



Modelling Substance Abuse in Botswana in Presence of Multiple Amelioration Stages and Outpatient Rehabilitation, Optimal Control and Fractional-Order Dynamics

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Declaration

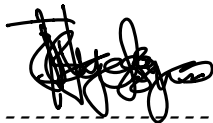
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Abstract

Substance abuse in Botswana is a growing problem with a variety of drugs being abused including cocaine, heroin, methamphetamine, marijuana and alcohol among others. At the front line of attempting to address the drug abuse problem is the Botswana Substance Abuse and Support Network (BoSASNet) which operates outpatient rehabilitation and support services that constitute its clinical programme. Due to the criminalisation and stigma associated with drug use and dealing in drugs, the number of individuals who seek rehabilitation from BoSASNet is believed to be much lower than the actual number of drug users who need the service. We developed mathematical models to; analyse the dynamics of substance abuse in Botswana, optimal control of substance in Botswana and fractional order model of substance abuse in Botswana to account for dependence of future values of drug users on the present and previous states. In this study, we derived three basic reproduction numbers $\mathcal{R}_0$, $\mathcal{R}_0^{OP}$ and $\mathcal{R}_0^{FDE}$ where $\mathcal{R}_0$ is for the model with multiple amelioration stages and out-patient rehabilitation, $\mathcal{R}_0^{OP}$ is for optimal control model and $\mathcal{R}_0^{FDE}$ is for the fractional-order model. The developed model has a globally asymptotically stable drug free equilibrium when the drug use threshold is less than unity. Sensitivity analysis of the parameters to the model output was carried out using the Latin hypercube Sampling scheme. Our results show that, the parameters with the highest positive partial rank correlation coefficients (PRCCs) are parameters related to contact between potential drug users and individuals using drugs. The parameters related to amelioration processes, quitting and rehabilitation were observed to have the highest negative PRCCs. Therefore, if the processes described by parameters with negative PRCCs are enhanced, it increases the likelihood of containing the drug epidemic. We recommend embarking on inpatient rehabilitation as this prevents contact between drug users in treatment and susceptible individuals reducing initiations, and accelerating quitting due to reduced accesses to substances. Our results in the optimal control model show that; if we implement the controls on the susceptible population, light drug users and accelerate the quitting rate from rehabilitation, then drug use can be contained. Our assessment in fractional order model shows that, if the contact rate is reduced at a very high fractional order value, then the progression rate of drug users can be reduced/contained. A high fractional-order of the value 1 predicts high peaks of the drug users in the short term but low values in the long term dynamics. The reverse is observed for reduced fractional-orders.

Keywords: Substance abuse; Rehabilitation; Sensitivity Analysis; Optimal Control; Fractional-order model

Dedications

*To God for giving me the wisdom and knowledge to be able to complete this thesis, my late mom Evelyn Gasebonno **May your soul rest in eternal peace**, my grandmother Tshoganetso Gasebonno, my brother and sister Kitso and Gaone Gasebonno and the rest of my family.*

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Chapter 1

Introduction

1.1 Substance Abuse

Substance abuse continues to be at the heart of many negative behaviours including but not limited to; crime (involving possession, use and distribution/sale of drugs), traffic offences (mainly driving while intoxicated) and risky behaviour that leads to intoxicated individuals engaging in risky sexual behaviour and offences such as rape/defilements [1, 2].

The resulting risky behaviour related with alcohol and drug abuse has led to high government expenditure of \$252 per capita on health [3] ranging from support for various government departments such as the health service sensitising the general population about the dangers of alcohol and drug abuse, the traffic department sensitising the public about the dangers of driving while intoxicated as well as responding to accidents associated with drunk driving and other offences related to drug abuse.

The major abused substances in Botswana include Alcohol (accounting for 95% of all drugs usage), followed by Dagga (Pot) at 4% and other drugs including ecstasy and glue accounting for the remaining 1% [4]. Dagga is the most used drug by students from junior schools and senior schools. The other predominant abused drug among students is CAT (methcathinone) which is mostly used by senior school and tertiary students [5].

One of the major problems to the high number of substance abuse cases in Botswana is that teachers are lacking the necessary skills and emotional guidance in handling substance abuse related cases. In schools, substance abuse leads to serious problems such as physical injury (through fighting), and poor academic performance. Alcohol is mostly abused by youth compared to adults in Botswana. Substance abuse may also lead to one person indulging

in risky sexual behaviour. A detailed association between consumption of alcohol and indulgence in risky sexual behaviours is given in [6]. A number of studies in sub-Saharan Africa have shown a clear correlation between drug use and risky sexual behaviour, such as indulging in multiple sexual partners, unprotected sex and commercial sex [7]. People indulge in substance abuse and drink alcohol for various reasons such as relieving stress, having fun, to remove shyness [8] among others. Substance abuse has brought up a major worry worldwide and it leads to a high increase in the number of death rates. Alcohol abuse leads to many different infections that are harmful to the body system such as respiratory diseases, cancer and HIV infection [9, 10].

Some organisations such as Botswana Substance Abuse Support Network (BOSASNet) [11] have been at the forefront of educating and sensitising the general public about the dangers of dependence and abuse of drugs/substances. BoSASNet's main modes of relaying information have been through messages on strategically placed Billboards, brochures, through mass media channels including radio stations, television, newspapers and printed publications among others [11]. Although these channels are designed to reach a greater community, we believe that a sizeable section of the population may not be reached and needs community based programmes to meet these risky groups from within their localities.

Psychoactive substance¹ use may lead to mental and psychosocial problems, job loss and difficulty in doing studies [14]. The psychoactive substance abusers always have a strong craving to repeat the dose [15]. Between the year 2010 and 2014 Botswana had 2985 cases on dagga weighing 7364 kilograms which resulted in the arresting of 4177 Batswana and 198 foreigners, and recorded 73 cocaine cases. Women have the highest number compared to men in dealing with drugs [14].

1.2 Major Substances abused in Botswana

1.2.1 Alcohol

Alcohol abuse could be a behaviour pattern that has issues of unregulated drinking, being passionate about alcohol, continued use of alcohol yet even drinking once can cause issues, having to drink a lot to urge a similar impact, or having withdrawal symptoms once not drinking [16]. Harmful use of alcohol creates serious public health consequences and is regarded as one of the pivotal risk factors for public health globally. Substance use exposes

¹Psychoactive substance is a chemical substance that alters the mental process resulting in alteration in perception, mood, consciousness, cognition, and or behaviour [12, 13].

adolescents to the risk of unwanted pregnancies, teenage pregnancy, and a high risk of getting sexually transmitted infections among others. Substance and alcohol abuse also leads to deliberate and non-deliberate injuries, mental health problems, sexual and reproductive health problems, and HIV infections [17]. Sexual dysfunction may be caused by chronic and persistent use of alcohol which may result in too much stress and interpersonal difficulty which can worsen alcohol abuse. Sexual dysfunction may lead to the depressant due to the use of alcohol, alcohol-related malady or because of a mess of psychological forces associated with the alcohol use [18].

Botswana is tussling with a growing alcohol problem that is increasingly becoming onerous to the country's development [19].

1.2.2 Heroin

An illicit extremely addictive drug made of anodyne, a natural substance taken from the seed pod of various flower plants [20]. People use heroin differently; either by injecting, sniffing or smoking. On the other hand, some people choose to mix it with crack cocaine, which is normally called speedballing. Heroin use may lead to the brain's white matter deterioration, which may affect decision-making abilities, as well as the ability to act responsibility in stressful situations [20]. Botswana is used as a warehouse for the heroin that is being transited to Europe [21] by some drug kingpins. This drug contributes to pain relief, limb heaviness and shallow breathing. This also destroys the kidneys and influences the lining of the heart and the valves [20, 22].

1.3 Project Motivation and Objectives of the Study

1.3.1 Motivation

In Botswana, substance abuse is a major challenge. As shown by BOSASNet [4], alcohol is the main abused substance in Botswana. There are many strategies to fight substance abuse and one of the strategy is using rehabilitation. Rehabilitation may be in two forms: in-patient rehabilitation and out-patient rehabilitation. The recovery process from substance abuse is a slow and carefully planned process. Otherwise, drug users have a higher likelihood of relapsing. The control process of drug use problem also ought to be properly studied as to effectively minimize the number of drug users whereas at the same time minimize the cost

of implementing controls. More still, there is always dependence of future values of cases on present and previous states. This condition ought to be studied.

1.3.2 Aims and Objectives

The main aim of this research is to model the dynamics of substance abuse. More specifically, we aim to build a useful mathematical models incorporating important macro-epidemiological parameters impacting the spread of the epidemic and possible control strategies. The specific objectives include

- Formulate a model incorporating multiple amelioration stages, drug addiction, drug dependence states and out-patient rehabilitation.
- Carry out mathematical analysis for the multiple amelioration stages and out-patient rehabilitation, to understand how the model behaves based on the equilibrium points, reproduction number and stability analysis.
- Use the optimal control approach to determine the possibility of minimizing the drug use problem and at the same time minimize the cost of implementation.
- Analyse the effect of dependence of future magnitude of drug use problem on the current and previous states.

1.4 Outline of the Thesis

The rest of the thesis is organized as follows. In Chapter 2, we review some of the studies done on modelling substance abuse. In Chapter 3, the model that incorporates multiple amelioration stages, drug addiction and rehabilitation is formulated and analysed. The model equilibrium points are determined and their stability analysis presented. Furthermore, the model basic reproduction number is calculated and used in the analysis. Finally in this chapter, numerical results as well sensitivity analysis results are presented and discussed. In Chapter 4, we reduced the model in Chapter 3 and look at rehabilitation in the form of in-patient and out-patient rehabilitation, and include the controls to check how substance abuse can be minimized. In Chapter 5, we develop a model based on fractional order Caputo-Fabrizio type to study substance dynamics abuse and lastly, in Chapter 6, we present the general discussion and conclusion to the thesis as well as recommendation for further research.

Chapter 2

Literature review

2.1 Substance Abuse Models

In 2006, White and Comiskey [23] modeled heroin epidemics, and looked at the impact of treatment using a system of Ordinary Differential Equations. They used the same approach used for a susceptible-infectious disease model, where they considered the susceptible individuals, heroin users on treatment and heroin users not on treatment as their classes. Their aim was to find a common model that identifies parameters of interest in the future-work. Nyabadza and Hove-Musekwa in 2010 [24], modeled substance abuse in a South African Province, and their model was an extension to the model by White and Comiskey [23]. In the model in [24], Nyabadza and Hove-Musekwa included the compartment of recovery class (quitters) and they divided the drug users in two compartments, the light drug users and the hard drug users. They also indicated that recovered drug users (quitters) can relapse to drug use but would only end up as hard drug users due to associated withdrawal symptoms.

In 2012 Njagarah and Nyabadza [25], developed a model examining the impact of rehabilitation, amelioration and relapse on the prevalence of drug epidemics. Their aim was to study the effect of rehabilitation, amelioration with just two stages between light users, heavy users, and relapse in drug epidemics. The authors also studied the global stability of the drug epidemic model constructed. They indicated that amelioration in presence of quitting for light users can reduce the prevalence of substance abuse. They also found out that prevention and rehabilitation plays a vital role in the reduction of drug epidemics.

Njagarah and Nyabadza [26], modelled the role of drug barons on the prevalence of drug

epidemics. Their aim was to establish the possible effects of drug lords on the dynamics of drug epidemics. They found out that stepping-up the law enforcement could lead to the reduction of the prevalence of substance abuse, which leads to the reduction of probability of susceptible population being initiated into using drugs. In 2017 Nyabadza and Coetzee modeled drug abuse and drug related crimes in the Western Cape of South Africa[27] using a systems approach. In their study, they investigated three changes within the system: They assumed that if cases that make it to court and have successful convictions are double for the next five years; the rate at which convicted individuals who are sent to rehabilitation centres is doubled over the next five years, then percentage of individuals that relapse back into substance abuse and drug related crime over the same period will be reduced. They found their results and findings as an informative tool on the process to improve and quantify the understanding of dynamics of substance abuse and drug-related crime syndemic over time.

Kanyaa *et al* 2018 [2], developed a mathematical model of substance abuse by commercial drivers. In their model they divided commercial drivers into four compartments, they considered the susceptible, all commercial drivers who use substance of any form are grouped under drug users, all drivers who abuse drug of any form and those who stopped using drugs either by abstinence or through rehabilitation. They determine a drug threshold and their model analysis was based on the parameters of threshold. They found out that an increase in contact rate leads to an increase in the population of drug users.

Mushanyu *et al* [28] developed a mathematical model that looks into both inpatient and outpatient forms of rehabilitation to study the dynamics of methamphetamine abuse in Cape Town South Africa. Their aim was to find suitable trends of the two forms of rehabilitation. They derived the reproduction number and used it to investigate the stability of equilibrium states and prevalence of methamphetamine abuse. They found out that the methamphetamine free equilibrium point is globally asymptotically stable whenever the reproduction number is less than 1. They also found that in-patient rehabilitation has more prospects of increasing chances of methamphetamine addicted users' recovery.

B. N. Kim, *et al* [29], developed an optimal control model for minimizing the deliberate self-harm epidemic. Their model is an extension of a mathematical model for self-harm epidemic and analysed it [30], by introducing time-dependent controls and an optimal control problem in-order to know cost-effective strategies to reduce deliberate self-harm. They found out that the long term success of optimal control is dependent on the implementation cost. They found out that if the costs are very high, then the controls can be used for a short term, and

they may fail on the long run. They also stated that the control strategies should be implemented early to help the fewer number of addicted individuals.

In 2018, Abderrahim Labzai *et al* [31], developed a discrete time model to study the optimal control dynamics of smokers and used a saturated incidence rate. They added 2 classes of light smokers who quit permanently and heavy smokers who die due to diseases associated with excessive smoking to the model, a case which was not considered by most previous researchers. They used three control strategies which are awareness programs through media and education, treatment and psychological support with follow-up to come up with the best strategy to minimise the number of smokers. Jun and Mingju [32], developed a model analysing drug transmission with family education and public health education, and their main aim was to try to find a successful proposal for drug transmission control. They found out that both the family and public health education can have an impact on the spread of drug use.

The typical description of evolution of populations in epidemiological models uses differential equations, with the derivatives being of integer order [33]. Replacing the integer order by fractional derivative, a memory kernel appears, which makes the state of the system dependent on past states (memory) [33, 34]. Fractional order derivatives are mostly suitable for modelling systems that are dependent on memory. The fractional order derivative has an advantageous approach which has been used to study the behaviour of diseases because it is a generalization of the integer-order derivative. The fractional-order derivatives has a nonlocal (global) nature while the integer derivative are local. The use of fractional-order derivatives can help in the reduction of errors occurring from the neglected parameters in modelling real life problems [35].

Dokuyucu [36], used the Caputo-Fabrizio fractional order derivative and integral operators to present the existence and uniqueness solutions of an alcoholism model which was developed by Huo and Zhang [37] who investigated alcoholism using an integer order model, and Gómez-Aguilar, [38] who examined an alcoholism model for existence and uniqueness of solutions using the Atangana-Baleanu fractional derivative. The main aim of the author was to show that the Caputo-Fabrizio fractional derivative and integral operators are useful in assessing the effect of memory of the system on the future numbers of drug users.

All models discussed in this chapter help us to have a better understanding on modelling the dynamics of substance abuse in general, apply optimal control to the model and also under-

stand the concepts of fractional-order derivatives in mathematical modelling. We thus propose a mathematical model for substance epidemic in which multiple amelioration, relapse and out patient rehabilitation are considered with the aim studying the global dynamics of the model and the effects of multiple amelioration processes on the dynamics. We propose a drug epidemic model in which initiation, light use, heavy use, addiction, rehabilitation, quitting, amelioration and relapse are considered. We use a suitable Lyapunov function to show suitable conditions that ensure global stability equilibria, the drug free equilibrium. The initial model is then reduced by combining all compartments of light users in one compartment of light drugs users, and then incorporating the influence of both in-patient and out-patient rehabilitation with possible controls. Lastly, we use the reduced model without controls and formulate a fractional-order model based on Caputo-Fabrizio fractional derivative to study the influence of previous and current states on the future values of the drug users.

Chapter 3

Model with Amelioration and Out-Patient Rehabilitation

3.1 Model formulation and analysis

We present a mathematical model used to study the dynamics of substance abuse inspired by trends in Botswana. The general population is classified into subgroups where the individuals within a subgroup/compartment are indistinguishable and homogeneously mix. Owing to the uncertainty in the initiation and general dynamics of the substance abuse in Botswana, we propose a system that analyses the dynamics of substance abuse in a heterogeneous population. The population N is classified into 8 subcategories; the susceptible population (S), light drug users (L_1), (L_2), and (L_3) heavy drug, (H), addicted drug users, (A), drug users in rehabilitation, (R), drug quitters, (Q). The total population at any time t is given by

$$N(t) = S(t) + L_1(t) + L_2(t) + L_3(t) + H(t) + A(t) + R(t) + Q(t)$$

Since as drug users get in contact with susceptible individuals, with their initiation rate not proportionally increased with an increase in the total population, the force of infection is assumed to follow standard incidence. The model assumes that individuals join the susceptible population at the rate π either through immigration or after reaching a substance abusing age. The susceptible individuals (S), are naive to getting initiated into drug abuse and have never used drugs before. Once an individual starts using drugs and goes through the various stages, they can never be susceptible again but quitters. As in our model, we focus on out-patient rehabilitation, and the individuals who quit, either do so permanently or relapse to light users, L_1 . Every sub-population can be reduced due to the natural mor-

tality at a rate μ except for heavy drug users H , and addicted drug users (A), who suffer additional substance abuse-related deaths at rates, δ_1 and δ_2 respectively. Once initiated, the individuals start by consuming small amounts of substances as they progress through classes of light drug users L_1 . With continued usage of substances, the once light substance-using individuals progress to heavy drug users H . Continued usage of substances may lead to addiction where individuals may only be able to reduce drug usage after intervention through rehabilitation, a case in which they are classified to be in the Rehabilitation class (R). Rehabilitation may be inpatient or outpatient. However, in the case of Botswana rehabilitation is predominantly outpatient. This means that individuals who are in rehabilitation are still able to access their preferred substances as well as meet with potential drug using initiates, thereby contributing to the initiation of new substance users. Substance users in rehabilitation can relapse becoming heavy users, or light users stage 3 (L_3) or quit. Users who take rehabilitation seriously often quit using substance permanently or some may quit for a few weeks or months, and then revert to light substance users. We assume that the susceptible population is led to substance abuse by active substance users at the rate of β . Thus, the force of substance abuse initiation is given as

$$\Lambda = \frac{\beta(L_1 + \eta_1 L_2 + \eta_2 L_3 + \eta_3 H + \eta_4 A + \eta_5 R)}{N},$$

where $\eta_i, i = 1, 2, 3, 4, 5$ are the rates at which drug users in categories L_2, L_3, H, A and R recruit new drug users relative to drug users in compartment L_1 .

The schematic diagram of the progression of individuals in different compartments is given in Figure 3.1,

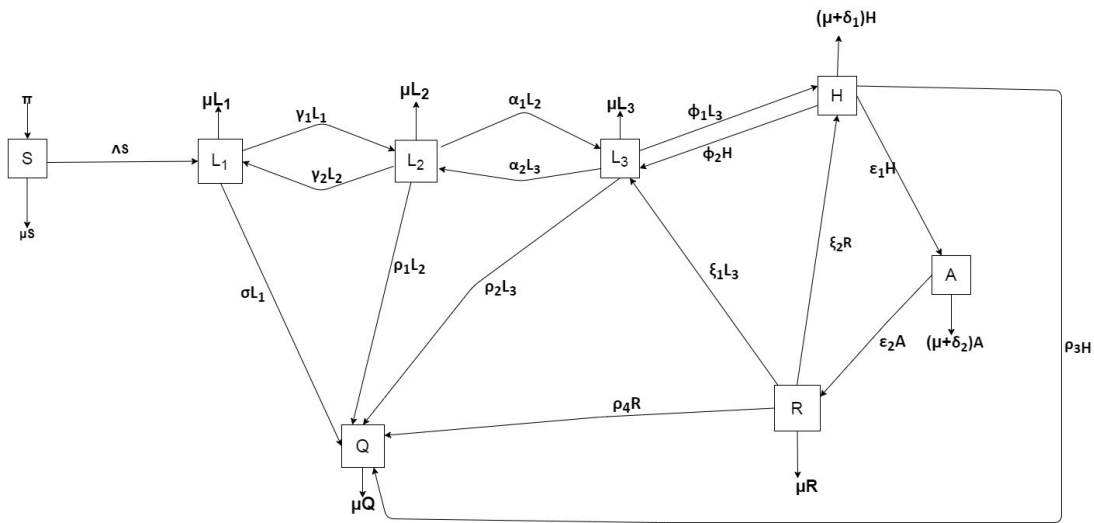


Figure 3.1: Sketch diagram of the model of drug abuse progression, involving amelioration, addiction, drug dependence, rehabilitation and quitting.

The description of state variables is given in Table 3.1 and the description of parameter values used is given in Table 3.2. The ordinary differential equations that represent the compartmental model are

$$\frac{dS}{dt} = \pi - \Lambda S - \mu S, \quad (3.1a)$$

$$\frac{dL_1}{dt} = \Lambda S + \gamma_2 L_2 - D_1 L_1, \quad (3.1b)$$

$$\frac{dL_2}{dt} = \gamma_1 L_1 + \alpha_2 L_3 - D_2 L_2, \quad (3.1c)$$

$$\frac{dL_3}{dt} = \alpha_1 L_2 + \phi_2 H + \xi_1 R - D_3 L_3, \quad (3.1d)$$

$$\frac{dH}{dt} = \phi_1 L_3 + \xi_2 R - D_4 H, \quad (3.1e)$$

$$\frac{dA}{dt} = \varepsilon_1 H - D_5 A, \quad (3.1f)$$

$$\frac{dR}{dt} = \varepsilon_2 A - D_6 R, \quad (3.1g)$$

$$\frac{dQ}{dt} = \sigma L_1 + \rho_1 L_2 + \rho_2 L_3 + \rho_3 H + \rho_4 R - \mu Q, \quad (3.1h)$$

where $D_1 = \mu + \sigma + \gamma_1$, $D_2 = \alpha_1 + \mu + \rho_1$, $D_3 = \mu + \alpha_2 + \phi_1 + \rho_2$,
 $D_4 = \phi_2 + \rho_3 + \varepsilon_1 + \mu + \delta_1$, $D_5 = \mu + \delta_2 + \varepsilon_2$, $D_6 = \mu + \xi_1 + \xi_2 + \rho_4$.

