understand the downstream consequences and characterize the dynamic context for the former. Within the application examined here, the individual-level simulation model incorporated machine learning as a component of individual-level policy targeting, with the agent-based model characterizing both the patient-provider encounters that required such evaluation, and the subsequent evolution of the patient trajectory, including their experience of adverse events. While other studies have examined the prescription or short-term outcome classification accuracy achieved by machine learning strategies on prescription drug use records [300, 139, 295, 106], the current modeling analysis is the first to demonstrate that the HMM-aided PDMP could be more beneficial in reducing overdose among patients who have been prescribed opioids than simple PDMP. More significantly, beyond the use of a simulation model serving to produce a set of well-grounded data to test the possibility of applying machine learning to healthcare problems, this implementation demonstrates that a simulation model can evaluate the trade-offs involved in application of machine learning algorithms in healthcare more broadly and in more textured contexts than is traditionally pursued, by evaluating the impact of healthcare machine learning-
supported decisions within and on the patient's life course.

This study is encumbered by a number of notable limitations. The scope of the model excludes consideration of measures that would reduce the necessity of continued opioid use, such as through the use of alternative pain management techniques. Furthermore, the current model differentiates neither between fatal and nonfatal overdoses, nor between accidental and intentional overdoses. However, based on patient adherence to opioid treatment, overdoses are classified into two categories: medical and nonmedical overdoses. This classification offers strong benefits in evaluating the suggested interventions. Moreover, the current model does not consider uses of illegitimate opioid prescriptions to obtain pharmaceutical opioids for resale; within the current work, such prescriptions are considered as being solely intended for personal use. Hidden Markov Model seeking to address the diversity of opioid use behaviors in a broader empirical context may require additional latent states and transitions to capture the distinct patterns of opioid seeking and transition dynamics observed in this broader context. This scoping of this part of the agent-based model may serve to partly compensate for the model's exclusion of consideration of other avenues of accessing diverted opioids, such as pharmaceutical opioids that were lost or stolen from community pharmacies, companies, or hospitals.

The current simulation model can render less stylized and by providing it with stronger empirical grounding data about pharmaceutical opioid use from other sources, including untraditional forms of data, such as from social media and wastewater surveillance systems. Moreover, extending the model domain to capture street drug use, criminal justice involvement, and social influence on illegitimate opioid prescription seeking and misuse of diverted pharmaceutical opioids could help support more granular estimates of the effects of the suggested interventions examined here. Finally, model representation of other components of patients' heterogeneity in the simulation model including sex and other demographics, history of trauma, mood and anxiety disorders, and the duration of pain complaints and pain location may have a positive impact on the discriminant capacity of an HMM-aided PDMP.

This study offers some support for possible policy avenues to lessen the distressingly heavy burden the opioid crisis has imposed on the Canadian population. However, there is a large population of individuals with existing opioid use disorders, and while the size of that population notably limits securing the full potential benefit of the policies studied here, it also emphasizes the need to ensure efficient prioritization and use of the limited flow of resources available for preventive strategies. Thus, while stylized, the current findings may offer steps towards aiding the public health community in enhancing the effectiveness of measures focused on preventing development of opioid use disorders via prescription drug pathways.
Figure 4.3: Opioid Prescribing state chart. This state chart seeks to depict states observable from the perspective of health care providers.
Figure 4.4: Medication Adherence state chart. This state chart seeks to depict states that are unobservable from the perspective of health care providers.
Figure 4.5: The distribution and moving average indicated by bar chart and dashed curve, respectively, of the number of people in an individual's social circle. The x-axis represents the number of people an individual may know, and the y-axis shows the fraction of the population with a given number of people in their circle.

Figure 4.6: (a) The proportion of people starting opioids without being prescribed opioids in the past year and (b) the proportion of people prescribed opioids, for the baseline scenario generated by the model fitted well with the references data (see Table 4.5 for the references data).
Figure 4.7: (a) The proportion of patients prescribed opioids who either underuse or overuse them, and (b) the proportion of patients who overuse them, for the baseline scenario, generated by the model fitted well with the references data (see Table 4.5 for the references data).

Figure 4.8: (a) The proportion of people prescribed opioids who were on long-term therapy, and (b) the proportion of patients who misuse prescription opioids transition to street opioid, generated by the model fitted well with the empirical data (see Table 4.5 for the references data).
Figure 4.9: The prevalence of illegitimate prescriptions (e.g., doctor shopping), generated by the model fitted well with the empirical data (see Table 4.5 for the references data).
**Figure 4.10**: ROC curve plot and associated AUC for different HMM thresholds (shown as number labels along-side the curve) within the HMM-aided PDMP. A no-skill classifier for PDMP which is no better than chance lies on the diagonal line on the ROC curve plot.

**Figure 4.11**: Precision-recall curve plot and associated AUC for different HMM thresholds (shown as number labels along-side the curve) within the HMM-aided PDMP. A no-skill classifier for PDMP which is no better than chance lies on a horizontal line on the precision-recall curve plot with a precision equal to ‘0.03124’.
Chapter 5

Evaluating the Impact of Increased Dispensing of Opioid Agonist Therapy Take-home Doses on Treatment Retention and Opioid-related Harm among Opioid Agonist Therapy Recipients: A Simulation Study

Abstract: Modified opioid agonist therapy (OAT) guidelines initially introduced during the COVID-19 pandemic allow prescribers to increase the number of take-home doses to fulfill the need for physical distancing and prevent treatment discontinuation. It is crucial to evaluate the consequence of administering higher take-home doses of OAT on treatment retention and opioid-related harms among OAT recipients to decide whether the new recommendations should be retained post-pandemic. This study used an agent-based model to simulate individuals dispensed daily or weekly OAT (methadone or buprenorphine/naloxone) with a prescription, over six months of treatment. Within the model simulation, a subset of OAT recipients was deemed eligible for receiving increased take-home doses of OAT at varying points in their treatment time course. Model results demonstrate that earlier dispensing of increased take-home doses of OAT are effective at achieving slightly higher treatment retention among OAT recipients. Extended take-home doses also increased opioid-related harms among buprenorphine/naloxone-treated individuals. Model results illustrate that expanding naloxone availability within OAT patients’ networks could prevent these possible side effects. Therefore, policymakers may need to strike a balance between expanding access to OAT through longer-duration take-home doses and managing the potential risks associated with increased opioid-related harms.

5.1 Introduction

Opioid agonist therapy (OAT) utilizes methadone or buprenorphine/naloxone to prevent withdrawal in individuals exhibiting opioid use disorder (OUD) [272, 58, 313] and elevate treatment retention, as achieving this goal is linked to a decreased risk of overdose [313, 319]. However, due to low treatment retention rates, OAT is often underutilized [37, 357, 351, 328, 341]. OAT recipients are required to frequently visit their prescribing doctors until they qualify for increased dispensing of opioid agonist therapy take-home doses. In these circumstances, many patients decline treatment or are not retained in the treatment sufficiently long
to secure approval for graduated numbers of take-home doses [341, 212].

In the context of COVID-19-related healthcare delivery modifications [62], in some jurisdictions, regular access to OAT and retention in treatment were further disrupted [80, 13], raising the risk of overdose and death for individuals who discontinue OAT [313, 13]. This pandemic experience calls for procedures and policies that guarantee constant access to OAT. New guidance for expanded access to OAT during the COVID-19 pandemic was approved in several countries, including the US and Canada [349, 68]. In Ontario, this guidance supported an increase in the number of take-home doses for individuals who may have been eligible under existing treatment guidelines [68]. Expanded access to OAT during the COVID-19 pandemic may lead to high treatment adherence [185, 131]. However, it is not clear if this new guideline for administering higher take-home doses of OAT will still be beneficial as the world moves beyond the unique circumstances of the COVID-19 pandemic.

Computational simulation models [18] are efficient tools for evaluating the possible effects of different intervention strategies and better understanding the mechanisms underlying observed trends. Agent-based modeling [330] is one of the primary types of computational simulation methods employed in public health, with that choice being generally dependent on the research question and scope of the respective study. Agent-based models can highlight heterogeneous properties with ease, reflect individual-level behaviours and generate potential health consequences and histories as a result of such behaviours. Although there exist some simulation models for studying OAT [20, 244, 345, 72], the current study is the first agent-based model simulation to assess the impact of increased dispensing of take-home doses of OAT by utilizing data sources from Canadian OAT recipients. In the present study, the implemented agent-based model aims to capture a clear understanding of the trajectory of patients using methadone or buprenorphine/naloxone for OAT and investigate the potential effects of administering higher take-home doses of OAT on treatment retention and opioid-related harms among OAT recipients.

