Modelling the dynamics of alcohol and methamphetamine co-abuse in the Western Cape Province of South Africa

by

Titus Okello Orwa

Thesis presented in partial fulfilment of the requirements
for the degree of Master of Science
at Stellenbosch University

Department of Mathematical Sciences,
University of Stellenbosch,
Private Bag X1, Matieland 7602, South Africa.

Supervisor: Prof. Farai Nyabadza

December 2014

Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

November 11, 2014

Titus Okello Orwa

Date

Abstract

Clinical results have indicated that abuse of multiple drugs/substances has devastating health and social consequences. The combined abuse of alcohol and the highly addictive methamphetamine has worsened the drug epidemic in South Africa, especially in the Western Cape Province. Using non-linear ordinary differential equations, we formulate a deterministic mathematical model for alcohol-methamphetamine co-abuse epidemic. We prove that the growth of the co-abuse epidemic is dependent on the threshold parameters of the individual substances of abuse. The substance with the maximum reproduction number dominates the epidemic. We also prove that the equilibria points of the co-abuse sub-models are locally and globally asymptotically stable when the sub-model threshold parameters are less than unity. Using parameters values derived from the sub-model fittings to data, a population estimate of co-users of alcohol and methamphetamine under treatment is estimated with a prevalence of about 1%. Although the results show of a small proportion of co-users of alcohol and methamphetamine in the province, the prevalence curve is indicative of a persistent problem. Numerical simulation results reveal that co-abuse epidemic would persists when both reproduction numbers are greater than one. Results from sensitivity analysis shows that the individual substance transmission rates between users of methamphetamine and/or alcohol and the general susceptible population are the most vital parameters in the co-abuse epidemic. This suggests the need to emphasise on preventive measures through educational campaigns and social programs that ensure minimal recruitment into alcohol or methamphetamine abuse. Model analysis using the time-dependent controls (policies) emphasizes the need to allocate even more resources on educational campaigns against substance abuse and on effective treatment services that minimizes or eliminates rampant cases of relapse into substance abuse.

Keywords: Alcohol. Methamphetamine. Co-use model. Latin Hypercube Sampling. Partial rank correlation coefficients. Multiple drug/substance abuse. Optimal control.

Opsomming

Kliniese resultate toon dat die misbruik van meer as een dwelmmiddel verwoestende gesondheids-en sosiale gevolge het. Die gekombineerde misbruik van alkohol en die hoogsverslawende methamphetamine het die dwelm-epidemie in Suid-Afrika vererger, veral in die Wes-Kaapse provinsie. Deur van nie-lineere gewone diffensiaalvergelykings gebruik te maak, formuleer ons 'n deterministiese wiskundige model vir epidemie van die gesamentlike misbruik van alkohol en methamphetamine. Ons toon aan dat die groei van die sogenaamde mede-misbruik epidemie afhanklik is van die drumpelparameters van die individuele middels wat misbruik word. Die middels met die grootste voortbringende syfer domineer die epidemie. Ons bewys ook dat die ekwilibriumpunte van die mede-misbruik submodelle plaaslik en globaal asimptoties stabiel is wanneer die sub-model drumpelparameters kleiner as een is. Deur die submodelle op werklike data te pas word waardes vir die drumpelparameters afgelei en word daar beraam dat daar ongeveer 1% van die populasie mede-misbruikers van alkohol en methamphetamine onder behandeling is. Alhoewel die data 'n klein persentasie van mede-misbruikers van alkohol en methamphetamine in die provinsie toon, dui die voorkomskurwe op 'n groeiende endemie en voortdurende probleem. Resultate uit numeriese simulasie toon dat die mede-misbruik epidemie sal voortduur indien beide reproduserende syfers groter as een sal wees. Resultate van sensitiwiteitsanalise toon dat die individuele middeloordragkoerse tussen gebruikers van methamphetamine en/of alkohol en die gewone vatbare populasie die mees noodsaaklike parameters in die mede-misbruik epidemie is. Dit stel voor dat daar meer klem gelê moet word op voorkomingsmaatreëls deur opvoedkundige veldtogte en sosiale programme om te verseker dat minder alkohol en/of methamphetamine misbruik sal word. Model-analise wat gebruik maak van tyd-afhanklike kontroles (beleide) lê verder klem op die feit dat selfs meer hulpbronne aan opvoedkundige veldtogte teen dwelmmisbruik toegewy moet word, asook die effektiewe behandeling wat gevalle van terugval in dwelmmisbruik sal minimeer of elimineer.