Table 3.1: State Variables summary

State Variable	Description
S	Susceptible population
L_1	Users who take drugs in small quantities
L_2	Users who take drugs in small quantities but more compared to L_1
L_3	Users who take drugs in small quantities but more compared to L_1 and L_2
H	Heavy substance users
A	Users addicted to substances
R	Users in out-patient rehabilitation
Q	Individuals who quit using substances

Table 3.2: Symbols and description of parameters used in the model

parameter	Description
π	Recruitment rate into the susceptible population
β	Effective contact rate between drug users and susceptible individuals
μ	Natural mortality rate
η_1	Ability to initiate new drug user by L_2 relative to users in L_1
η_2	Ability to initiate new drug user by L_3 relative to users in L_1
η_3	Ability to initiate new drug user by H relative to users in L_1
η_4	Ability to initiate new drug user by A relative to users in L_1
η_5	Ability to initiate drug user in R relative to users in L_1
γ_1	Progression rate from L_1 to L_2
γ_2	Amelioration rate from L_2 to L_1
α_1	Progression rate from L_2 to L_3
α_2	Amelioration rate from L_3 to L_2
σ	Rate at which drug users in L_1 quit
ϕ_1	Progression rate from L_3 to H
ϕ_2	Amelioration rate from H to L_3
ρ_1	Rate at which drug users in L_2 quit
ρ_2	Rate at which drug users in L_3 quit
ρ_3	Rate at which drug users in H quit
ρ_4	Rate at which drug users under rehabilitation quit
δ_1	Additional mortality rate related to heavy drug usage
δ_2	Additional mortality rate resulting to addiction to drugs
ε_1	Rate at which drug users move from H to A
ε_2	Recruitment rate into rehabilitation
ξ_1	Rate at which users under rehabilitation revert to light using class L_3
ξ_2	Rate at which users under rehabilitation revert to H

3.2 Model Analysis

3.2.1 Positivity of Solution

Using the fact that the model monitors populations, it is paramount to ensure that all the state variables are non-negative and bounded at all times. To show that solutions of system (3.1) with non-negative initial conditions are non-negative for all $t > 0$, we consider lemma 3.2.1

Lemma 3.2.1. *Given that the system has non-negative initial conditions $S^0, L_1^0, L_2^0, L_3^0, H^0, A^0, R^0, Q^0$,*

then the solution set $(S, L_1, L_2, L_3, H, A, R, Q)$ is non-negative for $t > 0$.

Proof. Let

$$t^* = \sup\{t > 0 : S, L_1, L_2, L_3, H, A, R, Q > 0\} \in [0, t].$$

Then, for $t > 0$ it follows from equation (3.1a) that

$$\frac{dS}{dt} \geq -(\hat{\Lambda} + \mu)S, \quad \text{where} \quad \hat{\Lambda} = \limsup_{t \geq 0} \{\Lambda(t)\}.$$

The resulting inequality can be solved by separation of variables to obtain

$$S(t) \geq S^0 e^{-(\hat{\Lambda} + \mu)t}$$

and consequently

$$S(t^*) \geq S^0 e^{-(\hat{\Lambda} + \mu)t^*} \geq 0.$$

From the equation (3.1b), we have

$$\begin{aligned} \frac{dL_1}{dt} &= \Lambda S + \gamma_2 L_2 - D_1 L_1, \\ &\geq -D_1 L_1, \end{aligned}$$

whose solution is obtained by separation of variables and integrating with respect to corresponding variables to obtain

$$L_1(t^*) \geq L_1^0 e^{-D_1 t^*} > 0.$$

The same method can be used to show that

$$\begin{cases} L_2(t^*) \geq L_2^0 e^{-D_2 t^*} > 0, \\ L_3(t^*) \geq L_3^0 e^{-D_3 t^*} > 0, \\ H(t^*) \geq H^0 e^{-D_4 t^*} > 0, \\ A(t^*) \geq A^0 e^{-D_5 t^*} > 0, \\ R(t^*) \geq R^0 e^{-D_6 t^*} > 0, \\ Q(t^*) \geq Q^0 e^{-\mu t^*} > 0. \end{cases}$$

for all $t^* > 0$. We note that all the state variables are non-negative. This completes the proof. $\square$

Lemma 3.2.2. For Ω defined as the feasible region defined by

$$\Omega = \left\{ (S(t), L_1(t), L_2(t), L_3(t), H(t), A(t), R(t), Q(t)) \in \mathbb{R}_+^8 \mid 0 \leq N \leq \frac{\pi}{\mu} \right\},$$

with the initial conditions $S^0 > 0$, $L_1^0 \geq 0$, $L_2^0 \geq 0$, $L_3^0 \geq 0$, $H^0 \geq 0$, $A^0 \geq 0$, $R^0 \geq 0$, and $Q^0 \geq 0$, then the solutions to system (3.1) are positive for all $t > 0$.

Proof. The model gives us a non-constant total population. Thus, the equation of the change in population is:

$$\begin{aligned} \frac{dN}{dt} &= \pi - \mu N - \alpha_2 L_3 - (\phi_2 + \delta_1)H - \delta_2 A \\ &\leq \pi - \mu N. \end{aligned} \quad (3.2)$$

The equation (3.2) is solved using a suitable integrating factor to obtain

$$N \leq \frac{\pi}{\mu} + \left(N^0 - \frac{\pi}{\mu} \right) e^{-\mu t}, \quad (3.3)$$

where $N(0) = N^0$. From equation (3.3) above, we can see that as $t \rightarrow \infty$, then $N(t) \rightarrow \frac{\pi}{\mu}$. If $N^0 \leq \frac{\pi}{\mu}$, then $\lim_{t \rightarrow \infty} N(t) = \frac{\pi}{\mu}$. Then, it can be easily observed that $\frac{\pi}{\mu}$ is the upper bound of N . Conversely, if $N^0 > \frac{\pi}{\mu}$, then N will decrease to $\frac{\pi}{\mu}$ as $t \rightarrow \infty$. That is, if $N^0 > \frac{\pi}{\mu}$, then the solution $\{S(t), L_1(t), L_2(t), L_3(t), H(t), A(t), R(t), Q(t)\}$ is in, or approaches Ω asymptotically. Therefore, Ω is positively invariant. $\square$

3.2.2 Drug Free Equilibrium

A drug free equilibrium in the model is given by

$$\mathbb{E}_0 := (S^*, L_1^*, L_2^*, L_3^*, H^*, A^*, R^*, Q^*) = \left(\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0, 0 \right).$$

To analyse the existence of equilibrium points, we ought to use the reproduction number evaluated in terms of the model parameters. This threshold value (reproduction number) is also vital in making conclusions about the stability of the obtained equilibrium points.

3.2.3 The Basic Reproduction Number

To obtain the reproduction number $\mathcal{R}_0$ of the model (3.1) we used the next generation matrix method described in [39]. We use the approach in [39] and adopt the same matrix notations for new initiations, and transfer terms. The matrices of rate appearance of new drug users as well as the rates of transfer of terms in and out of compartments are respectively given by

$$\mathcal{F} = \begin{pmatrix} \frac{\beta(L_1 + \eta_1 L_2 + \eta_2 L_3 + \eta_3 H + \eta_4 A + \eta_5 R)}{N} \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \text{ and } \mathcal{V} = \begin{pmatrix} -\gamma_2 L_2 + D_1 L_1 \\ -\gamma_1 L_1 - \alpha_2 L_3 + D_2 L_2 \\ -\alpha_1 L_2 - \phi_2 H_D - \xi_1 R + D_3 L_3 \\ -\phi_1 L_3 - \xi_2 R + D_4 H \\ -\varepsilon_1 H_D + D_5 A \\ -\varepsilon_2 A + D_6 R \end{pmatrix}.$$

The Jacobi of new initiations and transfer terms evaluated at the drug free equilibrium are respectively given as:

$$F = \begin{pmatrix} \beta & \beta\eta_1 & \beta\eta_2 & \beta\eta_3 & \beta\eta_4 & \beta\eta_5 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \text{ and } V = \begin{pmatrix} D_1 & -\gamma_2 & 0 & 0 & 0 & 0 \\ -\gamma_1 & D_2 & -\alpha_2 & 0 & 0 & 0 \\ 0 & -\alpha_1 & D_3 & -\phi_2 & 0 & -\xi_1 \\ 0 & 0 & -\phi_1 & D_4 & 0 & \xi_2 \\ 0 & 0 & 0 & -\varepsilon_1 & D_5 & 0 \\ 0 & 0 & 0 & 0 & -\varepsilon_2 & D_6 \end{pmatrix}.$$

The basic reproduction number is given as the spectral radius of the next generation matrix FV^{-1} such that

$$\mathcal{R}_0 = \rho(FV^{-1}) = \mathcal{R}_{01} + \mathcal{R}_{02} + \mathcal{R}_{03} + \mathcal{R}_{04} + \mathcal{R}_{05} + \mathcal{R}_{06}$$

with

$$\begin{cases} \mathcal{R}_{01} &= \frac{\beta[1-(\Phi_2+\Phi_3+\Phi_4+\Phi_5)+\Phi_2\Phi_4]}{D_1[1-(\Phi_1+\Phi_2+\Phi_3+\Phi_4+\Phi_5)+\Phi_1(\Phi_4+\Phi_3+\Phi_5)+\Phi_2\Phi_4]}, \\ \mathcal{R}_{02} &= \frac{\beta\eta_1\gamma_1[1-(\Phi_3+\Phi_4+\Phi_5)]}{D_1D_2[1-(\Phi_1+\Phi_2+\Phi_3+\Phi_4+\Phi_5)+\Phi_1(\Phi_4+\Phi_3+\Phi_5)+\Phi_2\Phi_4]}, \\ \mathcal{R}_{03} &= \frac{\beta\eta_2\alpha_1\gamma_1(1-\Phi_4)}{D_1D_2D_3[1-(\Phi_1+\Phi_2+\Phi_3+\Phi_4+\Phi_5)+\Phi_1(\Phi_4+\Phi_3+\Phi_5)+\Phi_2\Phi_4]}, \\ \mathcal{R}_{04} &= \frac{\beta\eta_3\alpha_1\gamma_1\phi_1}{D_1D_2D_3D_4[1-(\Phi_1+\Phi_2+\Phi_3+\Phi_4+\Phi_5)+\Phi_1(\Phi_4+\Phi_3+\Phi_5)+\Phi_2\Phi_4]}, \\ \mathcal{R}_{05} &= \frac{\beta\eta_4\alpha_1\gamma_1\phi_1\varepsilon_1}{D_1D_2D_3D_4D_5[1-(\Phi_1+\Phi_2+\Phi_3+\Phi_4+\Phi_5)+\Phi_1(\Phi_4+\Phi_3+\Phi_5)+\Phi_2\Phi_4]}, \\ \mathcal{R}_{06} &= \frac{\beta\eta_5\alpha_1\gamma_1\varepsilon_1\varepsilon_2\phi_1}{D_1D_2D_3D_4D_5D_6[1-(\Phi_1+\Phi_2+\Phi_3+\Phi_4+\Phi_5)+\Phi_1(\Phi_4+\Phi_3+\Phi_5)+\Phi_2\Phi_4]}, \end{cases}$$

where $\Phi_1 = \frac{\gamma_1\gamma_2}{D_1D_2}$, $\Phi_2 = \frac{\alpha_1\alpha_2}{D_2D_3}$, $\Phi_3 = \frac{\phi_1\phi_2}{D_3D_4}$, $\Phi_4 = \frac{\varepsilon_1\varepsilon_2\xi_2}{D_4D_5D_6}$, $\Phi_5 = \frac{\varepsilon_1\varepsilon_2\xi_1\phi_1}{D_3D_4D_5D_6}$. The reproduction number $\mathcal{R}_0$ is made of six components indicating the contribution of the six different groups in the drug initiation process. The reproduction number in our case is defined as the average number of secondary drug users produced by one drug users in contact with the population naive (susceptible) to initiation into drug use. Our definition of $\mathcal{R}_0$ in the context of the

substance abuse model (3.1) is a direct translation from the definition of $\mathcal{R}_0$ for epidemic models given by Diekmann *et al* [40]. The term Φ_1 accounts for the proportion of drug users who move back and forth between compartments L_1 and L_2 ; Φ_2 , is the proportion of drug users who move back and forth between compartments L_2 and L_3 ; Φ_3 , the proportion of drug users who move back and forth between compartments L_3 and H , Φ_4 , the proportion of drug users who move within the loop of compartments H , A , and R ; Φ_5 , the proportion of drug users who move within the loop L_3 , H , A and R . We note that $1-\Phi_i$, for $i = 1,2,3,4,5$ accounts for the proportion of drug users who do not cycle within aforementioned respective loops.

In line with Theorem 2 in [39], determination of $\mathcal{R}_0$ by the next generation matrix method presumes local stability of the drug free equilibrium of the epidemiological model considered. We therefore, have the following theorem.

Theorem 3.2.1. *The drug-free steady state of model (3.1) is locally asymptotically stable whenever $\mathcal{R}_0 < 1$ and unstable otherwise.*

3.2.4 Global Stability of the DFE

To show global stability of the drug free equilibrium, we use the following theorem

Theorem 3.2.2. *The drug-free-steady state $\mathbb{E}_0$ of the model system (3.1) is globally asymptotically stable when $\mathcal{R}_0 < 1$ and unstable whenever $\mathcal{R}_0 > 1$.*

Proof. To prove the theorem 3.2.2, we use a candidate Lyapunov function V such that

$$V(S, L_1, L_2, L_3, H, A, R, Q) = a_1 L_1 + a_2 L_2 + a_3 L_3 + a_4 H + a_5 A + a_6 R$$

for some non-negative constants a_i , $i=1,2,...,6$. The derivative of the Lyapunov function is given by

$$\begin{aligned} \frac{dV}{dt} &= a_1 \frac{dL_1}{dt} + a_2 \frac{dL_2}{dt} + a_4 \frac{dH}{dt} + a_5 \frac{dA}{dt} + a_6 \frac{dR}{dt} \\ &= a_1 \left(\frac{\beta(L_1 + \eta_1 L_2 + \eta_2 L_3 + \eta_3 H + \eta_4 A + \eta_5 R)}{N} S + \gamma_2 L_2 - D_1 L_1 \right) + a_2 (\gamma_1 L_1 + \alpha_2 L_3 - D_2 L_2) \\ &\quad + a_3 (\alpha_1 L_2 + \phi_2 H + \xi_1 R - D_3 L_3) + a_4 (\phi_1 L_3 + \xi_2 R - D_4 H) + a_5 (\epsilon_1 H - D_5 A) + a_6 (\epsilon_2 A - D_6 R), \\ &\leq a_1 (\beta(L_1 + \eta_1 L_2 + \eta_2 L_3 + \eta_3 H + \eta_4 A + \eta_5 R) + \gamma_2 L_2 - D_1 L_1) + a_2 (\gamma_1 L_1 + \alpha_2 L_3 - D_2 L_2) \\ &\quad + a_3 (\alpha_1 L_2 + \phi_2 H + \xi_1 R - D_3 L_3) + a_4 (\phi_1 L_3 + \xi_2 R - D_4 H) + a_5 (\epsilon_1 H - D_5 A) + a_6 (\epsilon_2 A - D_6 R), \\ &= (a_1 \beta - a_1 D_1 + a_2 \gamma_1) L_1 + (a_1 \beta \eta_1 + a_1 \gamma_2 - a_2 D_2 + a_3 \alpha_1) L_2 + (a_1 \beta \eta_2 + a_2 \alpha_2 - a_3 D_3 + a_4 \phi_1) L_3 \\ &\quad + (a_1 \beta \eta_3 + a_3 \phi_2 - a_4 D_4 + a_5 \epsilon_1) H + (a_1 \beta \eta_4 - a_5 D_5 + a_6 \epsilon_2) A + (a_1 \beta \eta_5 + a_3 \xi_1 + a_3 \xi_2 - a_6 D_6). \end{aligned}$$

To determine the non-negative constants $a_i, i=1,2,...,6$, we now set the coefficients of the state variables L_2, L_3, H, A and R to zero and simultaneously solve the resultant equations to obtain

$$\begin{cases} a_1 &= D_2 D_3 D_4 D_5 D_6 (1 - \Phi_2 - \Phi_3 - \Phi_4 - \Phi_5 + \Phi_2 \Phi_4), \\ a_2 &= \beta \eta_1 D_3 D_4 D_5 D_6 (1 - \Phi_3 - \Phi_4 - \Phi_5) + \beta \eta_2 \alpha_1 D_4 D_5 D_6 (1 - \Phi_4) + \beta \eta_3 \alpha_1 D_5 D_6 \phi_1 + \beta \eta_4 \alpha_1 \varepsilon_1 D_6 \phi_1 \\ &\quad + \beta \eta_5 \alpha_1 \varepsilon_1 \varepsilon_2 \phi_1 + \gamma_2 D_3 D_4 D_5 D_6 (1 - \Phi_3 - \Phi_4 - \Phi_5), \\ a_3 &= \frac{1}{D_3 D_4 D_5 D_6 (1 - \Phi_3 - \Phi_4 - \Phi_5)} [a_1 (\beta \eta_2 D_4 D_5 D_6 (1 - \Phi_4) + \beta \eta_3 D_5 D_6 \phi_1 \\ &\quad + \beta \eta_4 \varepsilon_1 D_6 \phi_1 + \beta \eta_5 \varepsilon_1 \varepsilon_2 \phi_1) + a_2 \alpha_2 D_4 D_5 D_6 (1 - \Phi_4)], \\ a_4 &= \frac{1}{D_4 D_5 D_6 (1 - \Phi_4)} [a_1 (\beta \eta_3 D_5 D_6 + \beta \eta_4 \varepsilon_1 D_6 + \beta \eta_5 \varepsilon_1 \varepsilon_2) + a_3 (\phi_2 D_5 D_6 + \varepsilon_1 \varepsilon_2 \xi_1)], \\ a_5 &= \frac{1}{D_5 D_6} [a_1 (\beta \eta_4 D_6 + \beta \eta_5 \varepsilon_2) + a_3 \varepsilon_2 \xi_1 + a_4 \varepsilon_2 \xi_2], \\ a_6 &= \frac{1}{D_6} (a_1 \beta \eta_5 + a_3 \xi_1 + a_4 \xi_2). \end{cases}$$

Substituting the constants into the derivative of the Lyapunov functions, we obtain

$$\frac{dV}{dt} \leq -D_2 D_3 D_4 D_5 D_6 [1 - (\Phi_1 + \Phi_2 + \Phi_3 + \Phi_4 + \Phi_5) + \Phi_1 (\Phi_3 + \Phi_4 + \Phi_5) + \Phi_2 \Phi_3] (1 - \mathcal{R}_0).$$

We observe that $\frac{dV}{dt} < 0$ whenever $\mathcal{R}_0 < 1$ and equality holds when $L_1^* = 0$, a case which is intandem with the drug free equilibrium. Although equality also holds for $\mathcal{R}_0 = 1$, we ought not to make such a strong statement since this point can also be rendered as a bifurcation point where the model equilibrium points switch from the drug-free equilibrium to a drug persistent equilibrium. Therefore, the largest compact invariant set in Ω such that $\frac{dV}{dt} < 0$ when $\mathcal{R}_0 < 1$ is the 8-tuple $\mathbb{E}_0$. By the LaSale invariance principle [41], the equilibrium $\mathbb{E}_0$ is globally stable when $\mathcal{R}_0 < 1$. In addition, $\mathbb{E}_0$ is unstable when $\mathcal{R}_0 > 1$ owing to at least a positive eigenvalue the Jacobian $J(\varepsilon_0)$ posses if evaluated for $\mathcal{R}_0 > 1$ [42]. This completes the proof. $\square$

3.3 Drug Persistent Equilibrium.

Theorem 3.3.1. *The model system (3.1) has a unique drug persistent equilibrium whenever $\mathcal{R}_0$ is greater than unity.*

Proof. At the endemic equilibrium, the model system of equations (3.1), satisfies the follow-

ing system of equations

$$0 = \pi - \Lambda^{**}S^{**} - \mu S^{**}, \quad (3.4a)$$

$$0 = \Lambda^{**}S^{**} + \gamma_2 L_2^{**} - D_1 L_1^{**}, \quad (3.4b)$$

$$0 = \gamma_1 L_1^{**} + \alpha_2 L_3^{**} - D_2 L_2^{**}, \quad (3.4c)$$

$$0 = \alpha_1 L_2^{**} + \phi_2 H^{**} + \xi_1 R^{**} - D_3 L_3^{**}, \quad (3.4d)$$

$$0 = \phi_1 L_3^{**} + \xi_2 R^{**} - D_4 H^{**}, \quad (3.4e)$$

$$0 = \varepsilon_1 H^{**} - D_5 A^{**}, \quad (3.4f)$$

$$0 = \varepsilon_2 A^{**} - D_6 R^{**}, \quad (3.4g)$$

$$0 = \sigma L_1^{**} + \rho_1 L_2^{**} + \rho_2 L_3^{**} + \rho_3 H^{**} + \rho_4 R^{**} - \mu Q^{**}, \quad (3.4h)$$

where $\Lambda^{**} = \frac{\beta(L_1^{**} + \eta_1 L_2^{**} + \eta_2 L_3^{**} + \eta_3 H^{**} + \eta_4 A^{**} + \eta_5 R^{**})}{S^{**} + L_1^{**} + L_2^{**} + L_3^{**} + H^{**} + A^{**} + R^{**} + Q^{**}}$.