The objective of this study is to evaluate the impact of increased dispensing of take-home doses of methadone and buprenorphine/naloxone on treatment retention and opioid-related harm among OAT recipients and examine the health consequences of whether the new guidelines for administering higher take-home doses of OAT should be continued in future. The remainder of this paper is organized as follows: Section 2 describes the model, including agent-based modeling, and the experimental design. Section 3 elucidates the results. Section 4 includes the corresponding discussion and concludes the paper.

5.2 Method

The impact of the clinical decision to increase the number of take-home doses of OAT and patient outcomes among OAT recipients is investigated using an agent-based model. This study presents the dynamics of individuals' behaviors actively treated with OAT (methadone or buprenorphine/naloxone). Data for the agent-based model presented in this work was obtained from a detailed study from Institute for Clinical
Evaluative Sciences (ICES) [291] which captures many relevant health variables for Ontario residents [131]. The simulation software AnyLogic Version 8.8.0 [53] was used to create the model.

5.2.1 Agent-based Modeling

The use of agent-based modeling in this study supports scenario-based assessment of the impact of the increase in dispensing of OAT take-home doses on treatment retention and opioid-related harm among individuals receiving daily or weekly dispensed OAT. The model features a single type of agent, representing an individual experiencing opioid use disorder (OUD).

Within the model, individuals experiencing opioid use disorder are endowed with sociodemographic characteristics that influence their possible peer network, including the location of residence (urban or suburb) and neighborhood income quintile.

OUD behaviour is governed by two state charts depicted in Figure 5.1. These state charts characterize the possible state space for individuals experiencing OUD whether they are undergoing treatment or not.

The treatment state-chart represents the dynamics of treatment options for each individual experiencing OUD. Individuals experiencing OUD are out of treatment if they never choose a treatment or have discontinued the previous one. An individual who has never previously entered treatment can choose either methadone or buprenorphine/naloxone treatment. Further, patients are dispensed OAT in a daily or weekly manner which is equivalent to one day supply or 5 - 6 days supply for all prescriptions, respectively. Individuals are classified among these four groups based on historical distributions [131]. During each visit to a physician for OAT, individuals who do not possess naloxone have the opportunity to obtain a naloxone kit. This kit can be used to assist their peers in the event of an opioid overdose.

Every patient in these four subsets of treatment might experience treatment disruption. The model treats such disruptions as being of two types: Gaps in therapy of 5 to 14 days are classed as interruptions, while those of more than 14 days are termed treatment discontinuations and lead the patient to enter the out-of-treatment state. There are specific hazard rates governing individuals in each treatment type and leading to occurrence of opioid overdose, opioid-related death, and all-cause death based on historical data [131]. Treatment retention is viewed as having been successfully achieved when the patient enters the post-treatment state after 6 months therapy without any interruptions.

The illicit opioid use status state-chart reflects the various illicit opioid use stages, determined by treatment, through which each OAT recipient progresses, including uncontrolled illicit opioid use, restricted opioid use while under treatment, and stopping illicit opioid use in a post-treatment stage. While an OAT recipient is in an in-treatment restriction state, they have a probability of being deemed eligible for dispensing of increased take-home doses of OAT, based on historical distributions [131].

Among buprenorphine/naloxone daily recipients without any change in their dose status, there are daily visits to the clinic for receiving dispensed take-home doses. Additionally, for those with a change in their take-home dose status, visits are scheduled every 14 days. Similarly, among buprenorphine/naloxone weekly
recipients with no change in their dose status, there are weekly visits to the clinic for dispensed take-home doses. For individuals with a change in their take-home dose status, visits are scheduled every 14 days. In a like manner, methadone daily recipients with no change in their dose status have daily visits to the clinic to receive dispensed take-home doses. However, for those with a change in their take-home dose status, visits occur every other day. Methadone weekly recipients without any change in their dose status have weekly visits to the clinic for receiving dispensed take-home doses. By contrast, for individuals with a change in their take-home dose status, visits are scheduled every 14 days.

As policymakers may consider implementing targeted interventions or additional support measures for patients at a higher risk of opioid-related harms due to increased dispensing of OAT, this study simulates the creation of a supportive peer network among patients to enhance access to naloxone kits for overdose prevention. Therefore, considering agent heterogeneity and preferential attachment, a network is constructed with multiple disconnected components, wherein OAT recipients, regardless of changes in their take-home dose, have the potential to acquire a naloxone kit when attending to receive their dispensed OAT; that kit can then be used to reverse overdoses amongst other patients in their network.

5.2.2 Network

To simulate the possibility of a patient receiving naloxone administration from peers in the case of opioid overdose, a network exhibiting preferential attachment is implemented between patients. Within this network, it is assumed that an individual (ego) is always intended to connect to alters in the same location of residence, neighborhood income, and treatment type. In order to achieve this objective, the network construction process proceeds through two steps. First, an Erdos-Renyi network [109] is first established connecting each ego with an average number of 15 candidate alters. Second, candidate alters that do not meet the desired criteria of having the same residence location, neighborhood income, and treatment type are then definitely removed, resulting in a network exhibiting preferential attachment composed of multiple disconnected components. Figure 5.2 illustrates the distribution of the final network.

5.2.3 Outcome Measures

Primary model outcome measures are cumulative opioid overdoses, cumulative opioid-related deaths, and cumulative treatment retention among people treated with methadone or buprenorphine/naloxone over six months of treatment without any interruptions.

5.2.4 Parameterization

The model is parameterized with assumptions characteristic of the Ontario adult population experiencing OUD and simulates a population of 50,000 individuals enrolled in OAT. The main source of data for parameterization is a published original investigation [131] which utilizes the Narcotics Monitoring System database.
and the ICES repository to detect prescription claims for OAT in Ontario between March 2020 to October 2020.

Despite the uncertainties associated with the data values presented in [131], due to the restrictions in the study population, the potential influence of pandemic-related factors, and the possibility of changes in take-home dose dispensing patterns [131], this data delivers significant value in informing for the current study. Table 5.5 presents a summary of the parameters for patients receiving methadone or buprenorphine/naloxone treatment, either on a daily or weekly basis, and considers their eligibility for changes in take-home doses of OAT. The parameters are reported in terms of rates per year and include opioid overdose, discontinuation and interruption of therapy, all-cause mortality, opioid-related death that are based on the parameterizations in [131]. Table 5.5 shows that – with the notable exception of weekly methadone patients eligible for increased take home doses – methadone patients generally have higher opioid overdose rates compared to buprenorphine/naloxone patients. This suggests that buprenorphine/naloxone may have a lower risk of overdose compared to methadone, possibly due to its partial agonist properties. Table 5.5 also indicates that buprenorphine/naloxone patients have higher rates of therapy discontinuation and interruption compared to methadone patients across different settings. This could be attributed to buprenorphine/naloxone being less effective for certain individuals in managing opioid dependency and limited availability of buprenorphine/naloxone treatment providers and clinics. Additionally, within Table 5.5, in cases where the number of deaths among recipients is small (≤5), either all-cause mortality or opioid-related mortality was treated as 0.001. However, the all-cause mortality and opioid-related death rates generally appear to be higher for methadone patients, particularly those who are not eligible for increased take-home doses. The data presented in Table 5.5 is utilized to specify the transition rates such as the opioid overdose rate, discontinuation rate of therapy, interruption rate in therapy, all-cause mortality rate, and opioid-related death rate, for each of the two different methadone or buprenorphine/naloxone recipient sub-state charts depicted in Figure 5.1.

Table 5.6 provides insights into socio-demographic factors related to the patients, including their urban location of residence and neighborhood income quintile [131]. The table showcases the distribution of patients residing in urban areas across various treatment groups and their eligibility for increased take-home doses. The data presented in Table 5.6 reveals that the majority of patients, irrespective of the medication type, reside in urban areas. This may suggest a higher number of opioid users in urban settings and potentially indicates that opioid treatment programs may be more accessible and concentrated in these areas. Further, in most cases (except for weekly methadone patients not eligible for increased take home doses) methadone patients have a higher percentage of individuals from urban areas compared to buprenorphine/naloxone patients. This may reflect accessibility or availability advantages in securing methadone treatment in urban settings. Table 5.6 also highlights the distribution of patients based on their eligibility for increased take-home doses. In general, patients who are eligible for increased take-home doses tend to exhibit higher levels of urban dwelling compared to those who are not eligible. This finding suggests that increased take-home doses may be more commonly provided to patients in urban settings, potentially indicating a higher likelihood
of meeting the criteria for extending take-home doses among patients in urban areas. Additionally, Table 5.6 presents the distribution of patients based on neighborhood income levels. The declining percentage of patients as one moves from the lowest to the highest income category implies a potential lower prevalence of extensive opioid use and/or individuals seeking opioid agonist treatment in higher-income neighborhoods. When interpreting this result, it is important to consider the difference between the total population residing in urban areas and rural areas. Additionally, the distribution of individuals across different neighborhood income levels should also be taken into account. The data presented in Table 5.6 is utilized to define custom distributions for the residence location and neighborhood income of diverse agents in the model.