Acknowledgements

My sincere gratitude goes to my academic supervisor Prof. Farai Nyabadza, for his extraordinary intellectual guidance, support, suggestions, useful discussions and understanding during my study period. It was wonderful and fulfilling to work with you again. Your academic research experience, dedication, and enthusiasm inspired me the most. The successful completion of this thesis project would not be possible without your support. Thank you.

Secondly, my special thanks goes to God the Almighty for the gift of life, to my family for their support and to my colleague student, Mr. John Njagarah for useful discussions and consultations during the entire project period.

Finally, I am extremely grateful to the Department of Mathematical Sciences, Stellenbosch University and the African Institute for Mathematical Sciences (AIMS) for their financial support.

Dedications

This thesis is dedicated to my parents, Mr. Joshua Orwa and Mrs. Leah Orwa for their love, support and hope. To my late brother and friend Mark Orwa, who always stood behind me and knew I would succeed. Am humbled by your sacrifices, determination and encouragement. My love to you all.

Publications

The following publications are extracts from this thesis. They are appended at the end of the thesis.

1. Estimating the population of alcohol and methamphetamine co-users in the Western Cape Province of South Africa. Submitted to the Journal of Applied Mathematics and Computation (Manuscript under Revision).
2. Application of optimal control to a dynamic model of alcohol and methamphetamine co-abuse. Submitted to the Journal of Biological Dynamics (Manuscript under Review).

List of Figures

List of Tables

Contents

Chapter 1

Introduction

1.1 Substance/drug abuse in South Africa

Substance abuse is a patterned use of a substance (or drug) in which the users consume the substance in amounts or with methods that are injurious to themselves or to others. According to the Diagnostic and Statistical Manual of mental disorders (DSM-IV), an individual is considered as a substance abuser if he or she meets any of the following four criteria within the last one year [6]:

1. Repeated use of the substance in ways that would be considered physically harmful.
2. Use of the substance is impacting negatively, the ability of the individual to meet their family, social, or work commitments.
3. Continued use of the substance despite evidence that it is leading to difficulties.
4. Legal problems due to use of the substance.

Individuals abuse substances for varied and sometimes complicated reasons. Some of these reasons include but not limited to peer pressure, stress, relationship problems, poverty, lack of employment, boredom, low self-esteem and the need to boost self confidence. Teenagers may abuse drugs for experimental and rebellious purposes. A poor home environment is a major contributor to substance abuse. Individuals who grow up in homes where substance use such as alcohol consumption is regarded as a normal behaviour are highly likely to become alcoholics [45].

Drugs/substances of abuse are categorised differently by different states and regions. For example, in the United States of America (USA), the Department of Justice classifies drugs/substance of abuse into five distinct schedules/categories depending upon the drug's acceptance, medical use and dependency potential [58]. In South Africa,

substance abuse can be generally grouped into 3 categories based on frequency of usage. They include those that are less frequently used, those that are moderately used and those that are extremely used.

Alcohol is the most prevalent substance of abuse in South Africa. Others in this category may be taken or used independently or in combinations. They include cannabis, cocaine, dagga (white pipe), mandrax and over-the-counter and prescription medicines such as slimming tablets, tranquillizers such as benzodiazepines (particularly alprazolam, temazepam, diazepam and clonazepam). The moderately used drugs include crack cocaine, cocaine (powder), heroin, speed, lysergic acid diethylamide (LSD), hashish, 3,4-methyllenedioxymethamphetamine (ecstasy) and methamphetamine (the most dominat substance of abuse in the Western Cape Province). Moreover, the less frequently used drugs include opium, Rohypnol, Ketamine, and Wellconal [62].

Although substances of abuse are categorized differently, it is important to observe that the majority of drug/substance users in South Africa like elsewhere, prefer to use the substances in combinations. That is, drug users do not just latch onto single drugs, but use them in combinations such as alcohol and methamphetamine, alcohol and cannabis and cocaine and heroin. These combinations produce 'admirable effects' to the users, which accounts for popularity of multiple substance/drug abuse [62].

Following the disbandment of South Africa's Narcotics Bureau (SANAB) in 2004, drug related crimes have increased exponentially by about 30% in South Africa [81]. The socio economic consequences of substance abuse are immense and cost the South African economy about R20 billion per annum [20, 81]. The country ranks among the top ten narcotic and alcohol abusers in the world according to the United Nations World Drug Report of 2011 [85]. It is approximated that South Africans consume about twenty litres of alcohol per person per year which makes the country one of the highest consumers worldwide.