From equation (3.4h), we obtain

$$Q^{**} = \frac{1}{\mu} [\sigma L_1^{**} + \rho_1 L_2^{**} + \rho_2 L_3^{**} + \rho_3 H^{**} + \rho_4 R^{**}].$$

From equation (3.4g), we obtain

$$A^{**} = \frac{D_6 R^{**}}{\varepsilon_2}. \quad (3.5)$$

from equation (3.4f), we obtain

$$H^{**} = \frac{D_5 A^{**}}{\varepsilon_1}. \quad (3.6)$$

Then substituting equation (3.5) into equation (3.6) we obtain

$$H^{**} = \frac{D_5 D_6 R^{**}}{\varepsilon_1 \varepsilon_2}. \quad (3.7)$$

From equation (3.4e), we obtain

$$\begin{aligned} H^{**} &= \frac{\phi_1 L_3^{**} + \xi_2 R^{**}}{D_4} \\ \Rightarrow \frac{D_5 D_6 R^{**}}{\varepsilon_1 \varepsilon_2} &= \frac{\phi_1 L_3^{**} + \xi_2 R^{**}}{D_4}. \end{aligned}$$

We then express L_3^{**} in terms of R^{**} and obtain

$$L_3^{**} = \frac{D_4 D_5 D_6 (1 - \Phi_4) R^{**}}{\phi_1 \varepsilon_1 \varepsilon_2}. \quad (3.8)$$

From equation (3.4d), we obtain

$$\alpha_1 L_2^{**} + \phi_2 H^{**} + \xi_1 R^{**} = D_3 L_3^{**}. \quad (3.9)$$

Substituting equation (3.8) into equation (3.9), we get

$$L_2^{**} = \frac{D_3 D_4 D_5 D_6 [1 - (\Phi_3 + \Phi_4 + \Phi_5)] R^{**}}{\alpha_1 \phi_1 \varepsilon_1 \varepsilon_2}. \quad (3.10)$$

From equation (3.4c), we obtain

$$D_2 L_2^{**} = \gamma_1 L_1^{**} + \alpha_2 L_3^{**}.$$

Substituting equation (3.8) and equation (3.10) into equation (3.3), we have

$$\begin{aligned} \frac{D_2 D_3 D_4 D_5 D_6 [1 - (\Phi_3 + \Phi_4 + \Phi_5)] R^{**}}{\alpha_1 \phi_1 \varepsilon_1 \varepsilon_2} &= \gamma_1 L_1 + \frac{\alpha_2 D_4 D_5 D_6 (1 - \Phi_4) R^{**}}{\phi_1 \varepsilon_1 \varepsilon_2} \\ \therefore L_1^{**} &= \frac{D_2 D_3 D_4 D_5 D_6}{\gamma_1 \alpha_1 \varepsilon_1 \varepsilon_2} [1 - (\Phi_2 + \Phi_3 + \Phi_4 + \Phi_5) + \Phi_2 \Phi_4] R^{**} \end{aligned}$$

We now express the steady state variables L_1^{**} , L_2^{**} , L_3^{**} , H^{**} , A^{**} and Q^{**} in terms of R^{**} as follows

$$\begin{cases} L_1^{**} &= \frac{D_2 D_3 \xi_2}{\gamma_1 \alpha_1 \phi_1 \Phi_4} [1 - (\Phi_2 + \Phi_3 + \Phi_4 + \Phi_5) + \Phi_2 \Phi_4] R^{**}, \\ L_2^{**} &= \frac{D_3 \xi_2}{\alpha_1 \phi_1 \Phi_4} [1 - (\Phi_3 + \Phi_4 + \Phi_5)] R^{**}, \\ L_3^{**} &= \frac{\xi_2}{\phi_1 \Phi_4} (1 - \Phi_4) R^{**}, \\ H^{**} &= \frac{D_5 D_6}{\varepsilon_1 \varepsilon_2} R^{**}, \\ A^{**} &= \frac{D_6}{\varepsilon_2} R^{**}, \\ Q^{**} &= \Phi_6 R^{**}, \end{cases} \quad (3.11)$$

where

$$\begin{aligned} \Phi_6 &= \frac{1}{\mu} \left[\frac{\sigma D_2 D_3 \varepsilon_2}{\gamma_1 \alpha_1 \phi_1 \Phi_4} [1 - (\Phi_2 + \Phi_3 + \Phi_4 + \Phi_5) + \Phi_2 \Phi_4] + \rho_1 \frac{D_3 \xi_2}{\alpha_1 \phi_1 \Phi_4} [1 - (\Phi_3 + \Phi_4 + \Phi_5)] \right. \\ &\quad \left. + \frac{\rho_2 \xi_2}{\phi_1 \Phi_4} (1 - \Phi_4) + \frac{\rho_3 D_5 D_6}{\varepsilon_1 \varepsilon_2} + \rho_4 \right]. \end{aligned}$$

Using equation (3.4b) and substituting the appropriate steady state variable terms (3.11), we obtain

$$\Lambda^{**} S^{**} = \Phi_7 R^{**} \quad (3.12)$$

where

$$\Phi_7 = \frac{D_1 D_2 D_3 D_4 D_5 D_6}{\gamma_1 \alpha_1 \phi_1 \varepsilon_1 \varepsilon_2} [1 - (\Phi_1 + \Phi_2 + \Phi_3 + \Phi_4 + \Phi_5) + \Phi_1 (\Phi_3 + \Phi_4 + \Phi_5) + \Phi_2 \Phi_4]$$

From the Left Hand Side (LHS) of equation (3.12), we have

$$\begin{aligned}\Lambda^{**}S &= \frac{S^{**}}{N^{**}} \times \beta(L_1^{**} + \eta_1 L_2^{**} + \eta_2 L_3^{**} + \eta_3 H^{**} + \eta_4 A^{**} + \eta_5 R^{**}) \\ &\Rightarrow \frac{S^{**}}{N^{**}} [\mathcal{R}_{01} + \mathcal{R}_{02} + \mathcal{R}_{03} + \mathcal{R}_{04} + \mathcal{R}_{05} + \mathcal{R}_{06}] R^{**} = R^{**},\end{aligned}$$

which can be rearranged to obtain

$$\frac{S^{**}}{N^{**}} \mathcal{R}_0 R^{**} = R^{**}. \quad (3.13)$$

From equation (3.13), we observe that one of the roots of equation (3.13) is $R^{**} = 0$ which corresponds to the drug-free equilibrium. Otherwise, we have

$$\frac{S^{**}}{N^{**}} = \frac{1}{\mathcal{R}_0}. \quad (3.14)$$

From equation (3.14), we make N^{**} the subject obtaining

$$N^{**} = \mathcal{R}_0 S^{**},$$

where $N^{**} = S^{**} + L_1^{**} + L_2^{**} + L_3^{**} + H^{**} + A^{**} + R^{**} + Q^{**}$. The state variable terms can be expressed in terms of the state variable R^{**} .

Then we have

$$\begin{aligned}\frac{(\mathcal{R}_0 - 1)S^{**}}{R^{**}} &= L_1^{**} + L_2^{**} + L_3^{**} + H^{**} + A^{**} + R^{**} + Q^{**} \\ &= \Phi_8.\end{aligned}$$

where

$$\begin{aligned}\Phi_8 &= \left[\frac{D_2 D_3 \zeta_2}{\gamma_1 \alpha_1 \phi_1 \Phi_4} [1 - (\Phi_2 + \Phi_3 + \Phi_4 + \Phi_5) + \Phi_2 \Phi_4] + \frac{D_2 \gamma_2}{\alpha_1 \phi_1 \Phi_4} [1 - (\Phi_3 + \Phi_4 + \Phi_5)] \right. \\ &\quad \left. + \frac{\zeta_2}{\phi_1 \Phi_4} (1 - \Phi_4) + \frac{D_5 D_6}{\varepsilon_1 \varepsilon_2} + \frac{D_6}{\varepsilon_2} + 1 + \Phi_6 \right],\end{aligned}$$

from which we obtain

$$S^{**}(\mathcal{R}_0 - 1) = \Phi_8 R^{**}.$$

Note that since the model assumes quitters quit permanently, the equilibrium proportion of the susceptible in the total population (3.14) takes the form $\frac{S^{**}}{N^{**}} = \frac{1}{\mathcal{R}_0}$, a similar ratio obtained in [25]. We also note that substituting the appropriate terms into equation (3.4), we obtain explicit expressions for $S^{**}, L_1^{**}, L_2^{**}, L_3^{**}, H^{**}, A^{**}, R^{**}$ and Q^{**} in terms of the model

parameters such that

$$\begin{cases} S^{**} &= \frac{\pi\Phi_8\mathcal{R}_0}{\Phi_8(\mathcal{R}_0-1)+\mu\Phi_8\mathcal{R}_0}, \\ L_1^{**} &= \frac{\Phi_9\pi(\mathcal{R}_0-1)}{\mu\Phi_8+\Phi_8\mathcal{R}_0(\mathcal{R}_0-1)}, \\ L_2^{**} &= \frac{D_3\xi_2\pi(\mathcal{R}_0-1)[1-(\Phi_3+\Phi_4+\Phi_5)]}{\Phi_8\alpha_1\phi_1\Phi_4[\mu+\mathcal{R}_0(\mathcal{R}_0-1)]}, \\ L_3^{**} &= \frac{\xi_2\pi(\mathcal{R}_0-1)(1-\Phi_4)}{\phi_1\Phi_4\Phi_8[\mu+\mathcal{R}_0(\mathcal{R}_0-1)]}, \\ H^{**} &= \frac{D_5D_6\pi(\mathcal{R}_0-1)}{\varepsilon_1\varepsilon_2\mu\Phi_8+\Phi_8\mathcal{R}_0(\mathcal{R}_0-1)}, \\ A^{**} &= \frac{D_6\pi(\mathcal{R}_0-1)}{\varepsilon_2\mu\Phi_8+\Phi_8\mathcal{R}_0(\mathcal{R}_0-1)}, \\ R^{**} &= \frac{\pi(\mathcal{R}_0-1)}{\mu\Phi_8+\Phi_8\mathcal{R}_0(\mathcal{R}_0-1)}, \\ Q^{**} &= \frac{\Phi_6\pi(\mathcal{R}_0-1)}{\mu\Phi_8+\Phi_8\mathcal{R}_0(\mathcal{R}_0-1)}, \end{cases}$$

where

$$\Phi_9 = \frac{D_2D_3\xi_2}{\gamma_1\alpha_1\phi_1\Phi_4}[1 - (\Phi_2 + \Phi_3 + \Phi_4 + \Phi_5) + \Phi_2\Phi_4]$$

Therefore, the model system (3.1) has a unique drug persistent equilibrium when $\mathcal{R}_0$ is greater than unity, but when $\mathcal{R}_0$ is less than or equal to 1, the drug persistent equilibrium collapses to drug free equilibrium. $\square$

3.4 Numerical Simulations

3.4.1 Parameter Estimation

Botswana's current average life expectancy is approximately 66.4 years with males having an average life expectancy of 63.6 years compared to 68.6 years for females [43]. These correspond to mortality rates 0.0151 per year, 0.0157 per year and 0.0146 per day respectively. The time people take to engage in excessive hazardous behaviour under the influence of drugs is not known, and it differs among people that are dependent on the sort of drug and quantity they devour [25]. It is as such difficult to estimate the precise mortality rate related to substance abuse. According to Pond [44], mortality rates of alcohol users and illicit drug users are 33.0 and 6.9 deaths per 100 000 people respectively. We use an estimated value for, the drug related mortality rate of heavy drug users $\delta_1 = 0.0014$ per day. The drug related mortality rate of addicted drug users is, $\delta_2 = 0.003$ per day higher than the drug related mortality rate of heavy drug users as addicted drug user are more prone to dangers associated with drug abuse. The progression rate from light user class L_3 to heavy use found by Kalula and Nyabadza [45] is 0.0244. Nyabadza and Hove-Musekwa [24] used the value between (0.003, 0.004), Njagarah and Nyabadza [26] used the value 0.56. We choose the progression

rate from L_3 to heavy use to be 0.056. While for the progression from L_1 to L_2 we choose it to be 0.035 and from L_2 to L_3 we chose the value 0.08 as from the literature light drug users were not subdivided into compartments compared as our model. In [24], the parameter for the treatment demand was bound in the interval (0.09, 0.3) for drug users in treatment. In [25] the author considered an average treatment demand of 22.3%. In our model, since we are only dealing with out-patient rehabilitation compared to the literature, we choose the rehabilitation rate to be 0.0223. For light users the probability of quitting is high due to side effects. In [46] the authors used values between (0, 3) and (1.8, 3) while in [45] the values in the interval (0, 0.3) were used. In our model, we choose 0.08. The summarized parameter values (per day) used in the model are shown by Table 3.3.

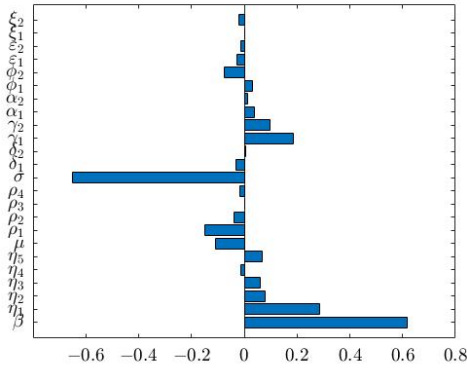
3.4.2 Sensitivity Analysis of the Model to Parameters

Sensitivity Analysis, is a technique used to vary input parameters of a model and determining how they will impact the dependent variable in the model solution [47, 48]. To perform sensitivity analysis of the model to the parameters, we examine which model parameter affect mostly the value of the reproduction number $\mathcal{R}_0$. We use the Latin Hypercube Sampling scheme (LHS), which is a simulation based reliability evaluation method, described in [49]. The Latin Hypercube Sampling scheme was developed to discuss the need for uncertainty evaluation for a specific class of problems [50]. The LHS is used as it is a stratified Monte Carlo sampling that provides for simultaneous sampling of the multi dimensional parameter space [51]. We compute partial rank correlation coefficients (PRCCs) with 1000 simulations per run. Figure 3.2(a) shows a Tornado plot of the PRCCs for the parameters in Table 3.3, and the box plot, Figure 3.2(b) shows the five number summary for the computed reproduction number from the sampled parameter space. The figure shows that contact rate β , has the highest positive influence on the reproduction number. This shows that an increase in β results in an increase in $\mathcal{R}_0$, which will lead to substance abuse becoming worse in the community. Reduction of person to person contact which is assumed to be through peer influence is seen as necessary in curtailing substance abuse.

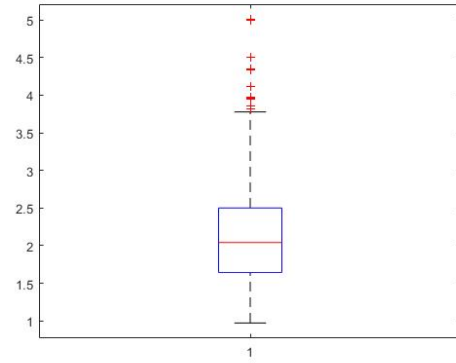
The rate at which substance users in L_1 quit σ , has the highest negative influence on $\mathcal{R}_0$. This shows that σ is an important parameter in the fight against substance abuse. Therefore, programmes that accelerate early quitting from drug use, play a vital role in containing drug use epidemics.

Table 3.3: Nominal values of parameters used in the model

parameter	selection range	Nominal Value	Source	Units
π	0.028-0.08	0.04	[24-26]	day ⁻¹
β	0.010-0.21	0.105	[24-26]	day ⁻¹
η_1	0-1	0.8	[26]	
η_2	0-1	0.6	[26]	
η_3	0-1	0.5	Estimated	
η_4	0-1	0.4	Estimated	
η_5	0-1	0.6	Estimated	
γ_1	0.015-0.045	0.035	Estimated	day ⁻¹
γ_2	0.010-0.040	0.030	Estimated	day ⁻¹
α_1	0.050-0.10	0.08	Estimated	day ⁻¹
α_2	0.10-0.30	0.20	Estimated	day ⁻¹
σ	0-0.15	0.08	[45, 46]	day ⁻¹
ϕ_1	0.0400-0.0700	0.0560	[24, 45, 46]	day ⁻¹
ϕ_2	0.010-0.030	0.025	[45, 46]	day ⁻¹
ρ_1	0.010-0.030	0.020	Estimated	day ⁻¹
ρ_2	0.010-0.030	0.016	Estimated	day ⁻¹
ρ_3	0-0.020	0.013	Estimated	day ⁻¹
ρ_4	0.010-0.040	0.030	[24, 45, 46]	day ⁻¹
δ_1	0.0-0.01	0.0014	[24, 25, 45, 46]	day ⁻¹
δ_2	0.0-0.01	0.003	[25]	day ⁻¹
ε_1	0.01-0.030	0.024	Estimated	day ⁻¹
ε_2	0.017-0.030	0.0223	[24, 25, 45, 46]	day ⁻¹
ζ_1	0.0-0.05	0.02	[46]	day ⁻¹
ζ_2	0.2-0.5	0.25	[45]	day ⁻¹



(a) Tornado plot



(b) Boxplot

Figure 3.2: Tornado plot showing the Partial Rank Correlation Coefficients (PRCCs) for full range of model parameters in Table 3.3

Figure 3.2(b) shows the boxplot of the $\mathcal{R}_0$. From the plot the five number summary recorded for $\mathcal{R}_0$ is a minimum of approximately 1, the lower quartile is approximately 1.5, median is 2, upper quartile is 2.5 and the maximum approximately 3.5. It is evident that there may be combinations of processes that can make the epidemic worse.

Table 3.4: Parameter PRCC Significance (FDR Adjusted p-values)

Variable	PRCC	p-value	Keep
β	0.6186	0.000e+00	TRUE
η_1	0.2860	0.000e+00	TRUE
η_2	-0.0792	4.339e-02	TRUE
η_3	0.0611	1.290e-01	FALSE
η_4	-0.0141	7.769e-01	FALSE
η_5	0.0699	7.360e-01	FALSE
ρ_1	-0.1476	1.582e-05	TRUE
ρ_2	-0.400	4.421e-01	FALSE
ρ_3	0.0024	9.826e-01	FALSE
ρ_4	-0.0184	7.63e-01	FALSE
σ	-0.6493	0.000e+00	TRUE
δ_1	-0.0331	5.328e-01	FALSE
δ_2	0.0064	9.218e-01	FALSE
γ_1	0.1874	1.834e-08	TRUE
γ_2	0.0991	7.304e-03	TRUE
α_1	0.0379	4.531e-01	FALSE
α_2	0.0147	7.639e-01	FALSE
ϕ_1	0.0304	5.624e-01	FALSE
ϕ_2	-0.0759	5.052e-02	FALSE
ε_1	-0.0270	6.119e-01	FALSE
ε_2	-0.0139	7.639e-01	FALSE
ξ_1	0.0007	9.826e-01	FALSE
ξ_2	-0.0186	7.639e-01	FALSE

The statistical significance test p -value is the probability of acquiring a test statistic nearest to the actual observed one[52]. Table 3.4 above shows the p -values of our parameters from the PRCCs list. We keep the parameters which have significant p -value ($p < 0.05$). The parameters that have significant p -value are indicated with "TRUE" in the last column of Table 3.4. The parameters that are not significant ($p > 0.05$) are indicated with "FALSE" in the last column of Table 3.4 and they are eliminated from the pairwise comparison.

From Table 3.4, we can see that PRCC values are in the range $[-1,1]$.

We perform pairwise comparison of parameters whose p -values are less than 0.05 to identify which parameters pairs are significantly different. The computed unadjusted p -values for the pairwise comparison are shown in Table 3.5 and the False Discovery Rate (FDR) adjusted p -values are given in Table 3.6. Based on the FDR adjusted p -values in Table 3.6, we summarise the parameters which are observed to be significantly different in Table 3.7.

Table 3.5: Pairwise PRCC comparisons (unadjusted p-values)

	β	η_1	η_2	ρ_1	σ	γ_1	γ_2
β		0	0	0	0	0	0
η_1			2.101e-06	0	0	0.02096	1.703e-05
η_2				4.772e-07	0	0.0149	0.6578
ρ_1					0	8.016e-14	4.297e-08
σ						0	0
γ_1							0.04638
γ_2							

Table 3.6: Pairwise PRCC Comparisons (FDR Adjusted p-values)

	β	η_1	η_2	ρ_1	σ	γ_1	γ_2
β		0	0	0	0	0	0
η_1			2.758e-06	0	0	0.02317	2.104e-05
η_2				6.681e-07	0	0.01738	0.6578
ρ_1					0 1.295e-13	6.446e-08	
σ						0	0
γ_1							0.0487
γ_2							

Table 3.7: Parameters different after FDR adjustment?

	β	η_1	η_2	ρ_1	σ	γ_1	γ_2
β		TRUE	TRUE	TRUE	TRUE	TRUE	TRUE
η_1			TRUE	TRUE	TRUE	TRUE	TRUE
η_2				TRUE	TRUE	TRUE	FALSE
ρ_1					TRUE	TRUE	TRUE
σ						TRUE	TRUE
γ_1							TRUE
γ_2							

We can observe that parameters σ , η_1 , η_2 , γ_1 and γ_2 have significant p-values when they are compared to other parameters. For parameters that have significant positive and negative PRCCs, we determine whether the monotone increasing or monotone decreasing trend is noteworthy when we vary the parameter while keeping others constant. To determine this, we choose the parameters with the highest absolute values of the PRCCs. Below are the results of the produced scatter plots:

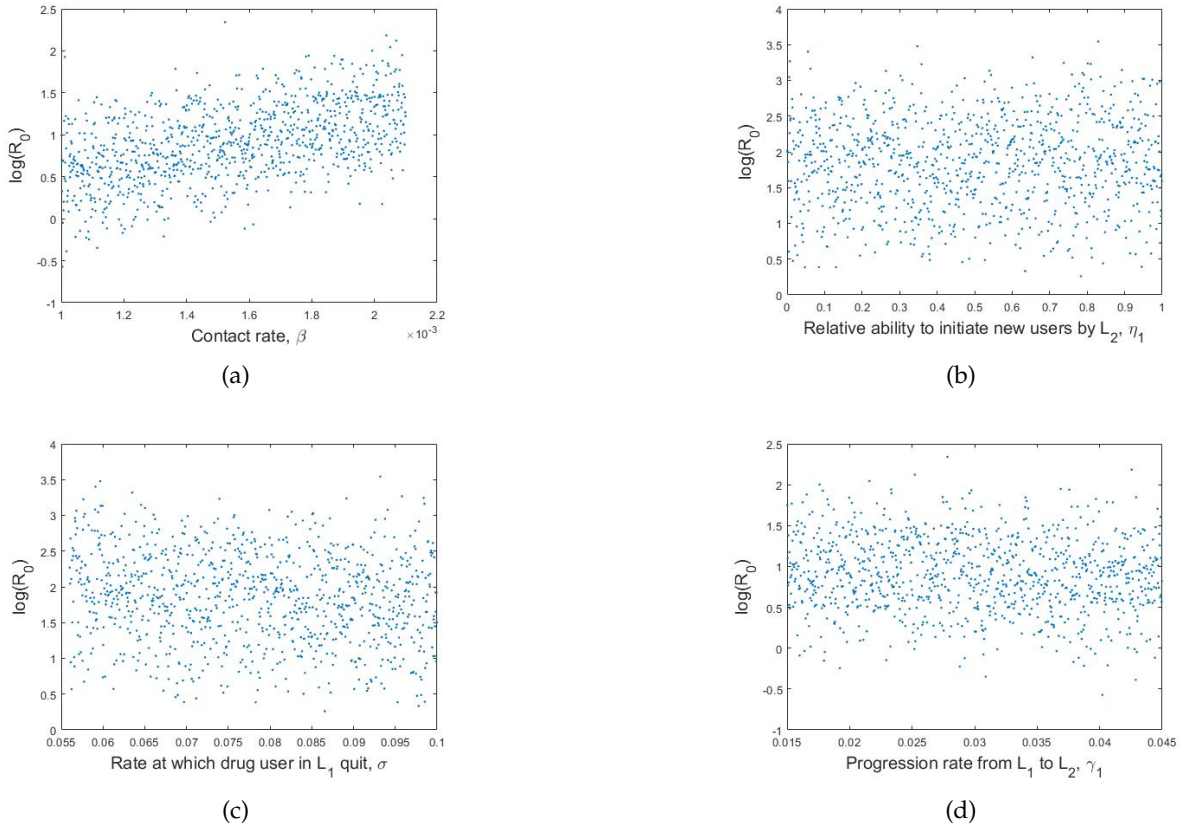


Figure 3.3: Monte Carlo simulations for the four parameters with the greatest absolute values of PRCC obtained using parameter values in Table 3.3.

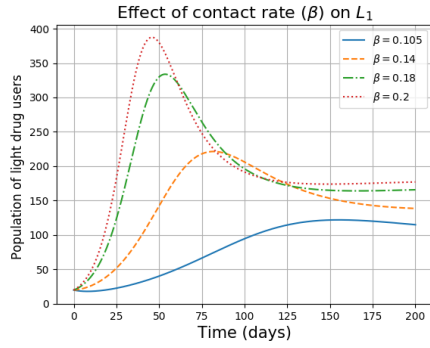
R_0 is monotone increasing with an increase in the contact rate (β), the relative ability to initiate new drug users by light drug users L_2 , η_1 , and the progression rate from light users L_1 to light users L_2 . The scatter plot for γ_1 shows no strong monotone relationship with R_0 which shows that progression from L_1 to L_2 alone may not have a strong influence on the drug epidemic. This is also partly because L_1 has a much higher potential to initiate susceptible individuals into drug use compared to L_2 . The scatter plot shows a decrease in R_0 when the rate at drug users in L_1 quit, σ is increased. This shows that it may be more practical to contain drug use if we accelerate quitting at the early stages of drug use.

3.4.3 Numerical Results

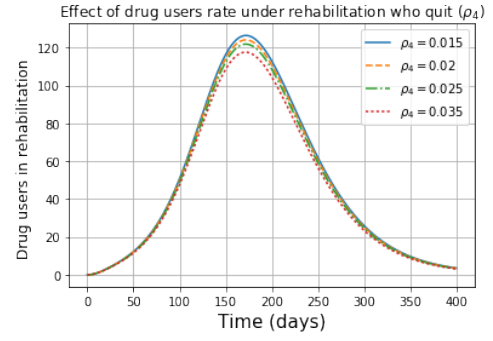
In this subsection, we present the numerical results showing the effect in some key parameters in drug epidemics. The contributions of quitting and rehabilitation are modelled with the parameters ρ_4 and ε_2 respectively. To examine the effect of contact rate, we varied the

values of contact rate *i.e.* $\beta = \{0.105, 0.14, 0.18, 0.2\}$ and obtained the corresponding plots of how the population of light users evolves over time, as shown in figure 3.4(a). We note from figure 3.4(a) that an increase in the contact rate results in the increase in the population of drug users. We also observe that there is a change in prevalence as the quitting rate changes. Keeping other parameters constant, and varying the quitting rates $\rho_4 = \{0.015, 0.02, 0.025, 0.035\}$, we obtain the corresponding plots of prevalence of drug abuse in the population progressing over time, as shown in figure 3.4(b). An increase in the quitting rate of drug users results in the decrease in prevalence. With varied quitting rate, we observe that higher quitting rates are associated with lower peak values of drug users in rehabilitation. However the long term numbers of drug users may not be significantly different most especially near the steady states. Similar to β and ρ_4 , we made other parameters constant and varied the values of the recruitment rate into rehabilitation, ε_2 , as shown in figure 3.4(c). We observed that an increase in the recruitment rate into rehabilitation results in a decrease in the prevalence of addicted drug users. In addition, increased effective recruitment into rehabilitation is associated with lower peak values of addicted users as well as lower long term numbers of addicted users.