Table 5.7 provides an overview of the remaining parameters, which involve different treatment types, varying disposal timings, and the potential for changes in disposal time [131]. The parameters listed in Table 5.7 are utilized as custom distributions to initialize the model and as parameters for implementing interventions during model simulation. Furthermore, Table 5.7 includes parameters that are specifically relevant to opioid users outside OAT settings, for which assumptions are grounded in the relevant literature. These parameters, such as the opioid overdose rate per year, all-cause mortality rate per year, and opioid-related death rate per year, are utilized to determine the transition rates in the illicit opioid use state chart, depicted as a sub-state chart in Figure 5.1.

Finally, the model underwent a thorough verification and validation process to assess its accuracy. Firstly, the assumptions made within the model were visually represented using state charts and possible transitions. This visual representation allowed for a clearer understanding of the assumptions and facilitated their evaluation for accuracy and coherence. The model’s assumptions were carefully articulated and validated against its code logic, ensuring there were no discrepancies or errors between the assumptions and the code. Secondly, the model’s emergent behavior was compared to real-world data to assess its accuracy. This step ensured that the model’s outcomes closely matched the observed outcomes in the real world [131], increasing confidence in its validity. Thirdly, the coefficient of variation for treatment retention was found to be less than 0.05 for both treatment types, indicating a relatively low level of variation. Similarly, the coefficient of variation for opioid overdose in both treatment types and opioid-related deaths in the methadone treatment group was less than 0.20. However, due to the limited number of opioid-related deaths amongst the buprenorphine/naloxone recipients (≤5), the coefficient of variation does not provide informative insights for this outcome in the buprenorphine/naloxone group. By fulfilling these requirements, the model successfully passed the tests by demonstrating the clarity of its assumptions provided by state charts and the alignment with real-world data [131].

5.2.5 Scenarios

Besides the baseline scenario that examines no extended take-home doses for OAT recipients across the 6-month treatment horizon, three scenarios are defined to explore the differential results of providing extended take-home doses for OAT recipients starting at different times of treatment. The number of eligible OAT
recipients for extended take-home doses remains constant within these three scenarios, while the time of
implementation of the extended take-home doses policy varies to begin after the second, third, and fourth
month of treatment, respectively. Furthermore, these three scenarios are combined with varying probabilities
of OAT patients obtaining a naloxone kit during a physician visit (i.e., 5%, 10%, and 15%) to study the impact
of naloxone disposal within OAT patients’ networks. For each scenario, an ensemble of 100 realizations was
run, each with varying random seeds. Finally, percentage changes from the baseline for all three outcomes
of interest are reported over the six-month treatment horizon.

5.3 Results

The baseline scenario posits approximately 10,500 individuals which represents 20.8% of the OAT population
receiving six-month buprenorphine/naloxone treatment, while approximately 39,700 individuals comprising
79.1% of the OAT population receive six-month methadone treatment.

Among people treated with buprenorphine/naloxone, 1,600 individuals representing 15.2% of this popu-
lation received daily dispensed buprenorphine/naloxone while others received weekly dispensed Buprenor-
phine/Naloxone. Among people treated with methadone, 13,900 individuals representing 35.0% of this
population received daily dispensed methadone, and the rest of the individuals received weekly dispensed
methadone. With no additional intervention, the baseline scenario yields approximately 80 opioid overdoses
and 10 opioid-related deaths occurred in six-month buprenorphine/naloxone treatment accounting for 0.7%
and 0.09% of this population, respectively; by contrast, methadone treatment gives rise to a higher burden,
with approximately 750 opioid overdoses, and 70 opioid-related deaths occurred in six-month accounting for
1.8% and 0.1% of this population, respectively. Finally, out of the population receiving six-month buprenor-
phine/naloxone treatment, 7,900 individuals, representing 75.4%, continued treatment without interrup-
tion and discontinuation for six-month, thereby achieving six-month retention in buprenorphine/naloxone
treatment; by contrast, 30,800 individuals, which is equivalent to 77.5%, achieved six-month retention in
methadone treatment. These results demonstrate the baseline distribution of OAT recipients in different
types of treatment and disposal methods based on empirical data [131].

5.3.1 Individuals Receiving Methadone Treatment

Among methadone-treated individuals receiving daily dispensed OAT, 8,200 individuals which is equivalent
to 58.8% were eligible to transition to take-home doses, and among methadone-treated individuals receiving
weekly dispensed OAT, 18,700 individuals, representing 72.5%, were eligible to extend to 13 take-home doses.

5.3.1.1 Providing Extended Take-home Doses among People Treated with Methadone

Table 5.1 shows the six-month outcomes of interest for providing extended take-home doses among people
treated with methadone within the successive time frames. Earlier permission for the provision of extended
methadone take-home doses to eligible patients has a beneficial impact on all three outcomes of interest. Providing extended take-home doses among people treated with methadone increases treatment retention (by 2.8%, 2.0%, and 1.4% when permission for extended take-home doses is granted within the second month of treatment, the third month of treatment, and the fourth month of treatment, respectively). Providing extended take-home doses among people treated with methadone decreases both the total number of opioid overdoses by 7.3%, 6.1%, and 3.5%, and the total number opioid-related deaths by 13.0%, 10.7% and 6.9%, when permission for extended take-home doses is granted within the second month of treatment, the third month of treatment, and the fourth month of treatment, respectively. The results suggest that ensuring guaranteed access to take-home doses of methadone as early as the second month of treatment can lead to higher treatment retention rates and reduced harm related to opioids. This positive outcome may be attributed to reducing barriers to accessing suitable methadone doses and providing relief from withdrawal symptoms and reducing cravings for methadone recipients.

Table 5.1: Results of providing extended take-home doses among people treated with methadone: Six-month outcome percentage change from the baseline.

<table>
<thead>
<tr>
<th>Policy</th>
<th>Change in Opioid overdose (%)</th>
<th>Change in Opioid-related death (%)</th>
<th>Change in Treatment retention (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Providing extended take-home doses after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second month</td>
<td>-7.3%</td>
<td>-13.0%</td>
<td>+2.8%</td>
</tr>
<tr>
<td>Third month</td>
<td>-6.1%</td>
<td>-10.7%</td>
<td>+2.0%</td>
</tr>
<tr>
<td>Fourth month</td>
<td>-3.5%</td>
<td>-6.9%</td>
<td>+1.4%</td>
</tr>
</tbody>
</table>

5.3.1.2 Providing Extended Take-home Doses and Expanding Naloxone Availability among People Treated with Methadone

Table 5.2 characterizes the six-month outcomes of interest arising from providing extended take-home doses and expanding naloxone availability among people treated with methadone. Across all outcomes, the greatest impact was achieved with a 15% naloxone expansion combined with permission for the provision of extended methadone take-home doses granted within the second month of treatment. The results highlight the significant reduction in opioid-related harms when Methadone recipients within the peer support network are empowered with readily available naloxone. By having naloxone readily available, Methadone recipients can promptly intervene during an opioid overdose emergency for their peers, potentially saving lives and reducing the severity of harm.
5.3.2 Individuals Receiving Buprenorphine/Naloxone Treatment

Among buprenorphine/naloxone-treated individuals receiving daily dispensed OAT, 700 individuals, representing 43.8%, were eligible to transition to take-home doses, and among buprenorphine/naloxone-treated individuals receiving weekly dispensed OAT, 6,600 individuals, representing 74.3%, were eligible to extend to 13 take-home doses.

5.3.2.1 Providing Extended Take-home Doses among People Treated with Buprenorphine/Naloxone

Table 5.3 shows the six-month outcomes of interest for providing extended take-home doses among people treated with buprenorphine/naloxone within the successive time frames. Earlier granting of permission for the provision to extend buprenorphine/naloxone take-home doses to eligible patients has a small beneficial impact on treatment retention and a large undesirable impact on opioid overdose and opioid-related deaths. Providing extended take-home doses among people treated with buprenorphine/naloxone increases treatment retention (by 1.5%, 1.0 %, and 0.7% when permission for extended take-home doses is applied within the second month of treatment, the third month of treatment and the fourth month of treatment, respectively). However, providing extended take-home doses among people treated with buprenorphine/naloxone
also increases both the total number of opioid overdoses by 8.9%, 7.7%, and 3.9% and the total number opioid-related deaths by 3.4%, 7.2% and 6.3% when permission to use extended take-home doses is granted within the second month of treatment, the third month of treatment and the fourth month of treatment, respectively. The results suggest that ensuring guaranteed access to take-home doses of buprenorphine/naloxone as early as the second month of treatment can lead to higher treatment retention rates. This finding suggests that when patients have the opportunity to receive take-home doses, they are more likely to remain engaged in their treatment program. However, this greater flexibility and convenience in managing their medication comes with some drawbacks for buprenorphine/naloxone recipients. The opioid-related harms tend to increase among them, which may be attributed to the lack of direct monitoring of patients receiving buprenorphine/naloxone in OAT. Unlike Methadone, buprenorphine/naloxone may be less effective in providing long-term stability due to its pharmacological properties [350]; while not directly represented in the model, such factors may contribute to patterns reflected in the empirical data used to parameterize the model. Furthermore, individuals receiving buprenorphine/naloxone treatment who are experiencing a change in their take-home dose status are scheduled for visits every 14 days. This extended interval between visits may result in a loss of contact with healthcare providers, which could potentially contribute to an increase in opioid-related harm.