Although some substances/drugs are produced within the borders of South Africa, many other drugs are shipped from other parts of the world, and especially from West African countries such as Nigeria [84]. According to the United Nations Office on Drug and Crime (UNODC), South Africa dominates as a regional hub for drug trafficking, and the largest transit zone for illicit drugs in Southern Africa. The Interpol listed it as one of the world's top four source countries for the illegal herb, according to the first UNODC country profile on drug and crime in South Africa [29]. Moreover, alcohol still remains the primary and most preferred substance of abuse among South Africans. The 2013 data from the South African Community Epidemiology Network on Drug Use (SACENDU), indicates high percentages of patients reporting for treatment as a consequence of alcohol abuse at specialist treatment centres across all sites

[66]. Other highly addictive and more dangerous drugs that have continued to cause havoc among the South African population include cocaine, marijuana, heroin and methamphetamine.

Some of the global measures for minimizing harm related to licit substances include: increasing taxation, reducing availability by allowing minimal number of outlets to sell the substances, raising age limits for those buying, treatment of resulting disorders, regulating marketing and conducting educational campaigns in support of effective policy measures [89].

1.1.1 Substance abuse and HIV/AIDS in South Africa

Although drug abuse has been shown to bear numerous consequences to their users, several research work have indicated that drug abuse greatly escalates the spread of HIV/AIDS in the affected communities as a consequence of increased risky sexual behaviour among drug users [42, 46, 51, 61, 67]. With an estimated 5.8-6.4 million people living with HIV virus, South Africa is the worst hit with the HIV scourge in the world to date. According to the 2012 report by the World Health Organization, South Africa experiences the highest HIV prevalence of 12.3% in a population of 60 million people [18, 29, 83, 90]. It is therefore understood that any increased abuse of substance/drugs in the country would directly thwart the effort to fighting the prevalence of HIV/AIDS.

1.1.2 Substance abuse and crime in South Africa

Substance abuse undermines both the human and national economic growth and development [84]. As illustrated in the South African Police (SAPS) report of 2013 [80], substance abuse still remains to be a major contributor to crime, gangsterism, domestic violence and family dysfunction in the country. It is also true that the fight against serial crimes has been threatened by the co-existence of substance abuse, poverty and unemployment. Other than the usual arrests on drug users, drug loads and the destruction of drug factories, more seemingly needs to be done so as to cub the progressively growing substance epidemic in the country. The SAPS figures reveal that alcohol and drug abuse were the key factors underlying violent crimes in South Africa. The report indicate that 60% of crimes nationally are related to substance abuse. In the Western Cape Province (WCP), for example, the robbery cases rose by about about 31.2% for the time duration between 2009/2010 to 2012/2013. See Figure 1.1. Crime by violence was unfortunately reported to have increased tremendously for the period 2012/2013 [80]. We argue that the rise in crime cases especially in the Western Cape Province, could have been fuelled by the increased cases of drug abuse. The highly addictive and dangerous methamphetamine is the most popular drug in

Common Robbery: 2009/10 – 2012/13

RATIO PER 100 000 POPULATION

PROVINCE	2008/09 Baseline	2009/10	2010/11	2011/12	2012/13	% Inc or Dec 08/09 – 12/13	% Inc or Dec 11/12 – 12/13
Eastern Cape	90.6	81.1	82.5	72.1	69.8	-23.0%	-3.2%
Free State	123.6	102.5	99.0	97.4	98.5	-20.3%	1.1%
Gauteng	197.2	190.9	162.7	141.3	124.7	-36.8%	-11.7%
KwaZulu-Natal	84.9	76.4	68.8	70.6	79.5	-6.4%	12.6%
Limpopo	63.2	62.9	57.5	68.3	61.5	-2.7%	-10.0%
Mpumalanga	121.9	110.0	98.0	92.4	78.0	-36.0%	-15.6%
North West	90.2	87.2	85.6	76.2	68.4	-24.2%	-10.2%
Northern Cape	115.7	117.2	106.5	86.6	93.0	-19.6%	7.4%
Western Cape	160.4	176.8	199.1	210.3	210.5	31.2%	0.1%
RSA	**121.7**	**116.7**	**109.8**	**104.7**	**102.4**	**-15.9%**	**-2.2%**

Figure 1.1: Common robbery cases per 100000 people per province in South Africa for the period 2009/2010 to 2012/2013. Source [80].

the province. Our argument is backed by the SACENDU reports in [66]. In the first half of 2013, about 28% of total patients under treatment for drug abuse reported methamphetamine as their primary or secondary drug of abuse.