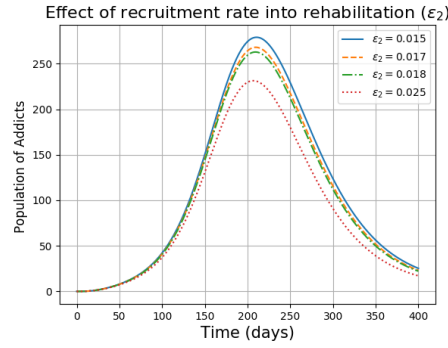
We note that if we increase the recruitment rate of drug users into rehabilitation, we accelerate the rate at which drug users quit, hence, leading to a decline in prevalence of drug use.



(a) The effect of contact rate β on population of drug users

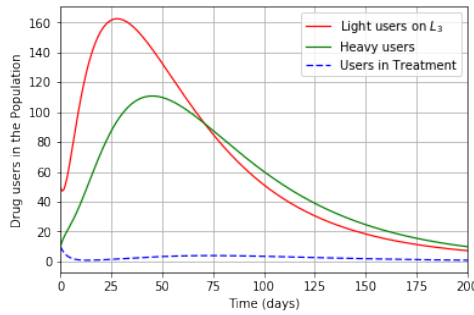


(b) The contribution of quitting on the prevalence of substance use

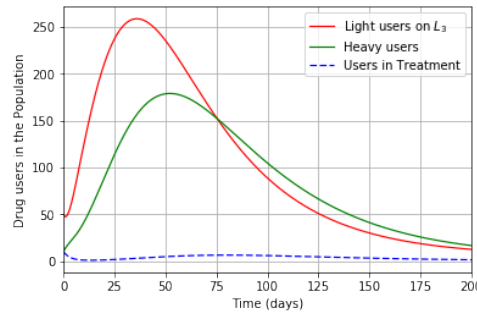


(c) The impact of rehabilitation on the prevalence of substance use

Figure 3.4: The impact of key parameters in drug epidemics



(a)



(b)

Figure 3.5: The trajectory of drug users (a) trajectory when $\mathcal{R}_0 = 0.952 < 1$ and (b) trajectory when $\mathcal{R}_0 = 1.042 > 1$

Figure 3.5, shows the evolution of population of drug users when $\mathcal{R}_0 < 1$ (Figure 3.5(a)) and when $\mathcal{R}_0 > 1$ (Figure 3.5(b)). When $\mathcal{R}_0 < 1$, the model predicts minimal numbers of drug users in the long term. When $\mathcal{R}_0$ is greater than unity as shown in figure 3.5(b), the

substance users future generation will be greater than their recruiters, and hence substance abuse persists in the population.

3.5 Conclusion

In this chapter, we presented a dynamical model of substance abuse in presence of multiple amelioration stages, heavy drug use, out-patient rehabilitation. We assumed a Botswana set-up where rehabilitation is typically out-patient rehabilitation. We analysed the model qualitatively by finding the positivity of solutions, and existence and stability of the steady states. The model considered during this study has a globally asymptotically stable drug free equilibrium if $\mathcal{R}_0 < 1$ and unstable otherwise. This shows that substance abuse can be reduced if there is the application of control measures and putting more effort on processes that can help in the reduction of the reproduction number to a value below 1. We noted that, when $\mathcal{R}_0 > 1$, the drug endemic equilibrium exists and is unique. That is, substance abuse will remain endemic in the population.

Numerical simulations and sensitivity were performed and we found out that, in-order to reduce substance abuse there is a need to; reduce the contact rate β , the relative initiation rates η_1, η_2, η_3 and η_5 , progression rates γ_1, α_1 and ϕ_1 . These aforementioned parameters have a positive correlation with the reproduction number. The other parameters with negative impact on the reproduction number indicate that the processes described by such parameters ought to be enhanced. This shows that an increase in parameters that have negative influence, result in a reduction of the prevalence of substance abuse.

From the model, we found out that light users are the role players in the increase of substance use prevalence, so to reduce substance use, then a control has to be implemented at an early stage of light drug use to accelerate quitting.

Chapter 4

Optimal Control

4.1 Mathematical Model

This model is a reduced version of the model considered in Chapter 3. In this model, we combine all the light drug user classes and consider them in one category, of light users. We also divided drug users in rehabilitation into 2 compartments, namely drug users in out-patient rehabilitation R_{out} and drug users in in-patient rehabilitation R_{in} . The assumptions in the model is that there is homogeneous mixing among individuals in the same compartment. Through a constant recruitment of individuals into the population the susceptible population is replenished. Effective interaction with substance users can lead to Susceptible individuals, S , being initiated into substance abuse as shown in Chapter 3. We divide the total population N evolving over time into non-intersecting subgroups depending on their substance abuse classifications to obtain

$$N(t) = S(t) + L(t) + H(t) + A(t) + R_{out}(t) + R_{in}(t) + Q(t).$$

Rehabilitation may be in-patient or out-patient, but in the case of Botswana rehabilitation is predominantly out-patient as outlined in Chapter 3. This means that individuals who are in out-patient rehabilitation are still able to access their preferred substances and even meet with potentially drug use epidemiologically naive individuals, thereby contributing to the initiation of a new substance user. We however consider both in-patient and out-patient in this Chapter as we study the control that can reduce/minimise drug use and ascertain the importance of in-patient rehabilitation as it has been a useful approach in the South African rehabilitation system. In addition, recruitment of drug users into in-patient rehabilitation

has been observed as an effective strategy in accelerating quitting and slowing down recruitment of potential drug users [28]. In the model in this Chapter, we introduce a time dependent control variable $v(t)$, accounting for the effectiveness of awareness programs. The likelihood of having individuals being involved in drug abuse is reduced by rates $u(t)$. we assume that fraction $u(t)$ get counselling on drug use and abuse while a fraction $\omega(t)$ accelerate quitting of drug users in both out- and in-patient rehabilitation. It is assumed that the government health organisation independent of the community specific health groups implement the controls. We assume that the susceptible population is led to substance abuse by active substance users at the rate β . Thus, the force of initiation of individuals λ is given by,

$$\lambda = \frac{\beta(L + \eta_1 H + \eta_2 A + \eta_3 R_{out})}{N},$$

where $\eta_i, i = 1, 2, 3$ are the rates at which drug users in categories H, A and R_{out} recruit new drug users relative to drug users in compartment L . Drug users in in-patient rehabilitation are not considered to be part of the initiation process because it is assumed they are locked in the rehabilitation centre where they may not be able to interact with potential drug users for a certain period, or for the entire duration of their rehabilitation process.

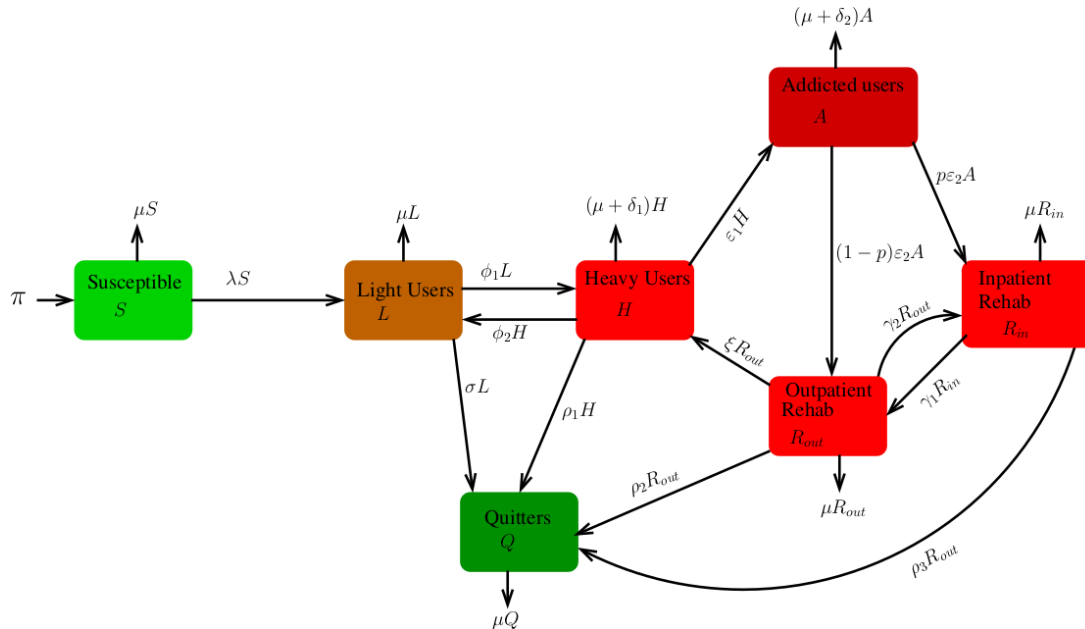


Figure 4.1: Schematic diagram of the reduced model of drug abuse progression. The drug users in rehabilitation involve both inpatient and out-patient rehabilitation programmes.

The system of equations that represent the compartmental model shown in Figure 4.1 are as follows

$$\frac{dS}{dt} = \pi - \mu S - (1 - \nu)\lambda S, \quad (4.1a)$$

$$\frac{dL}{dt} = (1 - \nu)\lambda S + \phi_2 H - (1 - u)\phi_1 L - D_1 L, \quad (4.1b)$$

$$\frac{dH}{dt} = (1 - u)\phi_1 L + \xi R_{out} - D_2 H, \quad (4.1c)$$

$$\frac{dA}{dt} = \varepsilon_1 H - \varepsilon_2 A - D_3 A, \quad (4.1d)$$

$$\frac{dR_{out}}{dt} = (1 - p)\varepsilon_2 A + \gamma_1 R_{in} - \omega \rho_2 R_{out} - D_4 R_{out}, \quad (4.1e)$$

$$\frac{dR_{in}}{dt} = p\varepsilon_2 A + \gamma_2 R_{out} - \omega \rho_3 R_{in} - D_5 R_{in}, \quad (4.1f)$$

$$\frac{dQ}{dt} = \sigma L + \rho_1 H + \omega \rho_2 R_{out} + \omega \rho_3 R_{in} - \mu Q, \quad (4.1g)$$

where $D_1 = \mu + \sigma$, $D_2 = \mu + \phi_2 + \rho_1 + \varepsilon_1 + \delta_1$, $D_3 = \mu + \delta_2$, $D_4 = \mu + \gamma_2 + \xi$, and $D_5 = \gamma_1 + \mu$.

4.1.1 Model Analysis

4.1.2 Positivity of Solution

We consider the positivity of system (4.1). We show that solutions of system (4.1) with initial conditions is positive for all $t > 0$. We consider the lemma below

Lemma 4.1.1. *Given that the system (4.1) has non-negative initial conditions $S^0, L^0, H^0, A^0, R_{in}^0, R_{out}^0, Q^0 > 0$, then the solution set $\{S, L, H, A, R_{out}, R_{in}, Q\}$ is non-negative for all $t > 0$.*

Proof. Suppose that

$$t^* = \sup\{t > 0 : S, L, H, A, R_{out}, R_{in}, Q > 0\} \in [0, t].$$

Therefore, for $t^* > 0$, and it follows from equation (4.1a) that

$$\frac{dS}{dt} \geq -((1 - \nu)\hat{\lambda} + \mu)S, \quad \text{where } \hat{\lambda} = \max_{t \geq 0} \{\lambda\}.$$

We thus separate variables and integrate both sides with respect to the corresponding variables

$$\int_{S_0}^S \frac{dX}{X} \geq - \int_0^t ((1 - \nu)\hat{\lambda} + \mu) dz.$$

Hence

$$\ln \left(\frac{S}{S_0} \right) \geq - \left[(1 - \int_0^t v(z) dz) \hat{\lambda} + \mu t \right],$$

so that

$$S(t^*) \geq S(0) e^{-[(1 - \int_0^t v(z) dz) \hat{\lambda} + \mu t]} \geq 0.$$

From the equation (4.1b), we have

$$\begin{aligned} \frac{dL}{dt} &= (1 - v) \lambda S + (1 - u) \phi_2 H - (\phi_1 + \sigma_2 + \mu) L, \\ &\geq -(\mu + \sigma_2 + \phi_1) L, \\ \Rightarrow L(t^*) &\geq L^0 e^{-(\mu + \sigma_2 + \phi_1) t^*} > 0. \end{aligned}$$

The same method can be used to show that

$$\begin{cases} H(t^*) \geq H^0 e^{-(\mu + \phi_2 + \rho_1 + \varepsilon_1 + \delta_1) t^*} > 0, \\ A(t^*) \geq A^0 e^{-(\mu + \delta_2) t^*} > 0, \\ R_{out}(t^*) \geq R^0 e^{-(\mu + \gamma_2 + \xi) t^*} > 0, \\ R_{in}(t^*) \geq R^0 e^{-(\gamma_1 + \mu) t^*} > 0, \\ Q(t^*) \geq Q^0 e^{-\mu t^*} > 0, \end{cases}$$

for all $t^* > 0$, and this completes the proof. $\square$

Lemma 4.1.2. Define the feasible region Ω_1 by

$$\Omega_1 = \left\{ (S(t), L(t), H(t), A(t), R_{in}(t), R_{out}(t), Q(t)) \in \mathbb{R}_+^7 \mid 0 \leq N \leq \frac{\pi}{\mu} \right\},$$

with initial conditions $S^0 > 0$, $L^0 \geq 0$, $H^0 \geq 0$, $A^0 \geq 0$, $R_{in}^0 \geq 0$, $R_{out}^0 \geq 0$, and $Q^0 \geq 0$, gives positive invariant and attracting with respect to system (4.1) for all $t > 0$.

Proof. To prove Lemma 4.1.2, we ought to show that the total population does not increase without bound. The model gives a non-constant total population. Thus, the change in population is defined by the following equation

$$\begin{aligned} \frac{dN}{dt} &= \pi - \mu N - \delta_1 H - \delta_2 A, \\ &\leq \pi - \mu N. \end{aligned}$$

We can now easily show that

$$N \leq \frac{\pi}{\mu} + \left(N^0 - \frac{\pi}{\mu} \right) e^{-\mu t},$$

where $N(0) = N^0$. Following the same approach as in Lemma 3.2.2, then the solution $\{S(t), L(t), H(t), A(t), R_{out}(t), R_{in}(t), Q(t)\}$ is in, or approaches Ω_1 asymptotically. Therefore, Ω_1 is positively invariant. $\square$

4.1.3 Drug Free Equilibrium

The model shows a drug free equilibrium given by

$$\mathbb{E}_0 := (S^*, L^*, H^*, A^*, R_{out}^*, R_{in}^*, Q^*) = \left(\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0 \right).$$

To analyse the existence of equilibrium points, we ought to use the reproduction number evaluated in terms of the model parameters. This threshold value (reproduction number) is also vital in making conclusions about the stability of the obtained equilibrium points of the model.

4.1.4 The basic reproduction number

The next generation matrix method was used to determine the reproduction number $\mathcal{R}_0^{OP}$ of the model (4.1) described in [39]. When computing the drug threshold however, we assume that the controls are constant so that the model system of equations is non-autonomous.

The matrices of new initiations and transition terms are given by

$$\mathcal{F} = \begin{pmatrix} \frac{\beta(1-\nu)(L+\eta_1 H+\eta_2 A+\eta_3 R_{out})}{N} \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad \text{and}$$

$$\mathcal{V} = \begin{pmatrix} -\phi_2 H + (1-u)\phi_1 + (\sigma + \mu)L \\ -(1-u)\phi_1 L - \xi R_{out} + (\phi_2 + \rho_1 + \varepsilon_1 + \delta_1 + \mu)H \\ -\varepsilon_1 H + \omega \varepsilon_2 A + (\mu + \delta_2)A \\ -\omega(1-p)\varepsilon_2 A - \gamma_1 R_{in} + (\xi + \omega \rho_2 + \mu + \gamma_2)R_{out} \\ -p\varepsilon_2 A - \gamma_2 R_{out} + \omega \rho_3 R_{in} + (\gamma_1 + \mu)R_{in} \end{pmatrix} \quad \text{respectively.}$$

Linearising the matrices at the drug free equilibrium respectively gives

$$F = \begin{pmatrix} \beta & \beta\eta_1 & \beta\eta_2 & \beta\eta_3 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \quad \text{and}$$

$$V = \begin{pmatrix} D_1 & -\phi_2 & 0 & 0 & 0 \\ -\phi_1(1-u) & D_2 & 0 & -\xi & 0 \\ 0 & -\varepsilon_1 & D_3 & 0 & 0 \\ 0 & 0 & -(1-p)\varepsilon_2 & -\gamma_1 & D_4 \\ 0 & 0 & -p\varepsilon_2 & -\gamma_2 & D_5 \end{pmatrix}.$$

The spectral radius of the next generation matrix FV^{-1} gives the basic reproduction number such that

$$\mathcal{R}_{0OP} = \rho(FV^{-1}) = \mathcal{R}_{0L} + \mathcal{R}_{0H} + \mathcal{R}_{0A} + \mathcal{R}_{0R_{out}}$$

where

$$\begin{cases} \mathcal{R}_{0L} &= \frac{\beta(1-\nu)(1-\Psi_2-\Psi_3-\Psi_4)}{D_1(1-(1-u)\Psi_1-\Psi_2-\Psi_3-\Psi_4+(1-u)\Psi_1\Psi_2)}, \\ \mathcal{R}_{0L} &= \frac{\beta\eta_1(1-\nu)\phi_1(1-\Psi_2)}{D_1D_2(1-(1-u)\Psi_1-\Psi_2-\Psi_3-\Psi_4+(1-u)\Psi_1\Psi_2)}, \\ \mathcal{R}_{0H} &= \frac{\beta\eta_2(1-\nu)\phi_1\varepsilon_1(1-\Psi_2)}{D_1D_2D_3(1-(1-u)\Psi_1-\Psi_2-\Psi_3-\Psi_4+(1-u)\Psi_1\Psi_2)}, \\ \mathcal{R}_{0R_{out}} &= \frac{\beta\eta_3(1-\nu)[D_5(1-p)+\gamma_1p]\phi_1\varepsilon_1\varepsilon_2}{D_1D_2D_4D_5(1-(1-u)\Psi_1-\Psi_2-\Psi_3-\Psi_4+(1-u)\Psi_1\Psi_2)}, \end{cases} \quad (4.2)$$

where

$$\Psi_1 = \frac{\phi_1\phi_2}{D_1D_2}, \quad \Psi_2 = \frac{\gamma_1\gamma_2}{D_2D_3D_4}, \quad \Psi_3 = \frac{\xi(1-p)\varepsilon_1\varepsilon_2}{D_2D_3D_4}, \quad \Psi_4 = \frac{\xi\gamma_1p\varepsilon_1\varepsilon_2}{D_2D_3D_4D_5}$$

The reproduction number $\mathcal{R}_0$ is given in four groups indicating the contribution of four different groups in the drug initiation process. The reproduction number in our case is defined as the average number of secondary drug users initiated by one drug users in contact with the population that is naive(susceptible) to initiation into drug use. The term Ψ_1 accounts for the proportion of drug users who move back between light drug users and heavy drug users compartments; Ψ_2 , is the proportion of drug users who move back and forth between compartments H and A . Ψ_3 is the proportion of drug users who cycle through a loop of compartments H, A and R_{out} . Ψ_4 is the proportion of drug users who cycle through a loop

of compartments H, A, R_{in} and R_{out} . We note that $1-\Psi_i$, for $i = 1, 2$ accounts for the proportion of drug users who do not move back and forth in the associated compartments. When calculating the reproduction number, constant controls are assumed so that the model system of equations are nonautonomous.

In line with Theorem 2 in [39], determination of $\mathcal{R}_0$ by the next generation matrix method presumes local stability of the drug free equilibrium of the epidemiological model considered. We therefore, have the following theorem:

Theorem 4.1.1. *The drug-free steady state of model(4.1) is locally asymptotically stable whenever $\mathcal{R}_0^{OP} < 1$ and unstable otherwise.*

4.1.5 Global stability of the DFE

To show global stability of the drug free equilibrium, we use the following theorem

Theorem 4.1.2. *The drug-free-steady state $\mathbb{E}_0$ of the model system (4.1) is globally asymptotically stable when $\mathcal{R}_{0OP} < 1$ and unstable whenever $\mathcal{R}_0^{OP} > 1$.*

The proof of Theorem 4.1.2 can be given by using the approach to the proof for Theorem 3.2.2 in Chapter 3. However, in this case we use the reproduction number calculated in equation (4.2) and the controls are assumed to be constant.

4.2 Optimal Control

Optimal control deals with finding a control law of the problem for a given system to achieve a certain optimal criterion.

The following process is involved when finding the general procedure of optimal control process in an epidemiological model [53]

1. Identifying controls that are pertinent to the model,
2. setting up the cost functional with controls,
3. developing the Hamiltonian,
4. assessing adjoint functions,
5. finding the threshold controls that can minimise the Hamiltonian.

The control can be derived using Pontryagins maximum principle which is also known as Pontryagins minimum principle or Pontryagins principle [54].

We use a Hamiltonian system of the form

$$\begin{aligned}\dot{x} &= \frac{\partial \mathcal{H}}{\partial \lambda}, \\ \dot{\lambda} &= -\frac{\partial \mathcal{H}}{\partial x},\end{aligned}$$

where

$$\mathcal{H} = P + \lambda^T a - \mu^T b$$

is an augmented Hamiltonian[55], with λ being the costate or adjoint and μ being the Lagrange multiplier associated with the path constraint and a and b as constants.