**Table 5.3:** Results of providing extended take-home doses among people treated with buprenorphine/naloxone: Six-month outcome percentage change from the baseline.

<table>
<thead>
<tr>
<th>Policy</th>
<th>Change in Opioid overdose (%)</th>
<th>Change in Opioid-related death (%)</th>
<th>Change in Treatment retention (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Providing extended</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>take-home doses after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second month</td>
<td>+8.9%</td>
<td>+3.4%</td>
<td>+1.5%</td>
</tr>
<tr>
<td>Third month</td>
<td>+7.7%</td>
<td>+7.2%</td>
<td>+1.0%</td>
</tr>
<tr>
<td>Fourth month</td>
<td>+3.9%</td>
<td>+6.3%</td>
<td>+0.7%</td>
</tr>
</tbody>
</table>
Table 5.4 shows the six-month outcomes of interest for providing extended take-home doses and expanding naloxone availability among people treated with buprenorphine/naloxone. Even with a 5% naloxone expansion, a beneficial impact relative to the baseline would be achieved over all three different time frames of providing extended take-home doses.

Achieving the best treatment retention and reducing both opioid overdose and opioid-related deaths has been made by a 15% naloxone expansion combined with an early (second treatment month) grant of permission for the provision of extended buprenorphine/naloxone take-home doses. When naloxone is easily accessible within the peer support network, it can be promptly administered during an overdose emergency. The timely administration of naloxone effectively counteracts the effects of opioids and restores normal respiration, thus reducing the risk of fatal outcomes associated with overdose incidents. Therefore, by empowering buprenorphine/naloxone recipients within the peer support network with readily available naloxone, the potential for reducing opioid-related harms is enhanced.
Table 5.4: Results of providing extended take-home doses and expanding naloxone availability among people treated with buprenorphine/naloxone: Six-month outcome percentage change from the baseline.

<table>
<thead>
<tr>
<th>Policy</th>
<th>Change in Opioid overdose (%)</th>
<th>Change in Opioid-related death (%)</th>
<th>Change in Treatment retention (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Providing extended take-home doses after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second month 5%</td>
<td>-10.2%</td>
<td>-10.2%</td>
<td>+1.4%</td>
</tr>
<tr>
<td>Second month 10%</td>
<td>-19.9%</td>
<td>-21.7%</td>
<td>+1.6%</td>
</tr>
<tr>
<td>Second month 15%</td>
<td>-23.3%</td>
<td>-22.6%</td>
<td>+1.4%</td>
</tr>
<tr>
<td>Third month 5%</td>
<td>-13.6%</td>
<td>-15.8%</td>
<td>+1.4%</td>
</tr>
<tr>
<td>Third month 10%</td>
<td>-21.5%</td>
<td>-26.5%</td>
<td>+1.1%</td>
</tr>
<tr>
<td>Third month 15%</td>
<td>-25.9%</td>
<td>-32.8%</td>
<td>+1.2%</td>
</tr>
<tr>
<td>Fourth month 5%</td>
<td>-15.9%</td>
<td>-17.2%</td>
<td>+0.8%</td>
</tr>
<tr>
<td>Fourth month 10%</td>
<td>-24.4%</td>
<td>-21.9%</td>
<td>+1.1%</td>
</tr>
<tr>
<td>Fourth month 15%</td>
<td>-28.5%</td>
<td>-20.8%</td>
<td>+0.8%</td>
</tr>
</tbody>
</table>

5.4 Discussion

This simulation study of individuals receiving OAT in a context inspired by data from Ontario, Canada suggests that facilitating methadone or buprenorphine/naloxone recipients’ transition to take-home doses or receiving extended take-home doses would result in higher treatment retention compared with the status quo. A key added finding of this study was that earlier expanding access to take-home doses in the subsequent six months among OAT recipients is likely to elevate treatment retention. Results further suggest that use of extended take-home doses would decrease opioid overdose and opioid-related death among methadone recipients. While among those prescribed buprenorphine/naloxone, results suggest that extended take-home doses might increase the risk of opioid overdose and opioid-related death, it further suggests that expanding naloxone availability can mitigate the adverse effect of increased take-home doses guidance on opioid overdose and opioid-related death among buprenorphine/naloxone recipients.

The differences in pharmacological properties between methadone and buprenorphine/naloxone may contribute to variations in treatment outcomes seen in the empirical data used for model parameterization. Factors such as the duration of action, receptor binding affinity, and pharmacokinetic profiles could impact treatment response and the risk of adverse events [350]. For example, the longer duration of action and higher
receptor binding affinity of methadone [190] may result in greater stability and decreased risk of overdose among those receiving extended take-home doses.

Alternatively, buprenorphine/naloxone has a shorter duration of action and lower receptor binding affinity compared to methadone, which could reduce effectiveness in providing long-term stability. As potential contributors to relevant patterns in the empirical data used to evidence the model, these factors may contribute to the current observation that increased availability of the buprenorphine/naloxone outside of the clinic without close supervision may lead to a higher risk of opioid misuse, overdose, and related deaths. Additionally, it is important to note that individual patient characteristics, such as tolerance levels, treatment history, and support systems, can influence the outcomes. The stability of patients in their treatment can also impact their response to take-home doses.

Moreover, it is important to emphasize that individuals undergoing buprenorphine/naloxone treatment and undergoing a change in their take-home dose status are required to attend clinic visits only every 14 days. This prolonged gap between visits for all individuals undergoing buprenorphine/naloxone treatment with a change in their take-home dose poses a concern, as it may reduce the frequency of contact with healthcare providers. The potential consequences of limited contact include a diminished opportunity to address any emerging challenges or concerns promptly, such as adjusting medication dosage or addressing new risk factors. The creation of supportive peer networks and the availability of naloxone have empirically demonstrated promising results in preventing opioid overdose incidents due to several reasons. Firstly, supportive peer networks provide individuals in OAT with a sense of belonging and mutual support, which may enhance treatment engagement and reduce the risk of relapse. Secondly – and in an effect captured in the model presented here – the availability of naloxone, a medication used to reverse opioid overdose, plays a critical role in harm reduction. When naloxone is readily accessible – including through such peer networks – it can be promptly administered during an overdose emergency, reducing the risk of fatal outcomes. By having naloxone available, one can act quickly to intervene and potentially save lives. The combination of supportive peer networks and naloxone availability creates a complementary approach to preventing opioid overdose incidents. Patient-centered care for OAT recipients involves adapting treatment and support services to meet the unique needs and preferences of each individual [80]. This study examined various aspects of patient-centered care, including the implementation of flexible take-home doses and the establishment of supportive peer networks. Reflecting the ability of patients to exercise greater control over their treatment through flexible take-home doses and reduced challenges in weaving their dose administration into daily scheduling, the model captures a resulting increase in treatment retention. Moreover, the creation of supportive peer networks, coupled with the availability of naloxone, demonstrated the potential to prevent opioid overdose incidents. In this context, concern has been raised that storage of a large quantity of OAT medication at home, particularly methadone, might place other family members or other co-domiciliaries at risk of opioid overdoses – a consideration that suggests the importance of promoting safe storage. Furthermore, there are specific criteria that must be met before providing patients with new or higher take-home doses, which adds
to the complexity of these clinical decisions.

Several limitations of this study need to be noted. First, while the implemented agent-based model monitors the behavior of OAT recipients over a six-month treatment period informed by reported data and investigates the patterns of changes between the baseline and subsequent scenarios, it is essential to recognize that it does not employ a conceptual framework with distinct evidence-based rules for the full diversity of causal mechanisms involved; indeed, the current state of evidence falls well short of what would be required to support such a representation. It is therefore particularly important to acknowledge that the main data source used in this model may still be subject to residual confounding, which can impact the reported results. Thus, it is advisable to interpret the findings with caution. Partly to support incorporation of evolving evidence, the implemented model is accessible online. Beyond incorporating updated parameter estimates, the availability of the model can further aid in refining model structural assumptions with refined theory. Second, it is important to note that the model simplifies the complexity of implementing and maintaining a peer support network among OAT patients in real-world settings. Establishing and maintaining a successful peer support network in practice requires significant effort and consideration of the diversity within the OAT population. Third, while the literature [3,29] suggests a potential for an elevated risk of overdose and mortality during the initial stages of methadone treatment, it bears emphasis that the model is not parameterized to reflect this aspect of the context, and does not report the timing of events within the six-month treatment time frame. This limitation is primarily attributed to the constraints imposed by the currently utilized data sources. Finally, additional evaluation may be required to validate the findings thoroughly. For instance, in accordance with the empirical data, opioid-related rates, including overdose or death, were not excluded from the all-cause death rate for OAT recipients. Moreover, due to the potential changes in tolerance levels among OAT recipients over time, there are uncertainties regarding opioid-related harm rates outside of OAT. However, since these rates remain constant across all scenarios and amounts of opioid-related harm outside of OAT are not among the outcomes of interest for the current study, these limitations are expected to have minimal impact on the overall results. Moreover, the model is simplified by greatly limiting its representation of agent heterogeneity by virtue of employing overall empirical data, and the model does not account for disparities in access to treatment services.

The findings of this study accord with that of several other previous case studies [30–35] in suggesting that benefits can be secured if the modified guidance for administering higher take-home doses of OAT continues beyond the COVID-19 pandemic. By implementing longer-duration take-home doses in methadone treatment programs, there is a potential to decrease the occurrence of opioid overdose and opioid-related deaths. To further address overdose incidents and prevent fatalities among OAT recipients, while also enhancing treatment retention, promoting the usage of naloxone among peers [192, 216], and facilitating its accessibility without a prescription [327] may be effective. Based on these results, policymakers may need to consider several factors when formulating or revising policies related to OAT. Policymakers may need to strike a balance between expanding access to OAT through longer-duration take-home doses and managing the potential risks asso-
associated with increased opioid-related harms, suggesting the value of conducting a thorough risk assessment and considering additional safety measures to ensure the well-being of patients. Moreover, policymakers may acknowledge that the benefits of longer-duration take-home doses vary among patients. They may underscore the significance of modifying treatment plans to individual needs and take into account factors such as gender, income level, residential location, and treatment history when assessing a patient’s stability and risk profile. This information might aid in determining the most suitable treatment duration and level of supervision for each patient. To reach this aim, policymakers might place an emphasis on establishing robust monitoring and surveillance systems to closely monitor the outcomes and safety of OAT patients receiving longer-duration take-home doses. This could involve regular check-ins, adherence monitoring, and systems to promptly identify and respond to any concerning trends or adverse events. Finally, this study highlights that policymakers may benefit from collaboration among systems scientists, healthcare providers, and data custodians to further investigate the impact of longer-duration take-home doses on treatment outcomes and opioid-related harms. Such collaborations facilitate research and studies that aim to identify context-specific policy recommendations that are highly dependent on patient populations, local regulations, and existing guidelines.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Opioid overdose rate (1/Year)</th>
<th>Discontinuation rate of Therapy (1/Year)</th>
<th>Interruption rate in therapy (1/Year)</th>
<th>All-cause mortality rate (1/Year)</th>
<th>Opioid-related death rate (1/Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Methadone</td>
<td>0.095</td>
<td>0.636</td>
<td>0.239</td>
<td>0.013</td>
<td>0.005</td>
</tr>
<tr>
<td>Patients Not Eligible for</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Take Home Doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly Methadone</td>
<td>0.018</td>
<td>0.196</td>
<td>0.074</td>
<td>0.011</td>
<td>0.003</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Increased Take Home Doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily Methadone</td>
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<td>Increased Take Home Doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly Methadone</td>
<td>0.014</td>
<td>0.141</td>
<td>0.051</td>
<td>0.008</td>
<td>0.001</td>
</tr>
<tr>
<td>Patients Eligible for</td>
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<td></td>
<td></td>
</tr>
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<td>Increased Take Home Doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily buprenorphine/naloxone</td>
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<td>0.293</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Patients Not Eligible for</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Increased Take Home Doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Weekly buprenorphine/naloxone</td>
<td>0.014</td>
<td>0.308</td>
<td>0.129</td>
<td>0.008</td>
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<td>Patients Not Eligible for</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased Take Home Doses</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Summary of opioid-related parameters for methadone and buprenorphine/naloxone treatment (continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Opioid overdose rate (1/Year)</th>
<th>Discontinuation rate of Therapy (1/Year)</th>
<th>Interruption rate in therapy (1/Year)</th>
<th>All-cause mortality rate (1/Year)</th>
<th>Opioid-related death rate (1/Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily buprenorphine/naloxone Patients Eligible for Increased Take Home Doses</td>
<td>0.065</td>
<td>0.851</td>
<td>0.253</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Weekly buprenorphine/naloxone Patients Eligible for Increased Take Home Doses</td>
<td>0.017</td>
<td>0.260</td>
<td>0.095</td>
<td>0.008</td>
<td>0.001</td>
</tr>
</tbody>
</table>
**Table 5.6:** Summary of socio-demographic parameters for methadone and buprenorphine/naloxone Treatment based on [131] used in the model parametrization: daily and weekly dispensing of OAT and eligibility for changes in take-home doses

<table>
<thead>
<tr>
<th>Parameters</th>
<th>location of residence</th>
<th>Neighborhood income</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urban</td>
<td>One (lowest)</td>
</tr>
<tr>
<td>Daily Methadone Patients Not Eligible for Increased Take Home Doses</td>
<td>88.7%</td>
<td>48.2%</td>
</tr>
<tr>
<td>Weekly Methadone Patients Not Eligible for Increased Take Home Doses</td>
<td>85.5%</td>
<td>41.3%</td>
</tr>
<tr>
<td>Daily Methadone Patients Eligible for Increased Take Home Doses</td>
<td>89.9%</td>
<td>39.4%</td>
</tr>
<tr>
<td>Weekly Methadone Patients Eligible for Increased Take Home Doses</td>
<td>88.1%</td>
<td>38.0%</td>
</tr>
<tr>
<td>Daily buprenorphine/naloxone Patients Not Eligible for Increased Take Home Doses</td>
<td>80.9%</td>
<td>48.8%</td>
</tr>
<tr>
<td>Weekly buprenorphine/naloxone Patients Not Eligible for Increased Take Home Doses</td>
<td>86.5%</td>
<td>34.0%</td>
</tr>
</tbody>
</table>
Summary of socio-demographic parameters for methadone and buprenorphine/naloxone treatment (continued)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>location of residence</th>
<th>Neighborhood income</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urban</td>
<td>One (lowest)</td>
<td>Two</td>
<td>Three</td>
<td>Four</td>
<td>Five (highest)</td>
<td></td>
</tr>
<tr>
<td>Daily buprenorphine/naloxone</td>
<td>88.2%</td>
<td>39.5%</td>
<td>24.1%</td>
<td>14.9%</td>
<td>11.8%</td>
<td>9.6%</td>
<td></td>
</tr>
<tr>
<td>Patients Eligible for Increased Take Home Doses</td>
<td>86.5%</td>
<td>34.8%</td>
<td>24.4%</td>
<td>17.9%</td>
<td>12.6%</td>
<td>10.3%</td>
<td></td>
</tr>
</tbody>
</table>
**Table 5.7:** Summary of remaining parameters in the model parametrization

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAT recipients’ population size</td>
<td>50,000</td>
<td>Assumed</td>
</tr>
<tr>
<td>The number of OAT recipients in each treatment type (Methadone and Buprenorphine/Naloxone)</td>
<td>Custom distribution</td>
<td>Parametrized [131]</td>
</tr>
<tr>
<td>The number of OAT recipients in each disposal timing (daily or weekly) across different treatment types</td>
<td>Custom distribution</td>
<td>Parametrized [131]</td>
</tr>
<tr>
<td>The number of OAT recipients considering their eligibility for changes in take-home doses across different treatment types and disposal timings</td>
<td>Custom distribution</td>
<td>Parametrized [131]</td>
</tr>
<tr>
<td>Rate of the opioid overdose per year for opioid users outside the OAT</td>
<td>Uniform distribution between 0.009 and 0.048</td>
<td>Assumed [131]</td>
</tr>
<tr>
<td>Rate of opioid-related death per year for opioid users outside the OAT</td>
<td>Uniform distribution between 0.0179 and 0.0562</td>
<td>Assumed [201]</td>
</tr>
<tr>
<td>Rate of non-opioid-related death per year for opioid users outside the OAT</td>
<td>0.001</td>
<td>Assumed [86]</td>
</tr>
</tbody>
</table>
Figure 5.1: Patient receiving OAT state-chart structure. When viewed in landscape mode, the Treatment state-chart is to the right and Illicit opioid use status state-chart is to the left.
Figure 5.2: The degree distribution for each individual’s social circle induced by the network construction process.
CHAPTER 6
CONCLUSION AND FUTURE WORK

6.1 Summary

Agent-based models and simulations offer the potential to unravel the complex interactions underlying the opioid crisis and evaluate the effectiveness of potential interventions by considering the dual effects of opioids which can provide effective pain relief when used as directed, but whose misuse and abuse can lead to severe physical and psychological harm or even death.