The objective cost functional for our problem is given by

$$\mathcal{J}(v, u, \omega) = \int_0^T (aL + bH + cA + dR_{out} + eR_{in} + \chi v^2 + yu^2 + z\omega^2) dt. \quad (4.3)$$

In the objective cost functional, the quantities a, b, c, χ, y , and z are associated with the costs over a finite period of time T . aL, bH, cA, dR_{out} and eR_{in} indicate the costs associated with minimising the drug abuse. χ, y , and z are relative cost weights for respective control measures. We assume that the controls are non-linear, hence the use of quadratic terms. We used the quadratic cost function because it is convex and smooth which makes evaluation of derivatives manageable and the Lyapunov functions can be easily defined. The goal is to minimize the population of drug users and the implementation cost of the controls. Therefore, we looked for optimal control v^*, u^* , and ω^* such that

$$\mathcal{J}(v, u, \omega) = \min_{v, u, \omega} \{ \mathcal{J}(v, u, \omega) | v, u, \omega \in \mathcal{U} \},$$

where

$$\mathcal{U} := \{ (v, u, \omega) | v, u, \omega : [0, T] \rightarrow [0, 1], \forall v, u, \omega \}.$$

To find the integral in (4.3), we apply the Hamiltonian with the necessary adjoint functions. Let $\lambda_S, \lambda_L, \lambda_H, \lambda_A, \lambda_{R_{out}}, \lambda_{R_{in}}$, and λ_Q be the adjoint functions related to the advancement of the corresponding state variables. The Hamiltonian is defined from the cost functional (4.3)

and the governing dynamics (4.1) in obtaining the optimality conditions:

$$\begin{aligned}
\mathcal{H} = & aL + bH + cA + dR_{out} + eR_{in} + \chi v^2 + yu^2 + z\omega^2 \\
& + \lambda_S [\pi - \mu S - (1 - \nu)\lambda S] \\
& + \lambda_L [(1 - \nu)\lambda S + \phi_2 H - (1 - u)\phi_1 L - (\sigma + \mu)L] \\
& + \lambda_H [(1 - u)\phi_1 L + \xi R_{out} - \phi_2 H - (\rho_1 + \varepsilon_1 + \delta_1 + \mu)H] \\
& + \lambda_A [\varepsilon_1 H - \varepsilon_2 A - (\mu + \delta_2)A] \\
& + \lambda_{R_{out}} [(1 - p)\varepsilon_2 A + \gamma_1 R_{in} - (\xi + \omega\rho_2 + \mu + \gamma_2)R_{out}] \\
& + \lambda_{R_{in}} [p\varepsilon_2 A + \gamma_2 R_{out} - (\mu + \omega\rho_3 + \gamma_1)R_{in}] \\
& + \lambda_Q [\sigma L + \rho_1 H + \omega\rho_2 R_{out} + \omega\rho_3 R_{in} - \mu Q].
\end{aligned}$$

To find the system of adjoint equations, we take the appropriate partial derivatives of the Hamiltonian with respect to the related state and control variables.

Theorem 4.2.1. *Given the optimal controls v^* , u^* and ω^* for system (4.1), let x^* be the state variable at equilibrium, and $\lambda_{(*)}$ be positive semidefinite piecewise differentiable functions for all $t \in [0, T]$. Then there exists adjoint variables λ_S , λ_L , λ_H , λ_A , $\lambda_{R_{in}}$, $\lambda_{R_{out}}$, and λ_Q satisfying*

$$-\frac{d\lambda_i}{dt} = \frac{\partial \mathcal{H}}{\partial i}$$

and with transversality conditions

$$\lambda_i(T) = 0, \quad \text{where } \lambda_i = \lambda_S, \lambda_L, \lambda_H, \lambda_A, \lambda_{R_{in}}, \lambda_{R_{out}}, \lambda_Q. \quad (4.4)$$

$$0 = \mathcal{H}_v(t, x^*, v^*, u^*, \omega^*, \lambda(t)) = \mathcal{H}_u(t, x^*, v^*, u^*, \omega^*, \lambda(t)) = \mathcal{H}_\omega(t, x^*, v^*, u^*, \omega^*, \lambda(t))$$

Then

$$\mathcal{H}(t, x^*, v^*(t), u^*(t), \omega^*(t), \lambda(t)) \leq \mathcal{H}(t, x^*, v(t), u(t), \omega(t), \lambda(t))$$

holds for the optimal controls v^* , u^* , and ω^* .

Proof. The existence of optimal control is ensured using the outcome by Fleming and Rishel [56]. To find the adjoint functions with respect to the dependent variables, we differentiate

the Hamiltonian with respect to each state variables to get

$$\begin{aligned}
\frac{d\lambda_S}{dt} &= (1-v)\beta(L + \eta_1 H + \eta_2 A + \eta_3 R_{out}) \left(\frac{L + H + A + R_{out} + R_{in}}{N^2} \right) (\lambda_S - \lambda_L) + \mu\lambda_S, \\
\frac{d\lambda_L}{dt} &= (1-v)\beta S \left[\frac{N - (L + \eta_1 H + \eta_2 A + \eta_3 R_{out})}{N^2} \right] [\lambda_S - \lambda_L] + (1-u)\phi_1(\lambda_L - \lambda_H) + \sigma(\lambda_L - \lambda_Q) + \mu\lambda_L - a, \\
\frac{d\lambda_H}{dt} &= (1-v)\beta S \left[\frac{N\eta_1 - (L + \eta_1 H + \eta_2 A + \eta_3 R_{out})}{N^2} \right] [\lambda_S - \lambda_L] + \phi_2(\lambda_H - \lambda_L) + \varepsilon_1(\lambda_H - \lambda_A) + \rho_1(\lambda_H - \lambda_Q) + \lambda_H(\delta_1 + \mu) - b, \\
\frac{d\lambda_A}{dt} &= (1-v)\beta S \left[\frac{N\eta_2 - (L + \eta_1 H + \eta_2 A + \eta_3 R_{out})}{N^2} \right] [\lambda_S - \lambda_L] + \varepsilon_2[\lambda_A - p\lambda_{R_{in}} - (1-p)\lambda_{R_{out}}] + (\mu + \delta_2)\lambda_A - c, \\
\frac{d\lambda_{R_{out}}}{dt} &= (1-v)\beta S \left[\frac{N\eta_3 - (L + \eta_1 H + \eta_2 A + \eta_3 R_{out})}{N^2} \right] [\lambda_S - \lambda_L] + \zeta(\lambda_{R_{out}} - \lambda_H) + \omega\rho_2(\lambda_{R_{out}} - \lambda_Q) + \gamma_2(\lambda_{R_{out}} - \lambda_{R_{in}}) + \mu\lambda_{R_{out}} - d, \\
\frac{d\lambda_{R_{in}}}{dt} &= (1-v)\beta S \left[\frac{L + \eta_1 H + \eta_2 A + \eta_3 R_{out}}{N^2} \right] [\lambda_S - \lambda_L] + \gamma_1(\lambda_{R_{in}} - \lambda_{R_{out}}) + \omega\rho_3(\lambda_{R_{in}} - \lambda_Q) + \mu\lambda_{R_{in}} - e, \\
\frac{d\lambda_Q}{dt} &= (1-v)\beta S \left[\frac{L + \eta_1 H + \eta_2 A + \eta_3 R_{out}}{N^2} \right] [\lambda_S - \lambda_L] + \mu\lambda_Q.
\end{aligned}$$

Note that for the transversality condition (4.4), the following hold

$$\begin{aligned}
\frac{d\lambda_S}{dt} &= -\frac{\partial \mathcal{H}}{\partial S}, \\
&\vdots \\
\frac{d\lambda_Q}{dt} &= -\frac{\partial \mathcal{H}}{\partial Q}.
\end{aligned}$$

The optimal controls are given by:

$$\begin{aligned}
v^*(t) &= \max(0, \min(\bar{v}(t), 1)), \\
u^*(t) &= \max(0, \min(\bar{u}(t), 1)), \\
\omega^*(t) &= \max(0, \min(\bar{\omega}(t), 1)).
\end{aligned}$$

From the maximum principle the standard control arguments on the controls are given by

$$v^* = \begin{cases} 0 & \text{if } \bar{v} \leq 0, \\ \bar{v} & \text{if } 0 < \bar{v} < 1, \\ 1 & \text{if } \bar{v} \geq 1. \end{cases}$$

The upper-bound of v^* shows that the correct awareness programs are more likely to be influential in the containing initiation into drug use, if they are given on time and maximised.

$$u^* = \begin{cases} 0 & \text{if } \bar{u} \leq 0, \\ \bar{u} & \text{if } 0 < \bar{u} < 1, \\ 1 & \text{if } \bar{u} \geq 1. \end{cases}$$

$u^* = 1$ is in tandem with effective counselling on drug use and assumes that users get the message, so that they refrain from drug use. It is usually difficult to track drug users who

got the counselling and eventually quit drug use.

$$\omega^* = \begin{cases} 0 & \text{if } \bar{\omega} \leq 0, \\ \bar{\omega} & \text{if } 0 < \bar{\omega} < 1, \\ 1 & \text{if } \bar{\omega} \geq 1. \end{cases}$$

The value $\omega^* = 1$ is a characteristic of a perfectly effective rehabilitation process. As it is usually the case, not all drug users who get into rehabilitation will quit immediately, some will relapse.

We differentiate the Hamiltonian $\mathcal{H}$ with respect to each control and obtain

$$\begin{aligned} \frac{\partial \mathcal{H}}{\partial v} &= 2\chi v + \lambda S(\lambda_S - \lambda_L), \\ \frac{\partial \mathcal{H}}{\partial u} &= 2yu + \phi_1 L(\lambda_L - \lambda_H), \\ \frac{\partial \mathcal{H}}{\partial \omega} &= 2z\omega + \rho_2 R_{out}[\lambda_Q - \lambda_{R_{out}}] + \rho_3 R_{in}[\lambda_Q - \lambda_{R_{in}}]. \end{aligned}$$

The controls characterizations, $\bar{v}$, $\bar{u}$, and $\bar{\omega}$, of the optimal controls v^* , u^* , and ω^* are obtained from $\frac{\partial \mathcal{H}}{\partial v} = \frac{\partial \mathcal{H}}{\partial u} = \frac{\partial \mathcal{H}}{\partial \omega} = 0$:

$$\begin{aligned} \bar{v} &= \frac{(\lambda_L - \lambda_S)\lambda S}{2\chi}, \\ \bar{u} &= \frac{\phi_1 L(\lambda_H - \lambda_L)}{2y}, \\ \bar{\omega} &= \frac{\rho_2 R_{out}[\lambda_{R_{out}} - \lambda_Q] + \rho_3 R_{in}[\lambda_{R_{in}} - \lambda_Q]}{2z}. \end{aligned}$$

The incidence of drug use plays a vital role in determining the curves of the state variables for the model with controls, without controls and the control variables over time. $\square$

4.3 Numerical Simulations

To solve the numerical optimal control problem, we used the forward-backward approach explained in Lenhart and Workman [57], to solve model system (4.1). The optimal control problem has been categorized as a quadratic programming problem because the controls are non-linear and are of a quadratic form. To numerically integrate the model system of equations with initial conditions for the states and final time conditions for the adjoints, we use the most accurate and elaborative technique known as a fourth-order Runge-Kutta Method in MATLAB.

4.3.1 Parameter Estimation

The parameter values used are estimated from published literature, due to lack of data. As the model system (4.1) was reduced from the model system in Chapter 3, most of the parameter values used are similar except for a few which were also estimated from published literature related to costs. The parameters related to the cost in the cost functional (4.3) were determined. For an individual to get access to rehabilitation in Botswana the estimated cost was about P1 612.90 per day [58]. The progression rate from light drug use class to heavy use class found by Njagarah and Nyabadza [25] is between (0.4, 0.7). Nyabadza and Hove-Musekwa [24] used the value between (0.003, 0.004), while Kalula and Nyabadza [45] used the value between (0, 0.9). From all these parameters we choose the progression rate from light use class to heavy use class to be 0.056. For the amelioration rate the value used in [25], is between (0.1, 0.6), while in [45] the value used is between (0, 0.9). We used 0.025 in our model as the amelioration rate. Recruitment rate into rehabilitation rate was found to be a value between (0, 0.05024) [28] while the proportion of drug users recruited into in-patient rehabilitation is 0.352. The transfer rates between drug users in both out-patient and in-patient rehabilitation were found to be in the intervals (0, 0.008) and (0, 0.06012) respectively [28].

4.3.2 Numerical Results

In the model simulations, we have a non-constant population and the initial conditions are given by: $S = 20000$; $L = 500$; $H = 200$; $A = 10$; $R_{out} = 5$; $R_{in} = 0$; $Q = 0$.

The algorithm for simulating the system follows the forward-backward sweep method [57]. The steps followed during the simulation are outlined as follows [53, 57].

Step 1. We divide the time interval over which the system is to be integrated into N equal subintervals. We then assume initial guesses of piecewise-constant controls $v_0(t)$, $u_0(t)$, and $\omega_0(t)$ on the time interval $t \in [t_i, t_{i+1}]$, for $i = 0, 1, \dots, N$.

Step 2. The system is numerically integrated forward in time $[0, T]$ according to its system of differential equations in the optimality system by using the assumed controls v_0 , u_0 , and ω_0 and the initial conditions $\vec{x}(0) = (S^0, L^0, H^0, A^0, R_{out}^0, R_{in}^0, Q^0)$ of the model.

Step 3. The transversality condition is integrated backward in time $[0, T]$ by using the assumed controls $v_0(t)$, $u_0(t)$, and $\omega_0(t)$ and values of $\vec{x}$, the costate system $\vec{\lambda}(t)$ in accordance with its system of differential equations.

Step 4. Enter the new state vector $\vec{x}$ and the costate values $\vec{\lambda}(t)$ in the optimal characterisations to update the control vector $\vec{v}$.

Step 5. Check the convergence of the iterations by discovering whether progressive iterations are negligibly close for some specified level of tolerance. Once this is achieved, stop the iteration, and record the output values as solutions. Otherwise, the algorithm is set back to Step 2.

Numerical results in the figures presented below illustrate the role of optimal intervention strategies in controlling substance abuse in the community. From Figures 4.2 - 4.5, it is clearly evident that optimal control intervention strategies can provide a effective approach on the reduction of substance abuse problem. Our results shows a significant difference between the numbers of drug users in a system with controls and in a system without controls.

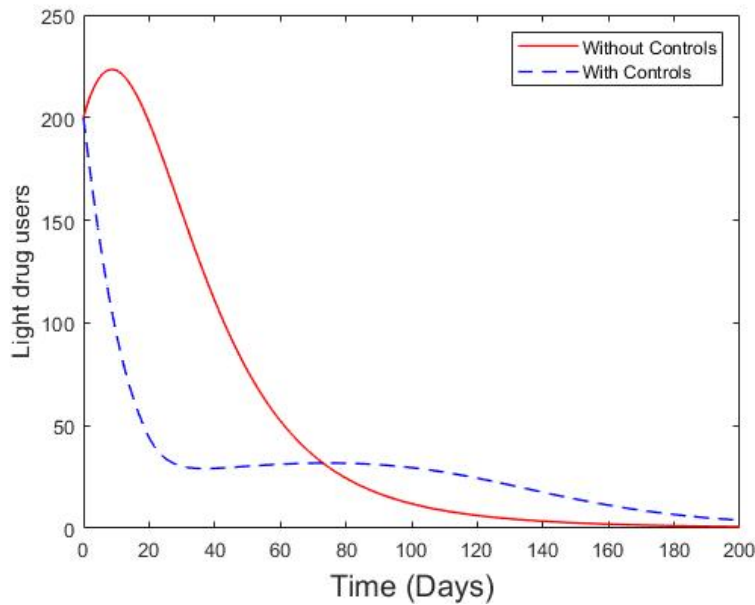


Figure 4.2: Light drug users Population in the community in presence and absence of controls

It can be seen in Figure 4.2 that the control strategy has a positive impact in the community

and is characterised by low levels of drug users more especially in the initial stages of the drug epidemic/initiation process.

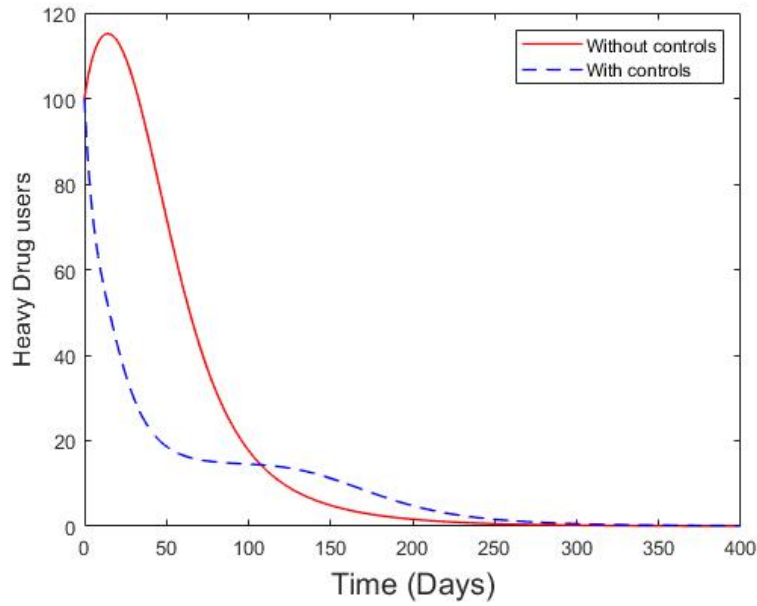


Figure 4.3: Heavy drug users Population in the community

The introduction of the control u on the light drug users class had an impact on the number of heavy drug users, as shown in figure 4.3. The level of heavy drug users decreases mainly due to the reduced progression rate from light drug users.

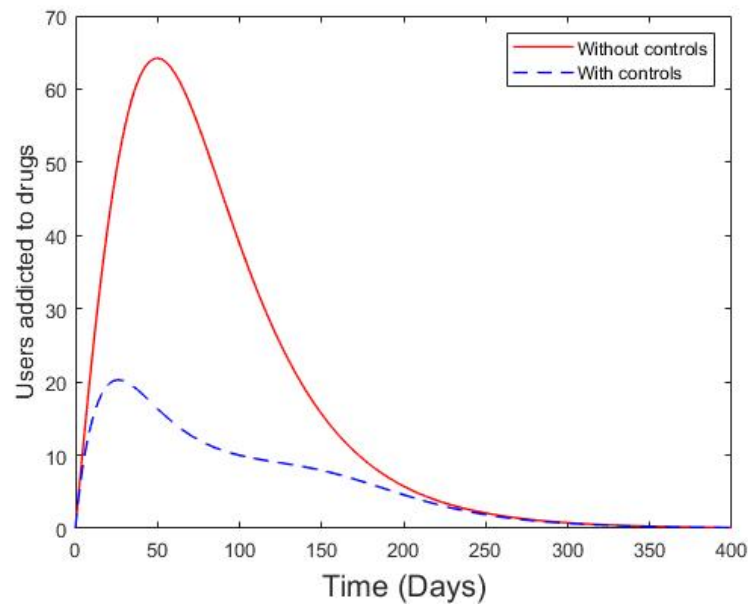
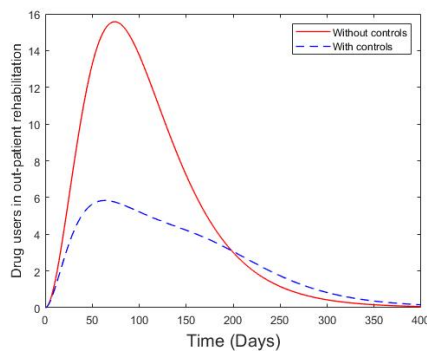
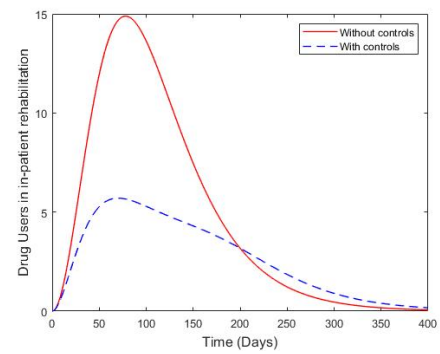


Figure 4.4: Population of Users addicted to drugs in the community

Figure 4.4 depicts that the control strategies plays a very important role in minimising addition to substance abuse. Introduction of rehabilitation helps reduce the users who are addicted to drugs by a significant number as shown in the Figure 4.4.



(a) out-patient rehabilitation



(b) in-patient rehabilitation

Figure 4.5: Population of drug users in an out- and in-patient rehabilitation in the community

Figure 4.5 shows that the control ω helps speed up the quitting rate of drug users in rehabilitation. The control helps in reducing the population of drug users in the rehabilitation centres generally curtailing the drug use problem as well as creating room for other addicted

users who may need to be rehabilitated.

The profiles of the controls explored in the model are shown in Figure 4.6. The profiles show that there is a need for a more strategical intervention at the beginning of the epidemic for substance use to be reduced or eliminated/contained.

Control with awareness program: Awareness programs play an important role as an intervention strategy in the reduction of substance use. We proposed an optimal intervention for this purpose. We proposed awareness to the susceptible population as a way of teaching them about the impact of substance abuse and the knowledge acquired would enable them make informed decisions and not get initiated into substance abuse.

Control with counselling: A proper counselling program can help with reducing drug use in the community. Figure 4.6(b) indicates the importance of the control u in minimising substance use. Figure 4.2 compares the evolution of light drug users with and without control through awareness programs which proves to be positive in decreasing light drug users.

Control with rehabilitation: With the help from counselling, it can be easy for drug users to be enrolled in rehabilitation. From our model, people who are enrolled in rehabilitation are those who are addicted to drugs. It should be noted however that it is difficult to enrol them as they are mostly dependent in drugs. Figure 4.6(c) shows that at the beginning the process of speeding up quitting in the rehabilitation centres was difficult, as we are dealing with out- and in-patient rehabilitation. Drug users in out-patient rehabilitation may decide not to adhere to the program while away from the rehabilitation centre.

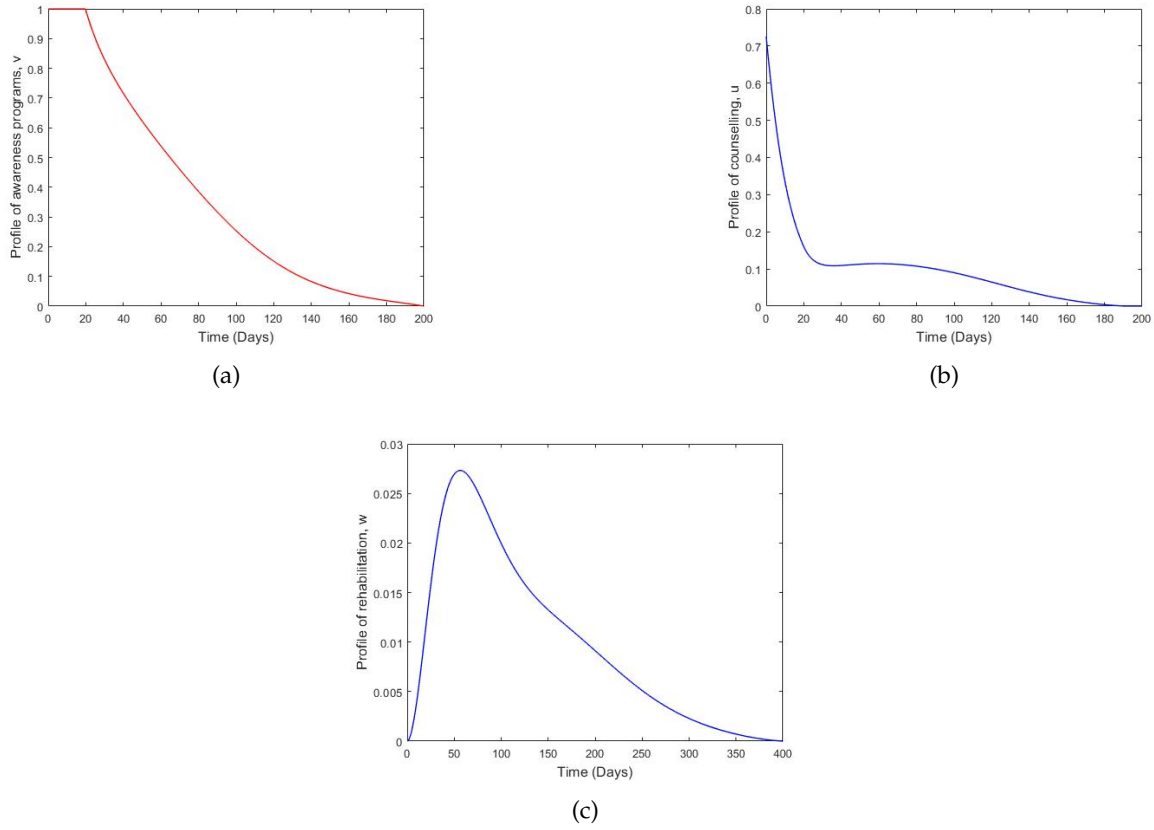


Figure 4.6: Profiles of the controls

4.4 Conclusion

In this Chapter, we introduced modelling of substance abuse with in- and out-patient rehabilitation in order to ascertain ways of minimising substance use in the community. We introduced three controls, control with awareness programs, control with counselling and control with related to accelerated quitting due to rehabilitation. The basic properties of the model were studied as well as the reproduction number $\mathcal{R}_0^{OP}$ of the model obtained and used to infer stability of equilibrium points. The Pontryagin's Maximum Principle was then employed to derive all necessary conditions that enhance substance use control. The numerical results shows that the application of control strategies on drug users in the community were controlled and the results showed the effectiveness of the proposed control strategies by slowing down the progression rate of drug users. The model did not categorize drug users according to their age which can help in choosing the controls that target specific age groups.