Chapter 2 consists of a literature review chapter that evaluates existing research on agent-based models and simulations related to the opioid crisis and provides an overview of the current state of the field. The review examines the modeling procedures, conceptualization, policy interventions suggested by the models, and their data sources.

Chapter 3 investigates youth substance use as a complex phenomenon shaped by a variety of factors such as peer pressure, ease of access to prescription opioids, and the surrounding culture and society. However, the closure of in-person schools may alter the risk factors that contribute to drug use among youth. This work employs an agent-based simulation, grounded in social impact theory, to explore the possible impacts of in-person school closures due to COVID-19 on non-medical prescription opioid use among youth. The simulation utilizes data from the Ontario Student Drug Use and Health Survey and considers the accessibility of prescription opioids within the home in the analysis. The results indicate that lifting in-person school closures could lead to an increase in non-medical prescription opioid use among youth, but this could be minimized by ensuring prescription opioids are stored securely during the period of in-person school closures.

Chapter 4 focuses on the use of opioid medications, as abuse of prescription opioids has led to increased morbidity and mortality in Canada over the past few decades and made it difficult for practitioners to assess and determine the legitimacy of opioid prescriptions. The fourth chapter emphasizes the significance of using dynamic modeling, simulation, and incorporating machine learning algorithms to study the effectiveness of policies targeting opioid prescription practices. An agent-based model was developed and applied to examine the effect of reduced prescribing and of prescription drug monitoring programs on overdose and escalation to street opioids among patients treated with prescribed opioids, and the legitimacy of opioid prescriptions over a five-year time horizon. Model findings suggest that decreasing the dosage of prescriptions has the most significant impact on decreasing morbidity and mortality over five years while placing a minimal burden on
patients who require pharmaceutical opioids for legitimate medical reasons. The results illustrate that the impact of these interventions is highly sensitive, meaning that even a slight decrease in dosage can result in a significant decrease in morbidity and mortality. Thus, this research highlights the importance of further investigating the relation between dosage changes and outcomes.

Chapter 5 was inspired by the fact that during the COVID-19 pandemic, guidelines for opioid agonist therapy (OAT) were modified to allow doctors to increase the number of take-home doses to meet the need for physical distancing and prevent treatment discontinuation. This chapter evaluates the impact of these new guidelines on treatment retention and opioid-related harms among OAT recipients to decide if these recommendations should continue beyond the pandemic. To probe the tradeoffs associated with increased take-home doses of OAT, this agent-based model simulates individuals receiving daily or weekly OAT (methadone or buprenorphine/naloxone) over six months of treatment. Within the simulation, a subset of OAT recipients is chosen to receive increased take-home doses of OAT at different stages of their treatment. Furthermore, the model is used to examine the effects of increasing the number of take-home doses of OAT on cumulative opioid overdoses, cumulative opioid-related deaths, and cumulative treatment retention among individuals receiving methadone or buprenorphine/naloxone over six months. This work finds that giving increased take-home doses of OAT earlier in treatment appears to result in slightly higher retention rates among those receiving methadone and buprenorphine/naloxone treatment. The study also finds that extending take-home doses increases the risk of opioid-related overdoses and deaths among individuals receiving buprenorphine/naloxone treatment, compared to the baseline frequency of take-home doses. Simulation model findings suggest that increasing the availability of naloxone within OAT patients’ networks could prevent these negative effects.

The models presented in this dissertation focus on factors related to the opioid crisis, aiming to explore different research questions about the underlying mechanisms of the opioid crisis and informing the design and evaluation of various policy interventions to mitigate its effects.

6.2 Model Validity Consideration for Simulation Models: Brief Remarks

The only completely accurate representation of the real world is the real world itself. For any other form of simulation representation, a certain level of abstraction is required. Such abstraction is also of foremost importance in light of the limited time, knowledge and human resources available to conduct modeling projects, the limited supply of which inevitably entail that investments in refining and representing detail in one area of the model will require less refinement in other areas of that model. This level of abstraction will generally be determined based on the research question, and will involve selecting a suitable model domain, level of analysis, model inputs and outputs, including the need to parameterize the model and compare its behavior against empirical data sources. While domain experts may prioritize including details that represent the subtleties of their disciplinary knowledge, it is important to orient the model towards the
research question and model purpose to prevent overloading it with unnecessary details. To achieve this, a generatively sufficient structure is created using abstraction and idealization of the real-world situation. Achieving a balance between the need for accuracy and the need for simplicity is a challenging task that requires a high level of sophistication in the field of systems science, and often involves observation of the emergent behavior of the model. The application of systems science knowledge, theories, methods, and tools involves acquiring a solid and broad understanding of the underlying structure of the system. This requires identifying dynamic and interconnected components, reciprocal causality, emergent properties, tipping points, path dependence, lock-in effects, and other non-linear behaviors within systems. Employing systems science entails utilizing mental models and constructing simulation models that reliably reflect the dynamic behavior of systems. There is a broad spectrum between systems science models used for theory building – where the model is often used to refine thinking but commonly makes use of little data – to those (on the opposite end of the spectrum) used for theory explication, for which empirical grounding is of considerable interest and importance. For simulation models in the latter category, once model results align with empirical data in terms of answering the research question, a model is commonly considered ready for policy analysis and further study of the dynamics in the investigated area. A key goal for many simulation models is to examine how outcomes for counterfactual scenarios – scenarios posing “what if” questions that have not been previously empirically observed – differ from those of some reference baseline scenario. Within such circumstances, systems scientists often draw additional confidence in a model’s suitability by reflecting on the fact that because the same model limitations will typically affect both the baseline scenario and counterfactual scenarios, the difference between the baseline and counterfactual scenarios will often be less heavily affected by such limitations, with many effects of such limitations “cancelling out” when that difference is taken. As long as no empirical data contradicts it, the implemented model is commonly considered to constitute a plausible dynamic hypothesis in the field of simulation modeling. However, if there is a pronounced discrepancy between the model’s insight and empirical data after the model has been developed, a well-analyzed step for revising the model structure or rethinking possible problems in the data-based analysis will commonly be necessary.

In this dissertation, each model has undergone a thorough process of verification, validation, and replication of empirical data, which is presented in each chapter individually. Based on this process, the semi-stylized models seem to have a good level of reliability. Additionally, to provide a more thorough view of the implemented models, the discussion section in each chapter includes discussions of limitations of each model. Outlined below is a brief summary of the validation process conducted in this dissertation.

The validity of the implemented models was ensured through various measures. Construct validity, which refers to the degree to which the model accurately represents the real-world system under study, and external validity, which refers to the extent to which the findings of the model can be generalized were assessed by comparison of model emergent behavior and available empirical data and using expert domain knowledge. Specifically, the assumptions made in the models were carefully evaluated and validated by articulating them
and depicting them using state charts and possible transitions; the declarative characterization of much of the model dynamics using such diagrams helped strongly reduce the likelihood of implementation errors. Sensitivity analysis served as an important tool to help ensure their reasonableness, as well as involving expert domain knowledge and background reviews to assess them. After a certain burn-in period, simulation time was chosen to ensure that model dynamics stabilize. To overcome sampling error, which can occur when the model is stochastic and different runs can give different results, the models were run using Monte Carlo simulation for an ensemble of at least 100 realizations.

Data validity, or the accuracy and reliability of the data used to parameterize and validate the model, was of minimal concern due to the utilization of reputable third-party open-source data or established literature. Parameter uncertainty, which is associated with the values assigned to the model’s parameters and can affect the accuracy of the model’s predictions, was addressed via sensitivity analysis and the calibration process. As for model structure, this was additionally assessed by comparing baseline scenarios with real-world data. To evaluate adequacy of scale, or the possibility of the number of agents in the model being too small to adequately capture the dynamics of the real system, the coefficient of variation was studied for outcomes of the simulation under different population sizes.

The work presented in this dissertation employed a variety of measures to verify and validate the implemented models and guarantee their validity according to the current understanding of the situation. Nonetheless, the opioid crisis is rapidly evolving, with the arrival of new synthetic opioids, changes in availability of opioid antagonists for overdose prevention, and advances in opioid agonists and other therapeutics for therapy [340]. The crisis is further co-evolving notably with a broader polydrug use crisis marked by shifts between drug classes based on price, supply availability, combination of substances, and availability of new compounds. Such evolution or insights via new data sources may challenge the future validity of the outcomes presented here, in which case it will likely be necessary to analyze and revise the model structure or reconsider potential issues in the data-based analysis, as is customary in the field of simulation modeling.

6.3 An Overview of the Scalability of the Implemented Simulation Models

Table 6.1 displays the time (in seconds) required to execute a single realization of the baseline scenario in the models outlined in this dissertation, varying the population sizes.

Notably, when dealing with smaller population sizes, it becomes evident that the most time-intensive task involves network configuration. For a population size of 1,000, as indicated in Chapter 5, the process of configuring a preferred attached network during initialization and running the model for six months consumes more time than setting up a random network for a model spanning ten years, such as are used in Chapter 4.

Furthermore, the computational burden is substantially increased by the process of identifying various ranges within the Moore neighborhood and calculating the effects of surrounding and acute opioid withdrawal
Table 6.1: Time in Seconds for Single Baseline Scenario Realization across Different Population Sizes

<table>
<thead>
<tr>
<th>Population Size</th>
<th>Model presented in Chapter 3</th>
<th>Model presented in Chapter 4</th>
<th>Model presented in Chapter 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000</td>
<td>2.80</td>
<td>1.21</td>
<td>1.39</td>
</tr>
<tr>
<td>10,000</td>
<td>16.39</td>
<td>5.01</td>
<td>3.52</td>
</tr>
<tr>
<td>100,000</td>
<td>1033.83</td>
<td>129.37</td>
<td>103.45</td>
</tr>
</tbody>
</table>

in the model presented in Chapter 3.

It is important to highlight that the versions of the AnyLogic software framework employed by this dissertation offers the capability of running multiple realization on different processor cores in parallel. Therefore, depending on the available cores and memory resources, these realizations can be executed concurrently. However, it is essential to acknowledge that limitations in memory capacity can impose restrictions on the number of realizations that can run in parallel efficiently. While the latency associated with a given realization imposes a lower bound on model execution time, as the count of realizations rises, such limitations in core availability and memory serve to govern the overall time consumption observed in practice. Such constraints reflect limitations in hardware resources rather than issues with the implemented model.

6.4 Future work

The process of developing semi-stylized agent-based simulation models for the opioid crisis within this dissertation yielded important lessons that can serve as a foundation for future research. Despite limited data and simplifying assumptions, the developed agent-based simulation models were able to explore the intricate nature of the opioid crisis. The implemented models in this dissertation separately examined key factors involved in three important aspects of the opioid crisis. These include the impact of in-person school closures on non-medical use of prescription opioids among youth, the possible trajectories of patients who have taken prescription opioids, and treatment retention issues for individuals on opioid agonist therapy. By incorporating key characteristics and rules related to the three endangered groups, the models revealed various aspects of the complex dynamics of the opioid crisis, offering valuable insights for evaluating, analyzing, and forecasting the effectiveness of policy interventions. Within this dissertation, it was observed that complex systems composed of many interacting agents can exhibit emergent behaviors that are difficult to anticipate within this area absent simulation modeling, such as rebound effects and tipping points. Furthermore, the implementation of an approach to investigate the development of tolerance to prescription opioids in a subset of patients was essential to explore the potential trajectories in opioid therapy. Finally, while recipients of opioid agonist therapy (OAT) have limited local interactions with a small number of other agents, these lo-
ocalized interactions play a crucial role in mitigating the risk of higher opioid-related harms at the aggregated level.

As a future direction, current semi-stylized models can be expanded to serve as decision-making tools for policy development in a modular manner. While these models are currently only used for research and academic purposes, they focus on breaking down the essential elements of the opioid crisis into separate, distinct components to better understand specific aspects of this complex issue. One of the foremost strengths of agent-based model is their ability to readily and scalably characterize heterogeneity between agents [251]. Consideration of additional dimensions of heterogeneity in the agents populations represented within the dissertation models can lead to more realistic results. To effectively provide decision support for policymakers, it is crucial that these existing models be accompanied by additional modeling taking into account the larger public health context, including the increasing danger of polysubstance use and the presence of fentanyl in drug supplies, regional and demographic differences in drug preferences, along with other heterogeneous factors among individuals such as adverse childhood experiences, substance use disorders in families, and comorbidities associated with substance use and mental health. A policy decision-making simulation model could be composed of the current semi-stylized models as well as other models developed separately, each with its own level of abstraction, but in a fashion compatible with the others with whom it interacts. By validating each stylized model individually, such models can be combined with minimal modification and further validate this complex system to provide a more comprehensive understanding of the opioid crisis and insight into how different aspects of the crisis interact and behave as a complex system. It is important to note that to effectively use this strategy, one should have a strong understanding of both systems science and the opioid crisis, as a lack of knowledge in either area may lead to unsuccessful results.

The experience of building the models for this dissertation highlighted the importance of model-based reasoning, expert collaboration, and system deconstruction in generating valuable insights into complex issues, even when data are scarce and other traditional methods like statistical models cannot be employed. By collaborating with various Canadian organizations and agencies that have access to public health and social data, it may be possible to integrate this information into a national-level simulation model that examines different aspects of the opioid crisis. This partnership could bring together a diverse group of policymakers and provide greater assurance that the empirically grounded model implements explicitly in support of policy decision-making. Group model-building events with cross-sectoral stakeholders and people with lived experience of substance use are likely to offer particular value in supporting the model structure, scenario selection, parameter estimates of such integrative modeling. Further events drawing broad participation could also offer notable advantages for confidence building in the modeling, tapping tacit knowledge of empirical patterns by participants, refining scenario definitions, and identifying important modeling gaps.


6.5 Conclusions

In conclusion, this dissertation provides valuable insights into the challenges of modeling complex public health problems, and the potential to inform policy decisions using simulation modeling alone and in concert with machine learning methods. Specifically, it demonstrates the use of agent-based modeling, as a powerful systems science tool, to explore and understand the complexities of the opioid crisis. By incorporating individual-level data and social and environmental factors, these agent-based models can capture the highly connected conditions surrounding of opioid use and misuse at the individual and population levels. This allows for a more detailed representation of the opioid crisis, enabling the exploration of non-linear relationships between different components of the problem, analysis of policy interventions' effectiveness, and identification of potential unintended consequences of different actions.

The chapter on the simulation of opioid use among youth during and after the COVID-19 pandemic makes a valuable contribution to the field of public health by offering a deeper understanding of the complex dynamics that may lead to increased opioid use among youth following in-person school closures, and by assessing the possible efficacy of various interventions. Theories of opinion dynamics are integrated into the agent-based model to provide a stylized characterization of the decision-making processes of youth regarding opioid use and to simulate how youth opinions change over time and how these changes affect the overall opioid use of the group. Ultimately, this chapter provides insights into how different interventions influence the opioid use of youth during and after in-person school closures.

The dissertation chapter with a specific focus on the impact of prescribing practices creates a conceptual model and uses it to develop an agent-based model that simulates the actions and interactions of patients who have taken prescription opioids. The model is used to identify key interventions and evaluate their potential impact, as well as to explore the potential unintended consequences of various policy options. Another important contribution of this dissertation chapter is the incorporation of the machine learning technique of HMM into the simulation model to identify patterns in data and make predictions about possible underlying states. The integration of machine learning techniques into the simulation model enables a more effective estimation of the impact of different policy interventions throughout a patient's life. By exploring different hypothetical questions about the underlying mechanisms of prescription opioid use and misuse, this model can aid in decision-making and enhance understanding of the potential consequences of various policies related to prescription opioids.

The final study of this dissertation examines the impact of varying levels of take-home doses of opioid agonist therapy on treatment retention. By simulating the option of obtaining naloxone within the community and encouraging interactions among individuals receiving opioid agonist therapy, this model sheds light on the tradeoffs confronting healthcare providers and health systems in terms of guidelines governing use and extension of take-home doses. Such information can ultimately help reduce potential unintended consequences of these interventions.
In brief, this dissertation demonstrates its significance by providing a deeper understanding of the complexities of modeling public health issues and the value of using cutting-edge modeling and simulation techniques and incorporating machine learning techniques into the simulation model to test explanatory hypotheses about the underlying mechanisms of the opioid crisis and inform policy decisions related to it.
REFERENCES


[61] Canadian Institute for Health Information. Opioid prescribing in Canada: how are practices changing?, 2019.


Appendix A

Glossary of Systems Science Terms

System: A set of interacting or interdependent components that form an integrated whole. Systems can be characterized by boundaries, inputs, and outputs.

Boundary: The delineation between a system and its external environment.