Chapter 5

Fractional Order Differential Equations

5.1 Introduction

Fractional-order calculus has been used to model a number of biological phenomena. The major motivation for use of fractional-order differential equations is their consistence in modelling phenomena that involve non-local behaviour, memory and hereditary properties which are characteristic attributes of various biological processes and systems [59]. The memory aspect of the system under study is under the presumption that future states of the system depend on current and previous states. Fractional-order differential equations have been used to model dynamics of various infections namely, Dengue fever [60], HIV [61, 62], cholera [63], TB [64] among others.

We start by stating important definitions of fractional order integrals and derivatives [65]. The fundamental definitions of fractional derivative and integral operators are outlined and more detailed information is presented in [65].

Definition 5.1.1. *The fractional order integral (Riemann-Liouville integral) [66] of $\alpha > 0$ for a function $f : R^+ \rightarrow R$ is defined by*

$$I^\alpha f(\theta) = \frac{1}{\Gamma(\alpha)} \int_0^\theta (\theta - \tau)^{\alpha-1} f(\tau) d\tau,$$

the fractional-order derivative of $f(\theta)$, $\theta > 0$ can be defined as

$$D^\alpha f(\theta) = I^{n-\alpha} D^n f(\theta),$$

where $\alpha \in (n-1, n)$, $n-1$ being the integer part of α and $D = \frac{d}{d\theta}$

Remark 5.1.1. *An effective way to solve these problems is to refrain from using the Riemann-*

Liouville derivatives and use fractional derivatives of Caputo's type, defined in [67] as:

$$D_a^\alpha f(\theta) = \frac{1}{\Gamma(n-\alpha)} \int_a^\theta (\theta-s)^{n-\alpha-1} \frac{d^n}{ds^n} f(s) ds$$

which is robust in handling initial value problems. We now outline some of the main properties of the fractional derivatives and integrals. Let $\beta, \gamma \in \mathbb{R}^+$ and $\alpha \in (0, 1)$, then

- if $I_a^\beta : L^1 \rightarrow L^1$ and $f(\theta) \in L^1$, then $I_a^\beta I_a^\gamma f(\theta) = I_a^{\beta+\gamma} f(\theta)$;
- $\lim_{\beta \rightarrow n} I_a^\beta f(t)$ uniformly on $[a, b]$, $n = 1, 2, 3, \dots$, where $I_a^1 f(\theta) = \int_a^\theta f(s) ds$
- $\lim_{\beta \rightarrow 0} I_a^\beta f(t) = f(\theta)$ weakly
- if $f(\theta)$ is absolutely continuous on $[a, b]$, then $\lim_{\alpha \rightarrow 1} D_a^\alpha f(\theta) = \frac{df(\theta)}{d\theta}$

Definition 5.1.2. The Caputo fractional derivative [62] of order $\alpha \in (n-1, n)$ of a continuous function $f : \mathbb{R}^+ \rightarrow \mathbb{R}$ is defined by

$$D^\alpha f(x) = I^{n-\alpha} D^n f(x), \quad \text{where } D = \frac{d}{dt}$$

Definition 5.1.3. Let $f \in H^1(a, b)$, $b > a$, $\alpha \in [0, 1]$ then the new Caputo derivative of fractional order i.e the Caputo-Fabrizio is defined as [68]

$$D_\theta^\alpha (f(\theta)) = \frac{M(\alpha)}{1-\alpha} \int_a^\theta f'(x) \exp \left[-\alpha \frac{\theta-x}{1-\alpha} \right] dx.$$

where $M(\alpha)$ is given as a normalization function for $M(0) = M(1) = 1$. However, if the function is not into $H^1(a, b)$ then, the derivative can be reformulated as

$$D_\theta^\alpha (f(\theta)) = \frac{\alpha M(\alpha)}{1-\alpha} \int_a^\theta f'(x) \exp \left[-\alpha \frac{\theta-x}{1-\alpha} \right] dx$$

Definition 5.1.4. The special functions of the form [69]

$$E_p(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(pk+1)}, \quad (p \in \mathbb{C}, \operatorname{Re}(p) > 0)$$

and a general function given by

$$E_{p,\mu}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(pk+\mu)}, \quad (p, \mu \in \mathbb{C}, \operatorname{Re}(p) > 0)$$

with $\mathbb{C}$ being the set of complex numbers, are known as Mittag-Leffler functions.

Definition 5.1.5. Let $0 < \alpha < 1$, The fractional integral of order α of a function u is defined by [68]

$$I_t^\alpha(u(t)) = \frac{2(1-\alpha)}{(2-\alpha)\mathcal{M}(\alpha)}u(t) + \frac{2\alpha}{(2-\alpha)\mathcal{M}(\alpha)} \int_0^t u(z)dz, \quad t \geq 0$$

Remark 5.1.2. The following remark is a follow-up to the definition, which says that the fractional Caputo type of order $0 < \alpha < 1$ is an average between the function $u(t)$ and its integer order and this imposes a condition:

$$\frac{2(1-\alpha)}{(2-\alpha)\mathcal{M}(\alpha)} + \frac{2\alpha}{(2-\alpha)\mathcal{M}(\alpha)} = 1$$

and therefore

$$\frac{2(1-\alpha)}{(2-\alpha)\mathcal{M}(\alpha)}\gamma + \frac{2\alpha}{(2-\alpha)\mathcal{M}(\alpha)}\gamma \leq 1 \quad \text{for } 0 < \gamma < 1$$

We note that there are other definitions of fractional derivatives including; Liouville-Caputo [64], Antangana-Baleanu fractional derivative [64] and Riesz derivative [70] among others

5.2 Model Formulation

In this chapter, we introduce a fractional order model of substance abuse which is a reduced model from Chapter 3 and also the same model as in Chapter 4 assuming there are no controls. Although there are many definitions of derivatives of fractional-order, we consider the Caputo's definition, due to its convenience when handling initial conditions of the fractional-order differential equations.

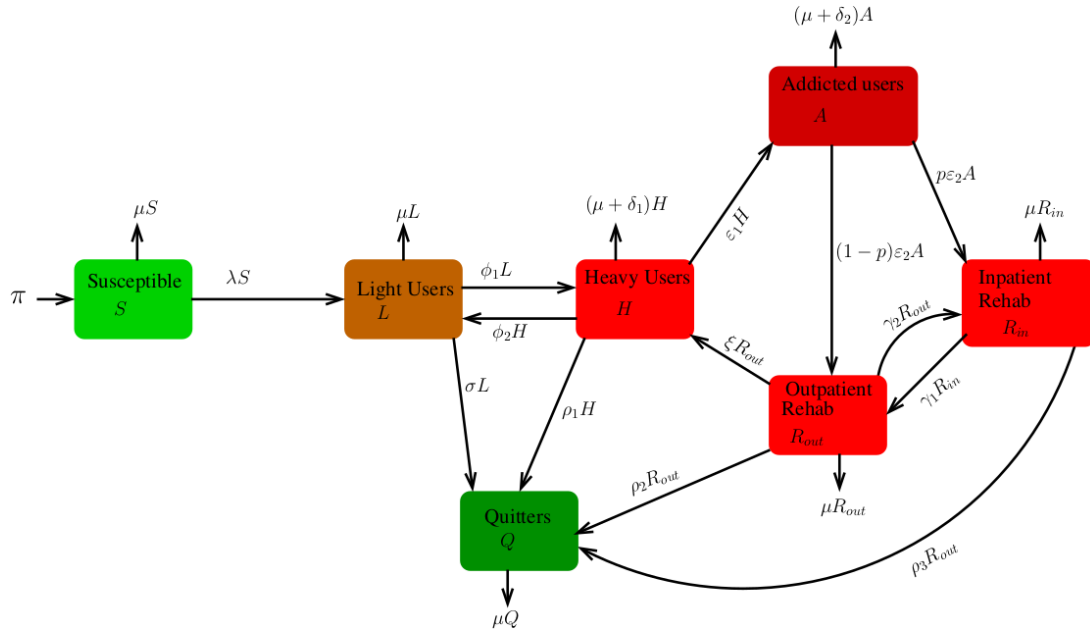


Figure 5.1: Schematic diagram of the model of drug abuse transmission

The model system of equations is given as

$$D^\alpha S = \pi - \mu S - \lambda S, \quad (5.1a)$$

$$D^\alpha L = \lambda S + \phi_2 H - D_1 L, \quad (5.1b)$$

$$D^\alpha H = \phi_1 L + \xi R_{out} - D_2 H, \quad (5.1c)$$

$$D^\alpha A = \varepsilon_1 H - D_3 A, \quad (5.1d)$$

$$D^\alpha R_{out} = (1-p)\varepsilon_2 A + \gamma_1 R_{in} - D_4 R_{out}, \quad (5.1e)$$

$$D^\alpha R_{in} = p\varepsilon_2 A + \gamma_2 R_{out} - D_5 R_{in}, \quad (5.1f)$$

$$D^\alpha Q = \sigma L + \rho_1 H + \rho_2 R_{out} + \rho_3 R_{in} - \mu Q, \quad (5.1g)$$

with the initial conditions

$$S(0) = S^0, \quad L(0) = L^0, \quad H(0) = H^0, \quad A(0) = A^0, \quad R_{out}(0) = R_{out}^0, \quad R_{in}(0) = R_{in}^0, \quad Q(0) = Q^0 \quad (5.2)$$

where $0 < \alpha \leq 1$, $D_1 = \phi_1 + \mu + \sigma$, $D_2 = \phi_2 + \mu + \rho_1 + \varepsilon_1 + \delta_1$, $D_3 = \mu + \delta_2 + \varepsilon_2$, $D_4 = \mu + \gamma_2 + \rho_2 + \xi$, and $D_5 = \rho_3 + \gamma_1 + \mu$.

5.3 Model Analysis

5.3.1 Positivity and Boundedness of Solutions

Since the model we are analysing studies the individuals, then we must ensure that the model is well-posed and the solutions are non-negative and bounded. We show this by the following theorem.

Theorem 5.3.1. *The solutions for the system (5.1) with non-negative initial conditions $\{S(0) = S^0, L(0) = L^0, H(0) = H^0, A(0) = A^0, R_{out}(0) = R_{out}^0, R_{in}(0) = R_{in}^0, Q(0) = Q^0\}$ are non-negative for all $t \geq 0$.*

Proof. To prove Theorem 5.3.1 for the fractional-order model, we transform the respective state variables into their corresponding Cauchy problems, and then use appropriate Mittag-Leffler functions.

It follows from equation (5.1a) that

$$D^\alpha S \geq \pi - (\mu + \hat{\lambda})S. \quad \text{where} \quad \hat{\lambda} = \limsup_{t \geq 0} \{\lambda\}.$$

We want to show that $S(t) > 0$ for all $t \geq 0$. Then equation (5.1a) can be expressed as:

$$D^\alpha S \geq -(\hat{\lambda} + \mu)S, \quad S(0) = S^0 \in \mathbb{N} \quad (5.3)$$

The inequality (5.3) is a Cauchy problem, whose solutions can be found in terms of the one parameter Mittag-Leffler function as

$$S(t) \geq S(0)E_\alpha[-(\hat{\lambda} + \mu)t^\alpha]. \quad (5.4)$$

For a special case, where $\alpha = 1$. Equation (5.4) becomes

$$S(t) \geq S_0 \exp\{-(\hat{\lambda} + \mu)t\}.$$

As $t \rightarrow \infty$ then $S(t) \rightarrow 0^+$. Hence, $S(t)$ is non-negative for all $t > 0$.

From the equation (5.1b)

$$\begin{aligned} D^\alpha L &= \lambda S + \phi_2 H - D_1 L, \\ D^\alpha L &\geq -D_1 L(0), \quad L(0) = L^0 \in \mathbb{N}, \end{aligned}$$

which is a Cauchy problem whose solution can be found in terms of a Mittag-Leffler function as

$$\Rightarrow L(t) \geq L^0 E_\alpha[-D_1 t^\alpha].$$

The same method can be used to show that

$$\begin{cases} H(t) \geq H^0 E_\alpha[-D_2 t^\alpha], \\ A(t) \geq A^0 E_\alpha[-D_3 t^\alpha], \\ R_{out}(t) \geq R_{out}^0 E_\alpha[-D_4 t^\alpha], \\ R_{in}(t) \geq R_{in}^0 E_\alpha[-D_5 t^\alpha], \\ Q(t) \geq Q^0 E_\alpha[-D_6 t^\alpha]. \end{cases}$$

Therefore, all the state variables are nonnegative for all $t \geq 0$, and this completes the proof. $\square$

5.3.2 Boundedness of Solutions

The total population in this model is not constant. Thus, the state variables and parameters are all positive for all $t > 0$. The analysis of the system will therefore be performed in a region of biological significance and the population is bounded.

Theorem 5.3.2. *The feasible region Ω_2 defined by*

$$\Omega_2 = \left\{ (S(t), L(t), H(t), A(t), R_{out}(t), R_{in}(t), Q(t)) \in \mathbb{R}_+^7 \mid N(t) \leq \frac{\pi}{\mu} \right\},$$

with initial conditions as given in (5.2), is positively invariant and attracting with respect to the system (5.1) for all $t > 0$.

Proof. Evolution equation for the change in population is given by

$$\begin{aligned} D^\alpha(N(t)) &= D^\alpha S(t) + D^\alpha L(t) + D^\alpha H(t) + D^\alpha A(t) + D^\alpha R_{out}(t) + D^\alpha R_{in}(t) + D^\alpha Q(t), \\ &= \pi - \mu N - \delta_1 H - \delta_2 A, \end{aligned}$$

which reduces to a heterogeneous Cauchy problem

$$D^\alpha N(t) = \pi - \mu N, \quad N(0) = N^0 \in \mathbb{N},$$

whose solution is given in terms of Mittag-Leffler function as

$$N(t) \leq N^0 E_\alpha[-\mu t^\alpha] + \pi \int_0^t (t-s)^{\alpha-1} E_{\alpha,\alpha}[-\mu(t-s)^\alpha] ds. \quad (5.5)$$

For an integer-order case, when $\alpha = 1$, equation (5.5) reduces to

$$N(t) \leq \frac{\pi}{\mu} + \left(N^0 - \frac{\pi}{\mu} \right) e^{-\mu t}.$$

Taking the limit on both sides, from the equation above, as $t \rightarrow \infty$, we get

$$\begin{aligned} \lim_{t \rightarrow \infty} N(t) &\leq \left(N^0 - \frac{\pi}{\mu} \right) \lim_{t \rightarrow \infty} e^{-\mu t}, \\ &= \frac{\pi}{\mu}. \end{aligned}$$

Therefore, it can be easily observed that $\frac{\pi}{\mu}$ is the upper-bound of $N(t)$. Conversely, if $N^0 > \frac{\pi}{\mu}$, then N will decrease to $\frac{\pi}{\mu}$ as $t \rightarrow \infty$. That is, if $N^0 > \frac{\pi}{\mu}$, then the solution $\{S(t), L(t), H(t), A(t), R_{out}(t), R_{in}(t), Q(t)\}$ approaches Ω_2 asymptotically. Therefore, Ω_2 is positively invariant. $\square$

5.3.3 Drug Free Equilibrium

The model has a drug free equilibrium given by

$$\mathbb{E}_0 := (S^*, L^*, H^*, A^*, R_{out}^*, R_{in}^*, Q^*) = \left(\frac{\pi}{\mu}, 0, 0, 0, 0, 0, 0 \right).$$

In order to analyse the existence of the equilibrium points, we ought to determine the reproduction number which is evaluated in terms of the model parameters.

5.3.4 The basic Reproduction Number

To calculate the reproduction number $\mathcal{R}_0^{FDE}$ of the model (5.1) we use the next generation matrix model described in [39]. We use the same procedure as used in Chapter 4. By assuming that the controls $\nu = u = 0$, except for the control ω which will be 1 because it is used as the acceleration for quitting for drug users in rehabilitation. Then our basic reproduction number is given as the spectral radius of the next generation matrix FV^{-1} such that

$$\mathcal{R}_0^{FDE} = \rho(FV^{-1}) = \mathcal{R}_{0L} + \mathcal{R}_{0H} + \mathcal{R}_{0A} + \mathcal{R}_{0R_{out}}$$

where

$$\begin{cases} \mathcal{R}_{0L}^{FDE} &= \frac{\beta(1-\Psi_2-\Psi_3-\Psi_4)}{D_1(1-\Psi_1-\Psi_2-\Psi_3-\Psi_4+\Psi_1\Psi_2)}, \\ \mathcal{R}_{0H}^{FDE} &= \frac{\beta\eta_1\phi_1(1-\Psi_2)}{D_1D_2(1-\Psi_1-\Psi_2-\Psi_3-\Psi_4+\Psi_1\Psi_2)}, \\ \mathcal{R}_{0A}^{FDE} &= \frac{\beta\eta_2\phi_1\varepsilon_1(1-\Psi_2)}{D_1D_2D_3(1-\Psi_1-\Psi_2-\Psi_3-\Psi_4+\Psi_1\Psi_2)}, \\ \mathcal{R}_{0R_{out}}^{FDE} &= \frac{\beta\eta_3[D_5(1-p)+\gamma_1p]\phi_1\varepsilon_1\varepsilon_2}{D_1D_2D_3D_4D_5(1-\Psi_1-\Psi_2-\Psi_3-\Psi_4+\Psi_1\Psi_2)}, \end{cases}$$

where

$$\Psi_1 = \frac{\phi_1 \phi_2}{D_1 D_2}, \quad \Psi_2 = \frac{\gamma_1 \gamma_2}{D_4 D_5}, \quad \Psi_3 = \frac{\xi(1-p)\varepsilon_1 \varepsilon_2}{D_2 D_3 D_4}, \quad \Psi_4 = \frac{\xi \gamma_1 p \varepsilon_1 \varepsilon_2}{D_2 D_3 D_4 D_5}$$

The reproduction number $\mathcal{R}_0$ is given in five components indicating the contribution of five different subpopulations in the drug initiation process. The same procedure in Chapter 4 was used to explain the terms used.

5.4 Drug Persistent Equilibrium

At the drug persistent equilibrium, the system satisfies

$$0 = \pi - \mu S^* - \lambda^* S^*, \quad (5.6a)$$

$$0 = \lambda^* S^* + \phi_2 H^* - D_1 L^*, \quad (5.6b)$$

$$0 = \phi_1 L^* + \xi R_{out}^* - D_2 H^*, \quad (5.6c)$$

$$0 = \varepsilon_1 H^* - D_3 A^*, \quad (5.6d)$$

$$0 = (1-p)\varepsilon_2 A^* + \gamma_1 R_{in}^* - D_4 R_{out}^*, \quad (5.6e)$$

$$0 = p\varepsilon_2 A^* + \gamma_2 R_{out}^* - D_5 R_{in}^*, \quad (5.6f)$$

$$0 = \sigma L^* + \rho_1 H^* + \rho_2 R_{out}^* + \rho_3 R_{in}^* - \mu Q^*, \quad (5.6g)$$

where

$$\lambda^* = \frac{\beta(L^* + \eta_1 H^* + \eta_2 A^* + \eta_3 R_{out}^*)}{S^* + L^* + H^* + A^* + R_{out}^* + R_{in}^* + Q^*}.$$

From equation (5.6g)

$$Q^* = \frac{1}{\mu} (\sigma L^* + \rho_1 H^* + \rho_2 R_{out}^* + \rho_3 R_{in}^*).$$

From equation (5.6e), we have

$$R_{in}^* = \frac{1}{D_5} (p\varepsilon_2 A^* + \gamma_2 R_{out}^*). \quad (5.7)$$

From equation (5.6f), we obtain

$$R_{out}^* = \frac{1}{D_4} ((1-p)\varepsilon_2 A^* + \gamma_1 R_{in}^*). \quad (5.8)$$

We now substitute (5.7) into (5.8) to obtain

$$R_{out}^* = \frac{1}{D_4} \left[(1-p)\varepsilon_2 A^* + \frac{\gamma_1}{D_5} (p\varepsilon_2 A^* + \gamma_2 R_{out}^*) \right].$$

We express R_{out}^* in terms of A^* and obtain

$$R_{out}^* = \frac{[D_5(1-p)\varepsilon_2 + \gamma_1 p\varepsilon_2] A^*}{D_4 D_5 (1 - \Psi_2)}. \quad (5.9)$$

From equation (5.6d), we obtain

$$H^* = \frac{\varepsilon_1 A^*}{D_3}. \quad (5.10)$$

From equation (5.6c), we have

$$H^* = \frac{1}{D_2} (\phi_1 L^* + \xi R_{out}^*). \quad (5.11)$$

Substituting equation (5.9) into equation (5.11) we obtain

$$H^* = \frac{D_4 D_5 \phi_1 (1 - \Psi_2) L^* + (D_5(1-p)\varepsilon_2 \xi + \gamma_1 p\varepsilon_2 \xi) A^*}{D_2 D_4 D_5 (1 - \Psi_2)}. \quad (5.12)$$

Substituting equation (5.10) into equation (5.12) we get

$$\begin{aligned} \frac{D_3 A^*}{\varepsilon_1} &= \frac{D_4 D_5 \phi_1 (1 - \Psi_2) L^* + (D_5(1-p)\varepsilon_2 \xi + \gamma_1 p\varepsilon_2 \xi) A^*}{D_2 D_4 D_5 (1 - \Psi_2)} \\ \Rightarrow L^* &= \frac{D_2 D_3 (1 - \Psi_2 - \Psi_3 - \Psi_4) A^*}{\phi_1 \varepsilon_1 (1 - \Psi_2)}. \end{aligned} \quad (5.13)$$

L^* can be expressed as $L^* = \Psi_5 A^*$ where $\Psi_5 = \frac{D_2 D_3 (1 - \Psi_2 - \Psi_3 - \Psi_4)}{\phi_1 \varepsilon_1 (1 - \Psi_2)}$. We now substitute equations (5.9), (5.12) and (5.13) into equation (5.6b) to get

$$\beta (L^* + \eta_1 H^* + \eta_2 A^* + \eta_3 R_{out}^*) \frac{S^*}{N^*} = D_1 L^* - \phi_2 H^*, \quad (5.14)$$

where $\lambda = \frac{\beta(L^* + \eta_1 H^* + \eta_2 A^* + \eta_3 R_{out}^*)}{N^*}$.

From the Left Hand Side (LHS) of equation (5.14), we have

$$\begin{aligned} LHS &= \frac{\beta S^*}{N^*} \left[\frac{D_2 D_3 D_4 D_5 (1 - \Psi_2) - (D_5(1-p)\varepsilon_1 \varepsilon_2 \xi + \gamma_1 p\varepsilon_1 \varepsilon_2 \xi)}{D_4 D_5 \phi_1 (1 - \Psi_2)} + \frac{\eta_1 D_3}{\varepsilon_1} + \eta_2 + \frac{\eta_3 [D_5(1-p)\varepsilon_2 + \gamma_1 p\varepsilon_2]}{D_4 D_5 (1 - \Psi_2)} \right] A^* \\ &= \frac{\beta S^* A^*}{N^*} \left[\frac{[D_2 D_3 D_4 D_5 (1 - \Psi_2) - (D_5(1-p)\varepsilon_1 \varepsilon_2 \xi + \gamma_1 p\varepsilon_1 \varepsilon_2 \xi)] + \eta_1 D_3 D_4 D_5 \phi_1 \varepsilon_1 (1 - \Psi_2) + \eta_2 D_4 D_5 \phi_1 \varepsilon_1 (1 - \Psi_2) + \eta_3 [D_5(1-p)\varepsilon_2 + \gamma_1 p\varepsilon_2] \phi_1 \varepsilon_1}{D_4 D_5 \phi_1 \varepsilon_1 (1 - \Psi_2)} \right]. \end{aligned}$$

The Right Hand Side (RHS) of equation (5.14) gives

$$\begin{aligned} RHS &= \left[D_1 \left[\frac{(D_2 D_3 D_4 D_5 (1 - \Psi_2) - (D_5 (1 - p) \varepsilon_1 \varepsilon_2 \xi + \gamma_1 p \varepsilon_1 \varepsilon_2 \xi))}{D_4 D_5 \phi_1 \varepsilon_1 (1 - \Psi_2)} \right] - \frac{\phi_1 \phi_2 D_3}{\varepsilon_1} \right] A^*, \\ &= \left[\frac{D_1 D_2 D_3 D_4 D_5 (1 - \Psi_2) - D_1 (D_5 (1 - p) \varepsilon_1 \varepsilon_2 \xi + \gamma_1 p \varepsilon_1 \varepsilon_2 \xi) - \phi_1 \phi_2 D_3 D_4 D_5 (1 - \Psi_2)}{D_4 D_5 \phi_1 \varepsilon_1 (1 - \Psi_2)} \right] A^*. \end{aligned}$$

We observe that one of the solutions is $A^* = 0$, which corresponds to the drug free equilibrium. If $A^* \neq 0$, then we have

$$\begin{aligned} RHS &= \frac{D_1 D_2 D_3 D_4 D_5 \left[(1 - \Psi_2) - \frac{(1 - p \varepsilon_1 \varepsilon_2 \xi)}{D_2 D_3 D_4} - \frac{\gamma_1 p \varepsilon_1 \varepsilon_2 \xi}{D_2 D_3 D_4 D_5} - \frac{\phi_1 \phi_2}{D_1 D_2} + \frac{\phi_1 \phi_2}{D_1 D_2} \Psi_2 \right]}{D_4 D_5 \phi_1 \varepsilon_1 (1 - \Psi_2)}, \\ &= \left[\frac{D_1 D_2 D_3 D_4 D_5 (1 - \Psi_1 - \Psi_2 - \Psi_3 - \Psi_4 + \Psi_1 \Psi_2)}{D_4 D_5 \phi_1 \varepsilon_1 (1 - \Psi_2)} \right]. \end{aligned}$$

Combining the LHS and RHS terms, we obtain

$$\frac{S^*}{N^*} \left[\frac{\beta D_2 D_3 D_4 D_5 (1 - \Psi_1 - \Psi_2 - \Psi_4) + \beta \eta_1 D_3 D_4 D_5 (1 - \Psi_2) \phi + \beta \eta_2 D_4 D_5 \phi_1 \varepsilon_1 (1 - \Psi_2) + \beta \eta_3 (D_5 (1 - p) + \gamma_1 p) \phi_1 \varepsilon_1 \varepsilon_2}{D_1 D_2 D_3 D_4 D_5 (1 - \Psi_1 - \Psi_2 - \Psi_3 - \Psi_4 + \Psi_1 \Psi_2)} \right] = 1.$$

The above equation gives

$$\frac{S^*}{N^*} [\mathcal{R}_0^{FDE}] = 1.$$

Then

$$\frac{S^*}{N^*} = \frac{1}{\mathcal{R}_0^{FDE}}. \quad (5.15)$$

Combining the equations (5.6a) and (5.6b), we obtain

$$\begin{aligned} 0 &= \pi - \mu S^* + \phi_2 H^* - D_1 L^* \\ \Rightarrow S^* &= \frac{\pi}{\mu} + \frac{1}{\mu} [\phi_2 H^* - D_1 L^*] \\ \therefore S^* &= \frac{\pi}{\mu} - \Psi_6 A^*, \quad \Psi_5 > 0 \end{aligned}$$

where $\Psi_6 = \frac{D_1 D_2 D_3}{\mu} \left[\frac{1 - \Psi_1 - \Psi_2 - \Psi_3 - \Psi_4 + \Psi_1 \Psi_2}{\phi_1 \varepsilon_1 (1 - \Psi_2)} \right]$

We express the steady state variables R_{in}^* and Q^* in terms of A^* as follows

$$\begin{cases} R_{in}^* &= \Psi_7 A^*, \\ Q^* &= \Psi_8 A^*, \end{cases}$$

where $\Psi_7 = \frac{[p\varepsilon_2 D_4 D_5 (1 - \Psi_2) + D_5 (1 - p)\varepsilon_2 \gamma_2 + \gamma_1 \gamma_2 p \varepsilon_2] A^*}{D_4 D_5^2 (1 - \Psi_2)}$ and

$$\Psi_8 = \frac{1}{\mu} \left(\frac{\sigma D_2 D_3 (1 - \Psi_2 - \Psi_3 - \Psi_4)}{\phi_1 \varepsilon_1 (1 - \Psi_2) + \frac{\rho_1 D_3}{\varepsilon_1} + \frac{\rho_2 (D_5 (1 - p)\varepsilon_2 + \gamma_1 p \varepsilon_2)}{D_4 D_5 (1 - \Psi_2)} + \rho_3 \Psi_6 \right).$$

We then express N^* in terms of A^*

$$\begin{aligned} N^* &= S^* + L^* + H^* + A^* + R_{out}^* + R_{in}^* + Q^* \\ &= \frac{\pi}{\mu} - \Psi_9 A^*, \end{aligned}$$

where $\Psi_9 = \Psi_6 - \Psi_5 - \frac{\varepsilon_1}{D_3} - 1 - \frac{D_5 (1 - p)\varepsilon_2 + \gamma_1 p \varepsilon_2}{D_4 D_5 (1 - \Psi_2)} - \Psi_7 - \Psi_8$.

Substitute for S^* and N^* into equation (5.15) to obtain

$$\frac{\frac{\pi}{\mu} - \Psi_6 A^*}{\frac{\pi}{\mu} - \Psi_9 A^*} = \frac{1}{\mathcal{R}_0^{FDE}}.$$

Finding the value of A^* we get

$$A^* = \frac{\frac{\pi}{\mu} (\mathcal{R}_0^{FDE} - 1)}{\Psi_6 (\mathcal{R}_0^{FDE} - 1) + \Psi_{10}},$$

where $\Psi_{10} = \Psi_5 + \frac{D_3}{\varepsilon_1} + 1 + \frac{D_5 (1 - p)\varepsilon_2 + \gamma_1 p \varepsilon_2}{D_4 D_5 (1 - \Psi_2)} + \Psi_7 + \Psi_8$.

We then obtain an explicit expression for S^* in terms of the model parameters such that

$$S^* = \frac{\frac{\pi}{\mu} \Psi_{10}}{\Psi_6 (\mathcal{R}_0^{FDE} - 1) + \Psi_{10}}.$$

Therefore, the model has a unique endemic equilibrium when $\mathcal{R}_0^{FDE} > 1$ and drug free equilibrium whenever $\mathcal{R}_0^{FDE} \leq 1$.

5.4.1 Existence and uniqueness of substance abuse fractional order solutions

In this section, existence and uniqueness of the solutions of system (5.1) is considered, with the help of fixed point theory [59]. The fraction integral operator used in the analysis was developed in [68] based on Caputo-Fabrizio derivative without a singular kernel. We use

the fractional integral operator in [68] and we obtain

$$\begin{aligned}
S(t) - S(0) &= I_t^\alpha \{\pi - \mu S - \lambda S\}, \\
L(t) - L(0) &= I_t^\alpha \{\lambda S + \phi_2 H - D_1 L\}, \\
H(t) - H(0) &= I_t^\alpha \{\phi_1 L + \xi R_{out} - D_2 H\}, \\
A(t) - A(0) &= I_t^\alpha \{\varepsilon_1 H - D_3 A\}, \\
R_{out}(t) - R_{out}(0) &= I_t^\alpha \{(1-p)\varepsilon_2 A + \gamma_1 R_{in} - D_4 R_{out}\}, \\
R_{in}(t) - R_{in}(0) &= I_t^\alpha \{p\varepsilon_2 A + \gamma_2 R_{out} - D_5 R_{in}\}, \\
Q(t) - Q(0) &= I_t^\alpha \{\sigma L + \rho_1 H + \rho_2 R_{out} + \rho_3 R_{in} - \mu Q\}.
\end{aligned}$$

We use the notations in [68] and we obtain:

$$\begin{aligned}
S(t) - S(0) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \{\pi - \mu S - \lambda S\} \\
&\quad + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t \{\pi - \mu S(z) - \lambda(z)S(z)\} dz, \\
L(t) - L(0) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \{\lambda S + \phi_2 H - D_1 L\} \\
&\quad + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t \{\lambda(z)S(z) + \phi_2 H(z) - D_1 L(z)\} dz, \\
H(t) - H(0) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \{\phi_1 L + \xi R_{out} - D_2 H\} \\
&\quad + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t \{\phi_1 L(z) + \xi R_{out}(z) - D_2 H(z)\} dz, \\
A(t) - A(0) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \{\varepsilon_1 H - D_3 A\} \\
&\quad + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t \{\varepsilon_1 H(z) - D_3 A(z)\} dz, \\
R_{out}(t) - R_{out}(0) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \{(1-p)\varepsilon_2 A + \gamma_1 R_{in} - D_4 R_{out}\} \\
&\quad + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t \{(1-p)\varepsilon_2 A(z) + \gamma_1 R_{in}(z) - D_4 R_{out}(z)\} dz, \\
R_{in}(t) - R_{in}(0) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \{p\varepsilon_2 A + \gamma_2 R_{out} - D_5 R_{in}\} \\
&\quad + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t \{p\varepsilon_2 A(z) + \gamma_2 R_{out}(z) - D_5 R_{in}(z)\} dz, \\
Q(t) - Q(0) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \{\sigma L + \rho_1 H + \rho_2 R_{out} + \rho_3 R_{in} - \mu Q\} \\
&\quad + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t \{\sigma L(z) + \rho_1 H(z) + \rho_2 R_{out}(z) + \rho_3 R_{in}(z) - \mu Q(z)\} dz
\end{aligned} \tag{5.16}$$

We let the functions add up to the kernels for the respective state variables which we interpret for clarity as:

$$K_1(t, S) = \pi - \mu S(t) - \lambda(t)S(t), \quad (5.17a)$$

$$K_2(t, L) = \lambda(t)S(t) + \phi_2 H(t) - D_1 L(t), \quad (5.17b)$$

$$K_3(t, H) = \phi_1 L(t) + \xi R_{out}(t) - D_2 H(t), \quad (5.17c)$$

$$K_4(t, A) = \varepsilon_1 H(t) - D_3 A(t), \quad (5.17d)$$

$$K_5(t, R_{out}) = (1 - p)\varepsilon_2 A(t) + \gamma_1 R_{in}(t) - D_4 R_{out}(t), \quad (5.17e)$$

$$K_6(t, R_{in}) = p\varepsilon_2 A(t) + \gamma_2 R_{out}(t) - D_5 R_{in}(t), \quad (5.17f)$$

$$K_7(t, Q) = \sigma L(t) + \rho_1 H(t) + \rho_2 R_{out}(t) + \rho_3 R_{in}(t) - \mu Q(t). \quad (5.17g)$$

Theorem 5.4.1. *The kernels $K_1, K_2, \dots, K_7$ hold the Lipchitz condition and contraction, if the following inequality $0 \leq \omega_1, \omega_2, \dots, \omega_7 < 1$, where*

$$\begin{cases} \omega_1 &= \mu + \hat{\lambda}, \\ \omega_2 &= \beta + D_1, \\ \omega_3 &= D_2, \quad \omega_4 = D_3, \\ \omega_5 &= D_4, \quad \omega_6 = D_5, \quad \omega_7 = \mu, \end{cases}$$

holds, where $\hat{\lambda} = \limsup_{t \geq 0} \{\lambda\}$.

Proof. We begin with kernel K_1 . Suppose that S and S^1 are functions such that $S = S(t)$ and $S^1 = S(t_1)$, then we have

$$\| K_1(t, S) - K_1(t, S^1) \| = \| -\mu(S(t) - S(t_1)) - \hat{\lambda}(S(t) - S(t_1)) \| . \quad (5.18)$$

Applying triangle inequality on equation (5.18), we get

$$\begin{aligned} \| K_1(t, S) - K_1(t, S^1) \| &\leq \mu \| (S(t) - S(t_1)) \| + \hat{\lambda} \| (S(t) - S(t_1)) \| \\ &\leq (\mu + \hat{\lambda}) \| S(t) - S(t_1) \| . \end{aligned} \quad (5.19)$$

Taking $\omega_1 = \mu + \hat{\lambda}$ then the inequality (5.19) can be written as

$$\| K_1(t, S) - K_1(t, S^1) \| \leq \omega_1 \| S(t) - S(t_1) \| .$$

For the remaining kernels, the Lipchitz condition can be easily verified and given as follows:

$$\begin{aligned}
& \| K_2(t, L) - K_2(t, L^1) \| \leq \omega_2 \| L(t) - L(t_1) \|, \\
& \| K_3(t, H) - K_3(t, H^1) \| \leq \omega_3 \| H(t) - H(t_1) \|, \\
& \| K_4(t, A) - K_4(t, A^1) \| \leq \omega_4 \| A(t) - A(t_1) \|, \\
& \| K_5(t, R_{out}) - K_5(t, R_{out}^1) \| \leq \omega_5 \| R_{out}(t) - R_{out}(t_1) \|, \\
& \| K_6(t, R_{in}) - K_6(t, R_{in}^1) \| \leq \omega_6 \| R_{in}(t) - R_{in}(t_1) \|, \\
& \| K_7(t, Q) - K_7(t, Q^1) \| \leq \omega_7 \| Q(t) - Q(t_1) \|.
\end{aligned}$$

Using the kernels in equations (5.17), then equation (5.16) becomes

$$\begin{aligned}
S(t) &= S(0) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_1(t, S) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_1(z, S) dz, \\
L(t) &= L(0) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_2(t, L) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_2(z, L) dz, \\
H(t) &= H(0) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_3(t, H) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_3(z, H) dz, \\
A(t) &= A(0) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_4(t, A) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_4(z, A) dz, \\
R_{out}(t) &= R_{out}(0) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_5(t, R_{out}) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_5(z, R_{out}) dz, \\
R_{in}(t) &= R_{in}(0) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_6(t, R_{in}) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_6(z, R_{in}) dz, \\
Q(t) &= Q(0) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_7(t, Q) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_7(z, Q) dz.
\end{aligned} \tag{5.20}$$

The following recursive formula is presented on system (5.20), and the resultant system is

$$\begin{aligned}
S_n(t) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_1(t, S_{n-1}) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_1(z, S_{n-1}) dz, \\
L_n(t) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_2(t, L_{n-1}) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_2(z, L_{n-1}) dz, \\
H_n(t) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_3(t, H_{n-1}) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_3(z, H_{n-1}) dz, \\
A_n(t) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_4(t, A_{n-1}) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_4(z, A_{n-1}) dz, \\
R_{out_n}(t) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_5(t, R_{out_{n-1}}) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_5(z, R_{out_{n-1}}) dz, \\
R_{in_n}(t) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_6(t, R_{in_{n-1}}) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_6(z, R_{in_{n-1}}) dz, \\
Q_n(t) &= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} K_7(t, Q_{n-1}) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t K_7(z, Q_{n-1}) dz.
\end{aligned}$$

With the initial conditions $S_0(t) = S(0)$, $L_0(t) = L(0)$, $H_0(t) = H(0)$, $A_0(t) = A(0)$, $R_{out_0}(t) = R_{out}(0)$, $R_{in_0}(t) = R_{in}(0)$, $Q_0(t) = Q(0)$

Then, we obtain the following expressions of each of the state variables of the recursive sys-

tem:

$$\begin{aligned}
\phi_n^S(t) &= S_n(t) - S_{n-1}(t) \\
&= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} (K_1(t, S_{n-1}) - K_1(t, S_{n-2})) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t (K_1(z, S_{n-1}) - K_1(z, S_{n-2})) dz, \\
\phi_n^L(t) &= L_n(t) - L_{n-1}(t) \\
&= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} (K_2(t, L_{n-1}) - K_2(t, L_{n-2})) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t (K_2(z, L_{n-1}) - K_2(z, L_{n-2})) dz, \\
\phi_n^H(t) &= H_n(t) - H_{n-1}(t) \\
&= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} (K_3(t, H_{n-1}) - K_3(t, H_{n-2})) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t (K_3(z, H_{n-1}) - K_3(z, H_{n-2})) dz, \\
\phi_n^A(t) &= A_n(t) - A_{n-1}(t) \\
&= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} (K_4(t, A_{n-1}) - K_4(t, A_{n-2})) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t (K_4(z, A_{n-1}) - K_4(z, A_{n-2})) dz, \\
\phi_n^{R_{out}}(t) &= R_{out_n}(t) - R_{out_{n-1}}(t) \\
&= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} (K_5(t, R_{out_{n-1}}) - K_5(t, R_{out_{n-2}})) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t (K_5(z, R_{out_{n-1}}) - K_5(z, R_{out_{n-2}})) dz, \\
\phi_n^{R_{in}}(t) &= R_{in_n}(t) - R_{in_{n-1}}(t) \\
&= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} (K_6(t, R_{in_{n-1}}) - K_6(t, R_{in_{n-2}})) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t (K_6(z, R_{in_{n-1}}) - K_6(z, R_{in_{n-2}})) dz, \\
\phi_n^Q(t) &= Q_n(t) - Q_{n-1}(t) \\
&= \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} (K_7(t, Q_{n-1}) - K_7(t, Q_{n-2})) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t (K_7(z, Q_{n-1}) - K_7(z, Q_{n-2})) dz.
\end{aligned}$$

We note that

$$\begin{cases}
S_n(t) &= \sum_{i=1}^n \phi_i^S(t), \\
L_n(t) &= \sum_{i=1}^n \phi_i^L(t), \\
H_n(t) &= \sum_{i=1}^n \phi_i^H(t), \\
A_n(t) &= \sum_{i=1}^n \phi_i^A(t), \\
R_{out_n}(t) &= \sum_{i=1}^n \phi_i^{R_{out}}(t), \\
R_{in_n}(t) &= \sum_{i=1}^n \phi_i^{R_{in}}(t), \\
Q_n(t) &= \sum_{i=1}^n \phi_i^Q(t).
\end{cases}$$

By using a step-by-step calculations using the kernel $K_1(t, S)$,

$$\begin{aligned}
\|\phi_n^S(t)\| &= \|S_n(t) - S_{n-1}(t)\| \\
&= \left\| \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} (K_1(t, S_{n-1}) - K_1(t, S_{n-2})) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t (K_1(z, S_{n-1}) - K_1(z, S_{n-2})) dz \right\|.
\end{aligned} \tag{5.21}$$

Applying the triangle inequality, equation (5.21) reduces to

$$\begin{aligned}
\|S_n(t) - S_{n-1}(t)\| &\leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \|K_1(t, S_{n-1}) - K_1(t, S_{n-2})\| \\
&\quad + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t \|K_1(z, S_{n-1}) - K_1(z, S_{n-2})\| dz.
\end{aligned}$$

Since the kernel satisfy the Lipchitz condition, we obtain

$$\begin{aligned} \| S_n(t) - S_{n-1}(t) \| &\leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \| S_{n-1}(t) - S_{n-2}(t) \| \\ &+ \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t \| S_{n-1}(z) - S_{n-2}(z) \| dz. \end{aligned} \quad (5.22)$$

Thus, equation (5.22) can be reduced to

$$\| \phi_n^S(t) \| \leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_1 \| \phi_{n-1}^S(t) \| + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_1 \int_0^t \| \phi_{n-1}^S(z) \| dz. \quad (5.23)$$

Similarly, using the same approach for the rest of the state variables, we obtain

$$\begin{aligned} \| \phi_n^L(t) \| &\leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_2 \| \phi_{n-1}^L(t) \| + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_2 \int_0^t \| \phi_{n-1}^L(z) \| dz, \\ \| \phi_n^H(t) \| &\leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_3 \| \phi_{n-1}^H(t) \| + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_3 \int_0^t \| \phi_{n-1}^H(z) \| dz, \\ \| \phi_n^A(t) \| &\leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_4 \| \phi_{n-1}^A(t) \| + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_4 \int_0^t \| \phi_{n-1}^A(z) \| dz, \\ \| \phi_n^{R_{out}}(t) \| &\leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_5 \| \phi_{n-1}^{R_{out}}(t) \| + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_5 \int_0^t \| \phi_{n-1}^{R_{out}}(z) \| dz, \\ \| \phi_n^{R_{in}}(t) \| &\leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_6 \| \phi_{n-1}^{R_{in}}(t) \| + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_6 \int_0^t \| \phi_{n-1}^{R_{in}}(z) \| dz, \\ \| \phi_n^Q(t) \| &\leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_7 \| \phi_{n-1}^Q(t) \| + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_7 \int_0^t \| \phi_{n-1}^Q(z) \| dz. \end{aligned} \quad (5.24)$$

□

In line with the results above, we state the following theorem

Theorem 5.4.2. *A solution to the fractional-order substance abuse model (5.1) exists, if there exists some t_0 such that*

$$\frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_1 + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_1 t_0 \leq 1.$$

Proof. The state variables $L(t)$, $H(t)$, $A(t)$, $R_{out}(t)$, $R_{in}(t)$, and $Q(t)$ are bounded and the Lipchitz condition holds for the kernels $K_i(t)$ for $i = 1, 2, \dots, 7$. Then by considering equations

(5.23) and (5.24), we obtain the following relations by using the recursive method:

$$\begin{aligned}
\| \phi_n^S(t) \| &\leq \| S_n(0) \| \left[\frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_1 + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_1 t \right]^n, \\
\| \phi_n^L(t) \| &\leq \| L_n(0) \| \left[\frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_2 + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_2 t \right]^n, \\
\| \phi_n^H(t) \| &\leq \| H_n(0) \| \left[\frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_3 + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_3 t \right]^n, \\
\| \phi_n^A(t) \| &\leq \| A_n(0) \| \left[\frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_4 + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_4 t \right]^n, \\
\| \phi_n^{R_{out}}(t) \| &\leq \| R_{outn}(0) \| \left[\frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_5 + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_5 t \right]^n, \\
\| \phi_n^{R_{in}}(t) \| &\leq \| R_{inn}(0) \| \left[\frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_6 + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_6 t \right]^n, \\
\| \phi_n^Q(t) \| &\leq \| Q_n(0) \| \left[\frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_7 + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_7 t \right]^n.
\end{aligned}$$

Hence, the existence and continuity of the above solutions is proved. In order to show that the function is a solution, we set the terms such that

$$\begin{aligned}
S(t) - S(0) &= S_n(t) - B_n(t), L(t) - L(0) = L_n(t) - C_n(t), H(t) - H(0) = H_n(t) - D_n(t), \\
A(t) - A(0) &= A_n(t) - E_n(t), R_{out}(t) - R_{out}(0) = (R_{out})_n(t) - F_n(t), R_{in}(t) - R_{in}(0) = (R_{in})_n(t) - G_n(t), \\
Q(t) - Q(0) &= Q_n(t) - I_n(t).
\end{aligned}$$

Therefore, we obtain

$$\begin{aligned}
\| B_n(t) \| &= \left\| \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} (K_1(t, S) - K_1(t, S_{n-1})) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_1 \int_0^t (K_1(z, S) - K_1(z, S_{n-1})) dz \right\| \\
&\leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \| (K_1(t, S) - K_1(t, S_{n-1})) \| + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_1 \int_0^t \| (K_1(z, S) - K_1(z, S_{n-1})) \| dz, \\
&\leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_1 \| S - S_{n-1} \| + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \omega_1 \| S - S_{n-1} \| t.
\end{aligned}$$

Repeating the recursive procedure, we obtain

$$\| B_n(t) \| \leq \left(\frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} t \right)^{n+1} \omega_1^{n+1} a.$$

Then, for $t = t_0$ the inequality becomes

$$\| B_n(t) \| \leq \left(\frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} t_0 \right)^{n+1} \omega_1^{n+1} a.$$

We observe that $\lim_{n \rightarrow \infty} \| B_n(t) \| = 0$. Applying the same principle, it can be shown that $\| C_n(t) \|, \| D_n(t) \|, \| E_n(t) \|, \| F_n(t) \|, \| G_n(t) \|, \| I_n(t) \|$ tend to 0 as n tends to ∞ . $\square$

Theorem 5.4.3. *The model system (5.1) gives a unique solution when the following condition*

$$\frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)}\omega_1 + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)}\omega_1 t \leq 1.$$

holds.