Complexity: The intricate and non-linear behavior that emerges from the interactions and relationships among the components of a system.

Complex system: A system that is made up of an – often large – number of interconnected components whose behavior cannot be understood by looking at its individual parts in isolation.

Systems science: An interdisciplinary field that involves the integration of knowledge and methods from multiple disciplines to understand different systems by analyzing their emergent properties, feedback loops, adaptations, delays, boundaries, couplings, and self-organizing processes, and non-linearities.

Complexity theory: A specific branch or subset of systems science that deals with complex systems. It delves into the inherent complexity and emergence observed in complex systems, investigating the patterns, dynamics, and behaviors that arise from the interactions between components.

Feedback loops: A reciprocal process whereby a change in a system triggers a cascading set of subsequent changes that loop back to amplify or push back against that original change. Positive feedback amplifies changes, while negative feedback dampens changes.

Delays: Lags in a system that slow down the effects of interactions.

Tipping point: A critical threshold that, when crossed, leads to large and often irreversible changes in a system.

Holism: An approach that emphasizes understanding a system as a whole, rather than just the individual components, in accordance with the observation that, for a complex system, “the whole can be greater than the sum of its parts”.

Emergence: The spontaneous appearance of new properties or behaviors in a complex system at a meso- or macro-level, resulting from the interactions between its micro-level components, rather than being predetermined by any component or imposed by external forces. Examples of common emergent phenomena include traffic jams, the rise and fall of the infected population in an epidemic, population cycles in ecosystems, and herd-immunity for vaccine-preventable childhood infections.

Self-organization: A dynamical autonomous adaptive process in which systems acquire and maintain order structure, without external control.

Nonlinearity in Behavior: Behavior of a system in which the change in a system’s behavior does not depend proportionally on its state, or which exhibits nonlinear interactivity. Such relationships can lead to chaotic behavior in which small differences in a situation can lead to markedly different outcomes, self-organisation, and non-additive effects of interventions.

Nonlinear interactivity: Interactions in a system that are not directly proportional to inputs.
**Local contextual dependence:** The concept that the behavior or characteristics of a component within a system are influenced by the immediate context or conditions surrounding it.

**Reciprocal causality:** A situation where two or more variables have a mutual cause-and-effect relationship with each other.

**Path dependence:** Also known as Lock-in effects, a situation where the current state or outcome of a system is heavily influenced by past historical circumstances and becomes difficult to change, even if an alternative option might be more efficient or desirable in the long run.

**Adaptation:** The ability of a complex system to adjust to changes in its environment. Adaptation often occurs through feedback loops that sense changes in the environment and prompt adjustments and influence the system towards a different response.

**Coupling:** The degree of interdependence between components in a system. Tightly coupled systems have strong interactions and dependencies between components, while loosely coupled systems have weaker interactions and can operate more independently.

**Causal loop diagram:** A visualization tool to map the feedback structure of a system. Causal loop diagrams consist of variables with clear directionality connected by arrows – each associated with clear polarities (+ vs. -) – denoting the causal influences between variables. The polarities associated with pathways (including loops) are dictated by the product of the polarity of the arrows by which it is composed. Balancing loops indicate negative feedback, while reinforcing loops indicate positive feedback.

**Generative sufficiency:** The ability of a model or system to generate – often as emergent behavior – an adequately wide range of outputs or behaviors to achieve its goals or objectives.

**Leverage point:** A place in a system’s structure where a solution can be applied, characterized as low leverage if a small change force produces a small change in system behavior, and high leverage if a small change force produces a large change in system behavior.
Appendix B

Glossary of Drug Related Terms

**Drug:** Any substance (other than food) that is used to prevent, diagnose, treat, or relieve symptoms of a physical or psychological disease or abnormal condition.

**Opioid:** A family of drugs that act by attaching to endogenous mu, kappa and delta receptors in the brain and share a common set of clinical effects, including analgesia, sedation, constipation, and respiratory depression.

Opioids fall into four main categories:

1. Endogenous opioids (e.g., endorphins), which occur naturally in the body
2. Opiates, consisting of opium alkaloids (e.g., morphine and codeine) which are isolated from the opium poppy (*Papaver somniferum*).
3. Semi-synthetic opioids (e.g., heroin and oxycodone), which are modified forms of opium alkaloids.
4. Fully synthetic opioids (e.g., methadone, fentanyl), which have similar properties and effects as the alkaloids and semi-synthetics, but are completely man-made.

**Nonmedical prescription opioid use:** Use of prescription opioids without a prescription for a non-medical purpose such as altering one’s state of consciousness, (e.g., “achieving a high or euphoric feeling”).

**Acute Withdrawal:** A phase of physical discomfort produced by abrupt cessation of a drug.

**Opioid use disorder:** A condition in which individuals continue to use opioids despite experiencing harmful effects. The severity of the disorder can range from mild, with fewer symptoms, to severe, with more severe symptoms. Moderate to severe opioid use disorder is sometimes referred to as dependence or addiction, and commonly involves disruption of effective functioning in day-to-day life.

**Dose:** An amount of a medication that a patient takes at one specific time.

**Pain management plan:** A comprehensive approach aimed at helping individuals with chronic (long-lasting) pain to reduce their pain, improve their physical and emotional well-being, and enhance their overall quality of life.

**Legitimate Medical Purpose:** A therapeutic treatment regimen or program generally recognized and accepted in the field of medical science as being safe and effective in the diagnosis, treatment, correction or alleviation of the specific medical condition of the patient under all relevant circumstances.

**Prescription Drug Monitoring Program:** An electronic database used by prescribers, pharmacies and law enforcement to track particular prescription medications.

**Overdose:** An accidental, intentional, or unknown manner of poisoning occurring when a person uses enough of a drug to produce a life-threatening reaction.

**Tolerance:** A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more opioid effects over time, thus requiring a greater dose to achieve the same effect.

**Physical dependence:** A state which is characterized by the symptoms of tolerance and in which acute withdrawal symptoms would be triggered by abrupt cessation. It is possible to have a physical dependence without being addicted.
Addiction: A state characterized by an inability to stop using a substance or engaging in a behaviour, even though it may cause psychological or physical harm.

Nonadherence: The failure or refusal of patients to take medications as prescribed by their healthcare providers.

Abuse: Any use of an illegal drug (e.g., heroin), or the intentional self-administration of a medication (e.g., methadone) for a non-medical purpose such as altering one’s state of consciousness, (e.g., “achieving a high or euphoric feeling”).

Misuse: The use of an opioid in ways other than those intended by the prescribing physician.

Prescription opioid overuse: The use of prescription opioid in excessive amounts for other purpose than those for which they are meant to be used by a healthcare provider.

Prescription opioid underuse: The act of filling a prescription for opioids but taking them in fewer doses than intended or prescribed by a healthcare provider.

Street opioids: Street-obtained opioids which includes the medical opioids that are diverted (e.g., oxycodone) or produced illegally (e.g., fentanyl) and illegal opioid drugs (e.g., heroin).

Opioid agonist therapy (OAT): A treatment for addiction to opioid drugs which involves administration of the opioid agonists methadone (Methadose) or buprenorphine/naloxone (with Suboxone, Zubsolv and other trade names). The following terms are defined as they related to opioid agonist therapy:

Treatment retention: Continued participation in Opioid agonist therapy for its full duration without interruption or discontinuation, and without experiencing any opioid-related harm.

Interruption of therapy: The temporary cessation of participation in opioid agonist therapy for a short period of time.

Discontinuation of therapy: The persistent cessation of participation in opioid agonist therapy without returning to it for a prolonged time.

Opioid-related harm: The experience of opioid overdose, opioid use disorders, or any other harmful effects related to opioid use.

Take-home doses: Additional doses of medication provided to patients to use at home over a period of days.

Methadone: A long-acting synthetic opioid agonist medication that can prevent withdrawal symptoms and reduce craving in an opioid-addicted individual.

Buprenorphine/Naloxone: A long-acting semi-synthetic opioid agonist medication as a safer option than methadone for preventing withdrawal symptoms and reduce craving in an opioid-addicted individual. Sold under the different trade names, including Suboxone and Zubsolv.

Naloxone: A fast-acting opioid antagonist used to temporarily reverse the effects of opioid overdoses by displacing opioids from opioid receptors and binding to those receptors instead. It is available in injectable (naloxone hydrochloride) or nasal spray formulations, including under the NARCAN trade name.

A list of prescription opioid medications was identified on toxicology (including but not limited to): Methadone, Hydrocodone, Oxycodone, Morphine, Propoxyphene, Fentanyl, Oxymorphone, Codeine,
Tramadol, Hydromorphone, acetylmorphine, Meperidine, Dihydrocodeine, Pentazocine, Dihydrocodone, Hydrocodeine.