Proof. To show the uniqueness of the system of solutions (5.1), suppose that there is another solution of system (5.1) given as $S^1, L^1, H^1, A^1, R_{out}^1, R_{in}^1, Q^1$, then

$$S(t) - S^1(t) = \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)}(K_1(t, S) - K_1(t, S^1)) + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t (K_1(z, S) - K_1(z, S^1)) dz.$$

By applying the norm on both sides, we get

$$\|S(t) - S^1(t)\| \leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \|K_1(t, S) - K_1(t, S^1)\| + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)} \int_0^t \|K_1(z, S) - K_1(z, S^1)\| dz.$$

Using the Lipchitz condition of the kernels leads to

$$\|S(t) - S^1(t)\| \leq \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)}\omega_1 \|S(t) - S^1(t)\| + \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)}\omega_1 t \|S(t) - S^1(t)\|,$$

After factorizing we get

$$\|S(t) - S^1(t)\| \left(1 - \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)}\omega_1 - \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)}\omega_1 t\right) \leq 0. \quad (5.25)$$

if $\left(1 - \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)}\omega_1 - \frac{2(1-\alpha)}{\mathcal{M}(\alpha)(2-\alpha)}\omega_1 t\right) > 0$, then the equality (5.25) holds when

$$\|S(t) - S^1(t)\| = 0$$

which implies that $S(t) = S^1(t)$.

Using the same approach, it can be shown that $L(t) = L^1(t), H(t) = H^1, A(t) = A^1, R_{out}(t) = R_{out}^1, R_{in}(t) = R_{in}^1, Q(t) = Q^1$ which shows the solution of the model system (5.1) is unique. $\square$

5.5 Numerical Simulations

In this section, we numerically solve the fractional-order model. We used the nominal values of parameters in Table 3.3 which was used in Chapter 3 to provide graphical results for different values of $\alpha \in (0, 1]$. We use the generalised Adams-bashforth-Moulton for the numerical solutions of a system of fractional order differential equations [71], with the initial conditions, $S(0) = 20000; L(0) = 500; H(0) = 200; A(0) = 10; R_{out}(0) = 5; R_{in}(0) = 0; Q(0) = 0$. The changes in the drug using population is given in Figures 5.2, 5.3, 5.4 with $\alpha = 0.7, 0.9$ and 1 respectively. We present the results of our simulations where we are varying the val-

ues of the contact rate β . For both light, heavy and addicted drug users when the contact rate is increased the prevalence also increases. As such, when the reproduction number $\mathcal{R}_0^{FDE} > 1$ for $\beta = 0.3$, then drug users persist. We observe that reducing the derivative order α is associated with an increase of the memory effect of the system, and this is characterised by high numbers of drug users in the long term. When α tends to 1 there is reduction on the memory effect characterized by fractional derivative. Reducing memory effect is associated with high peaks of drug users in the short term but lower long term values when compared with a system with lower fractional order values.

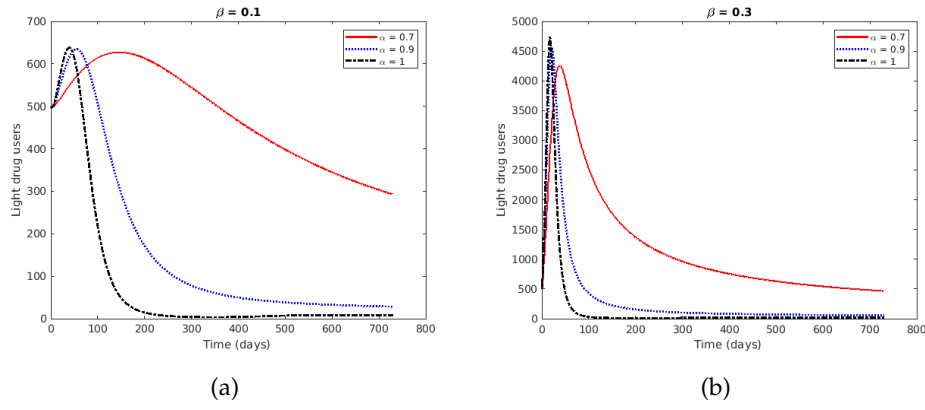


Figure 5.2: fractional order variations of contact rate β for light drug users

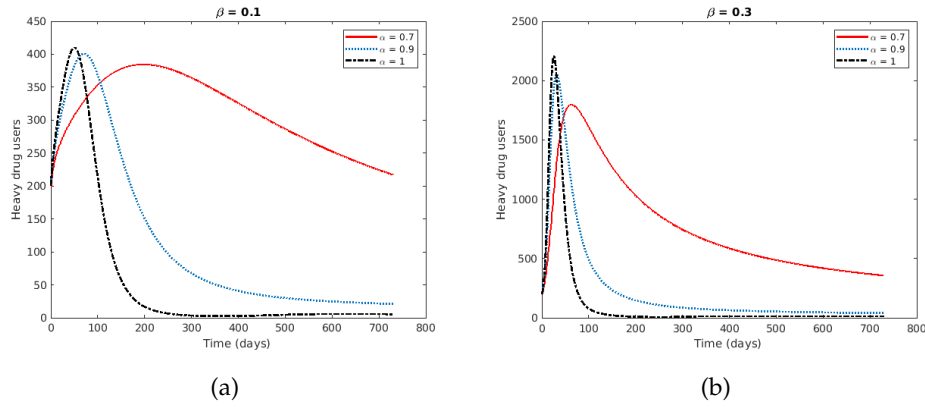


Figure 5.3: fractional order variations of contact rate β for heavy drug users

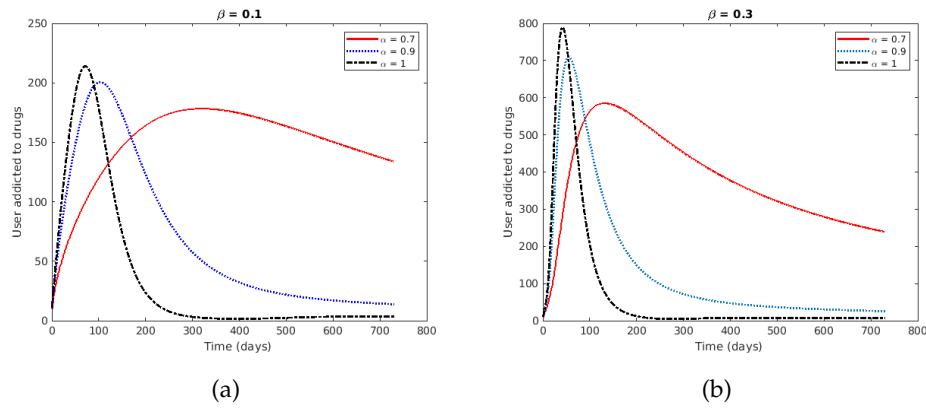


Figure 5.4: fractional order variations of contact rate β for addicted drug users

In Figures 5.2, 5.3, 5.4 we can observe that the population of light, heavy and addicted drug users increases with the fractional values of $\alpha = 0.7, 0.9, 1$ but after time level 100, they decrease. Figures 5.2, 5.3, 5.4 shows that when the fractional order value is high, the peak of the graph becomes high and the long term values has lower values. When the derivative order α is reduced the peak of the graph is low and has higher long term values which is characterised by high numbers of drug users compared to when the derivative value is increased. This reduction is likely caused by other drug users being recruited to other levels of drug usage, others being recruited to rehabilitation, quitting permanently or through self limitation where there are not enough susceptibles to initiate. We also varied the values of β for the figures above to find how the contact rate affect the initiation rate. The figures shows that an increase in the contact rate leads to an increase in the population of drug users.

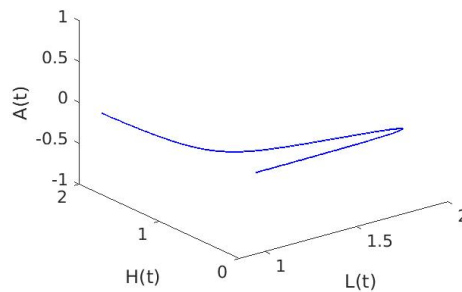


Figure 5.5: Proportions Comparing Substance Users

The figure above compares the light drug users, heavy drug users and addicted drug users. The figure shows that when the number of light users is higher the number of heavy users is

low as the users would have not progressed to being heavy users or they have ameliorated to being light users. When the number of heavy users is high the number of light users is low as the progression rate would be higher and the amelioration rate would be low.

5.6 Conclusion

In this study, we examined the fractional-order model for substance abuse in presence of in-patient and out-patient rehabilitation dynamics using the Caputo-Fabrizio type of fractional order derivative. The basic model properties such as positivity and boundedness of solutions were analysed using a one parameter Mittag-Leffler function. To explore the existence and uniqueness of solutions of the fractional-order model we used the fixed-point theory. We used an iterative method to obtain solutions of the fractional order model. The numerical simulations were carried out to explore the prevalence of substance abuse for different orders of a fractional derivatives. When the derivative order α is reduced the peaks of the drug users population decrease and the population of drug users is high in the long term. The results shows that when the derivative order α is 1 the peak is highest and is attained at an earlier time compared to when the derivative order α is reduced from 1. The results show that the future states depend on the current and previous states, hence the derivative order α gives more effective understanding of the impact of rehabilitation on drug users compared to the standard model with integer-order derivatives. The results show that using a fractional order model gives flexibility of prediction of the drug use trends. We note that, the model depicts that there is an explosive outbreak in the initial stages of the epidemic followed by a decline after the peaks are reached. This reduction is presumed to be due to self-regulation of the system resulting from a reduced number of susceptible individuals thereby lowering the likelihood of drug users initiating new individuals. We observed that the memory (lower values of α) is associated with lower peaks of drug users in the initial stages of the epidemic but higher long term values of drug users.

Chapter 6

Conclusion and discussion

In this thesis, we studied substance abuse in general, we investigated the extent to which substances are abused and found that different levels of abuses where drugs are abused heavily, moderately and some used at a lower extents in some cases.

In this study, we presented a dynamical model of substance abuse in presence of multiple amelioration stages and out-patient rehabilitation which was presented as the first model out of the 3 models that we presented and it was presented in Chapter 3. The model incorporates key aspects such as multiple amelioration stages, relapse, quitting of light users and recruitment into out-patient rehabilitation. The model was analysed qualitatively by determining the stability of the steady states and positivity of solutions. The analysis shows that there exists a drug free steady states which is globally asymptotically stable whenever $\mathcal{R}_0 < 1$ and a unique persistent steady state when $\mathcal{R}_0 > 1$. This shows that substance abuse can be annihilated if the reproduction number is reduce to a value less than unity. The sensitivity analysis of the model shows that the prevalence of substance abuse increases with the increase in the influence of drug users on the susceptible population, as well as progression rate from L_1 to L_2 . Also, prevalence of substance abuse decreases with increase in progression rate from L_3 to H , as well when light users quit. The model was reduced in Chapter 4 where the compartments of light drugs users were combined into one compartment and we considered rehabilitation as in-patient and out-patient. In Chapter 4, we wanted to investigate measures to use in order to control the rising number of substance abuse. In the model, we used awareness, counseling and rehabilitation as the controls. Our results indicate that the controls are needed as a measure of reduction of substance abuse in Botswana. The basic properties of the model were studied and as well as the basic reproduction number $\mathcal{R}_0$ of the substance abuse model. The Pontryagin's Maximum Principle was then used to derive all necessary conditions that enhance substance use control. The numerical results showed that

the application of control strategies on drug users in the community were controlled and the results showed the adequacy of the proposed control strategies.

In Chapter 5, we presented a model on substance abuse using fractional-order derivatives. We used the same model used in Chapter 4, to develop our fractional-order model. The Caputo-Fabrizio type of fractional order derivative was used owing to its flexibility when analysing initial value problems. The basic model properties such as positivity and boundedness of solutions were analysed using a one parameter Mittag-Leffler function. To show existence and uniqueness of solutions of the fractional order model, the fixed-point theory was used. To obtain numerical solutions of the fractional order model we used an iterative method. The numerical simulations were carried out to explore the prevalence of substance abuse for different orders of a fractional derivatives.

For further research on this topic, we recommend the use data collected from various institutions (e.g. police, rehabilitation centres) of number of drug users to parametrize the model and obtain parameters that are specific for Botswana. Structuring of populations according to gender and age would be useful to ensure targeted controls. This will help on being able to find the different genders who abuse specific drugs mostly and the control programs can be designed easily with much focus point. Age can be structured in a way that differentiates students and adults. This will give us the focus point on which age group has a high number of drug users in the population. It will also be easy to implement the control programs as they will be directed to a certain age. Sport play an important role on the development of an individual. As such we recommend a model on substance abuse in sports to establish the extent of the drug problem in sports. Education is the most important factor in building the future of an individual. We therefore recommend a model on substance abuse in schools, focusing on the substance abuse problem in schools and how to curtail the epidemic at that level.

PARAPDFs

name	kind	start	finish	peak
beta	0	0	1	0.695
eta1	0	0	1	0.92
eta2	0	0	1	0.68
eta3	0	0	1	0.75
mu	0	0	0.002	0.00027
rho	0	0	1	0.75
alpha1	0	0.001	0.09	0.008
alpha2	0	0.002	1	0.007
sigma	0	0.00001	0.0009	0.00008
gamma	0	0.02	0.5	0.2142
phi	0	0	1	0.244
deltaA	0	0	1	0.0057
deltan	0	1	1	0.0031
deltam	0	0	1	0.0095
delta	0	1	1	0.0042

% I have to run LHS first , then define a new matrix C to be para .

```

for i=1:1000;
    Pi = 1687;
    beta(i)=para(i,1);
    eta1(i)=para(i,2);
    eta2(i)=para(i,3);
    eta3(i)=para(i,4);
    mu(i)=para(i,5);
    rho(i)=para(i,6);
    alpha1(i)=para(i,7);
    alpha2(i)=para(i,8);
    sigma(i)=para(i,9);
    gamma(i)=para(i,10);
    phi(i)=para(i,11);
    deltaA(i)=para(i,12);
    deltan(i)=para(i,13);
    deltam(i)=para(i,14);
    delta(i)=para(i,15);
    Q1(i) = (1+mu(i)+ delta(i));
    Q2(i) = (mu(i)+ deltan(i)+gamma(i)+phi(i));
    Q3(i) = (sigma(i)+alpha1(i)+mu(i)+deltam(i));
    Q4(i) = (alpha2(i)+mu(i) +deltaA(i));
    Phi1(i) = (gamma(i).*sigma(i))./(Q2(i).*Q3(i));
    Phi2(i) = (sigma(i).*phi(i).*alpha2(i))./(Q2(i).*Q3(i).*Q4(i));
    Phi3(i) = (alpha1(i).*alpha2(i))./(Q3(i).*Q4(i));
    Phi4(i) = Phi1(i)+ Phi2(i)+ Phi3(i);

    denomstar(i) = Q1(i).*Q2(i).*Q3(i).*(1-Phi4(i));
    RI(i) = beta(i)./Q1(i);
    RIn(i) = (beta(i).*eta1(i).*(rho(i).*sigma(i)+Q3(i).*(1-rho(i)).*(1-Phi3(i)
    RIm(i) = (beta(i).*eta2(i).*((1-rho(i)).*(Q4(i).*gamma(i)+phi(i).*alpha2(i)
    RA(i) = (beta(i).*eta3(i).*((1-rho(i)).*(Q3(i).*phi(i)+gamma(i).*alpha1(i))
    R_C(i)=(RI(i)+RIn(i) + RIm(i) +RA(i));
end

```

```
v=0;
```

```
figure(1)
```

```
plot(beta, log(R_C), '. ', beta, v)
```

```
xlabel('Contact_rate ,_\beta', 'FontSize',15)
```

```
ylabel('log(R_0)', 'FontSize',15)
```

```
figure(2)
```

```
plot(rho, log(R_C), '. ', rho, v)
```

```
xlabel('Proportion_of_screened_individuals ,_\rho', 'FontSize',15)
```

```
ylabel('log(R_0)', 'FontSize',15)
```

```
figure(3)
```

```
plot(gamma, log(R_C), '. ', gamma, v)
```

```
xlabel('Enrolment_into_medication_for_I_n_individuals ,_\gamma', 'FontSize',15)
```

```
ylabel('log(R_0)', 'FontSize',15)
```

```
figure(4)
```

```
plot(sigma, log(R_C), '. ', sigma, v)
```

```
xlabel('Withdrawal_rate_from_medication ,_\sigma', 'FontSize',15)
```

```
ylabel('log(R_0)', 'FontSize',15)
```

```
%
```

```
figure(9)
```

```
boxplot(R_C)
```

```
axis([0.5 1.5 0 10])
```

```
ylabel('log(R_0)', 'FontSize',15)
```

```

function [R_C] = calculation(para)

for i=1:1000;
    Pi = 1687;
    beta(i)=para(i,1);
    eta1(i)=para(i,2);
    eta2(i)=para(i,3);
    eta3(i)=para(i,4);
    mu(i)=para(i,5);
    rho(i)=para(i,6);
    alpha1(i)=para(i,7);
    alpha2(i)=para(i,8);
    sigma(i)=para(i,9);
    gamma(i)=para(i,10);
    phi(i)=para(i,11);
    deltaA(i)=para(i,12);
    deltan(i)=para(i,13);
    deltam(i)=para(i,14);
    delta(i)=para(i,15);
    Q1(i) = (1+mu(i)+ delta(i));
    Q2(i) = (mu(i)+ deltan(i)+gamma(i)+phi(i));
    Q3(i) = (sigma(i)+alpha1(i)+mu(i)+deltam(i));
    Q4(i) = (alpha2(i)+mu(i) +deltaA(i));
    Phi1(i) = (gamma(i).*sigma(i))./(Q2(i).*Q3(i));
    Phi2(i) = (sigma(i).*phi(i).*alpha2(i))./(Q2(i).*Q3(i).*Q4(i));
    Phi3(i) = (alpha1(i).*alpha2(i))./(Q3(i).*Q4(i));
    Phi4(i) = Phi1(i)+ Phi2(i)+ Phi3(i);

    denomstar(i) = Q1(i).*Q2(i).*Q3(i).*(1-Phi4(i));
    RI(i) = beta(i)./Q1(i);
    RIn(i) = (beta(i).*eta1(i).*(rho(i).*sigma(i)+Q3(i).*(1-rho(i)).*(1-Phi3(i)
    RIm(i) = (beta(i).*eta2(i).*((1-rho(i)).*(Q4(i)).*gamma(i)+phi(i).*alpha2(i)
    RA(i) = (beta(i).*eta3(i).*((1-rho(i)).*(Q3(i).*phi(i)+gamma(i).*alpha1(i))
    R_C(i)=(RI(i)+RIn(i) + RIm(i) +RA(i));

end

```

```

clear;

% Calling program to generated PRCC for LHS; call the LHS program which
% generates the sample; all input variables are included in the LHS program
% and output of the program is the matrix CC from Blower's technique paper

LHS; % call the LHS program
b = size(latin_output);
c = length(latin_output);

%      test1 = 1./latin_output(:,7);
%      test2 = 1./latin_output(:,8);
%      test3 = 1./latin_output(:,9);
%
% latin_output(:,7) = test1;
% latin_output(:,8) = test2;
% latin_output(:,9) = test3;
num = b(2);

% delcare initial parameters

rank_outcome = zeros(1000,1);
rank = zeros(1000,10);
outcome = zeros(1000,100);
parameters = zeros(1000,10);
CC = zeros(10, 10);
lengthofmatrix = b(2);
% read in data from LHS; program creates matrices outcome and
% parameters that are used to calculate the PRCCs
% variables are then ranked and results are put into rank_outcome
% matrix which is fed into create_rank_matrix which creates a matrix of the
% parameter for each simulation; the CC matrix then created in the last
% program

[parameters, outcome] = read_in_data(N, num, latin_output);
[rank_outcome] = create_outcome_rank(N, num, outcome);

```

```

[rank, ranks] = create_rank_matrix(N, num, parameters, rank, rank_outcome);
[CC] = make_c_matrix(N, num, rank);
RCCMatrix = [CC];
Prcclist = RCCMatrix(:,16)

set(0,'defaulttextinterpreter','tex');
fig11 = figure(11);
barh(CC(1:length(CC)-1,length(CC)))

set(gca,'YTick',1:15);
[hx,hy] = format_ticks(gca,...
    {'$-0.6$','$-0.4$','$-0.2$','$0$','$0.2$','$0.4$','$0.6$','$0.8$'},...
    {'$\beta$','$\eta_1$','$\eta_2$','$\eta_3$','$\mu$','$\rho$','$\alpha_1$'},...
    -0.6:0.2:0.8,[],0,0,[],...
    'FontSize',14, 'FontWeight', 'Bold');

```

```
pvalfile <- read.table(file="PrccList.txt", header=T) # file from Matlab
#pvalfile <- read.table(file="prcc.txt", header=T) # file from Matlab
source("prcccomp.R") # Source the function prcc

## Sample size if common
N <- 1000

parcorr <- pvalfile$PRCC # PRCC from Matlab
vars <- pvalfile$Variable # Variable names
ns <- rep(N, length(parcorr)) # Sample sizes

## Run PRCC comparisons using default alpha = 0.05
## No FDR adjustment to choose important parameters
prcc(parcorr, ns, var.names = vars, FDR = F)

## Run PRCC comparisons using alpha = 0.01
## No FDR adjustment to choose important parameters
prcc(parcorr, ns, var.names = vars, FDR = F, alpha = 0.05)

## Run PRCC comparisons using default alpha = 0.05
## FDR adjustment to choose important parameters
prcc(parcorr, ns, var.names = vars, FDR = T)

prcc(parcorr, ns, var.names = vars, FDR = TRUE, round4 = FALSE)

## Run PRCC comparisons using default alpha = 0.05
## FDR adjustment (default) to choose important parameters
## No variable names provided (uses order as names)
prcc(parcorr, ns)
```

symbol	name
π	pi
β	beta
μ	mu
η	eta
γ	gamma
α	alpha
σ	sigma
ϕ	phi
ρ	rho
δ	delta
ε	varepsilon
ξ	xi
λ	lambda
Λ	Lambda
Φ	Phi
Ω	Omega
ν	nu
ω	omega
Ψ	Psi
θ	theta
Σ	sum

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