Historically, data on substance abuse has been difficult to come by. This is because possession and use of most drugs is considered illegal in most countries. Apart from the usual police arrests, and data on drug seizures, researchers have relied on data from cross-sectional research studies, which are often conducted for a specific location or region and may therefore be limited in reliability in some cases [61]. Other sources of data on substance abuse in South Africa include science councils such as the Human Science Research Council (HSRC), the Medical Research Council (MRC) and from non-governmental organizations such as the Institute for Health Training and Development (IHTD), the Centre for Alcohol and Drug Studies, the South African National Council on Alcoholism and Drug Dependence (SANCA), and the South African Brain Research Institute (SABRI). The creation of new systems such as SACENDU, the South African Alliance for the Prevention of Substance Abuse (SAAPSA), the South African Researcher-Practitioner Association (SARPA), the National Information System for Social Welfare (NISWEL) have greatly improved data collection of substance abuse in the country.

1.2 Alcohol abuse in South Africa

Alcohol (also known as ethyl alcohol or ethanol) is a liquid psychoactive substance that is consumed in thousands of varieties of alcoholic drink as beer, wine, cider and spirits. The alcoholic drinks vary in alcohol concentrations, colour and taste, depending on their ingredients and how they are made. Pure alcohol is however colourless. The depressant has a very strong taste that feels like a burning sensation and negatively affects the central nervous system of the user.

Although alcohol is generally taken as a social drink, it is often abused by its lovers. Alcohol abuse is associated with numerous negative consequences both to the consumer, his family, friends, colleagues and to the wider public. Some of the effects of the alcohol abuse include alcoholism, decreased inhibition, slurred speech and decreased muscle control. Chronic alcohol abuse leads to family breakups, personal injuries and ill-health, traffic accidents, violent character, deteriorating levels of productivity in places of work and even death.

Globally, alcohol abuse accounts for 4% of all deaths [89]. It results into about 2.5 million deaths per annum. Alcohol abuse also causes illnesses, injuries and increasingly affects younger generations and drinkers in developing countries. Most alcohol-related deaths emanate from injuries, cancer, cardiovascular diseases and liver cirrhosis. Further, about 320,000 young people aged 15-29 years die annually, from alcohol-related causes, resulting in 9% of all deaths in that age group [89].

Causes of alcohol abuse in South Africa are a complex combination of many factors. The youth particularly begin to use alcohol due to peer pressure and a desire to fit in, poor home environments and boredom, ignorance of alcohol's harms, and the relative cheapness of alcohol products and their ease of access [69]. The high youth unemployment rates must be an exacerbating factor to abuse of alcohol and other drugs. The alcoholic drinks are readily purchased in from shebeens, bottle stores, supermarkets, bars and from other unlicensed liquor outlets majority of which are found among poor communities, see [61].

Definition 1.2.1. *Alcoholism (also called alcohol dependence) is an alcohol related disorder in which an individual is addicted to alcohol either physically or mentally, and continues to use alcohol despite significant areas of dysfunction, evidence of physical dependence, and/or related hardship [91].*

South Africa has one of the highest per capita alcohol consumption rates in the world, with over five billion litres consumed annually [1]. While statistics suggest that alcohol affects around 17.5 million South Africans, Thomas Creamer [32], believes the burden of alcohol abuse is felt heavily by many more millions of South Africans.

He argues that road accident statistics is a clear indicator of the harrowing extent of alcohol abuse in SA. In 2009, the Status Report on Road Safety in WHO African Region and the South African Medical Research Council reported that 60% and 50% respectively of road traffic deaths in South Africa involved alcohol abuse [88].

Alcohol abuse among the youth in South Africa is of a particular concern. The South African youth is an active participant in binge drinking [69]. Data collected by SACENDU [66] and shown in Table 1.1 indicates that majority of the patients under treatment for substance abuse had alcohol as their primary substance of abuse. Patients of alcohol abuse were the highest in all the sites except the Western Cape (WC) with 20% population seeking treatment for alcohol abuse. Methamphetamine cases were highest in the province (28%). Alcohol abuse was reported highest in the Central Region, CR (Free State, North West and North Central Provinces) and Kwa-Zulu-Natal (KZN) Province with about 51% of patients in treatment having alcohol as the primary substance of abuse. Reports from other regions remained fairly stable across all sites; that is, Eastern Region (ER), Gauteng (GT) and Northern Region (NR) reporting 37%, 27% and 22% respectively.

Prevalence of alcohol abuse among the youth (under the age 20) in the country was also noted to be variant among the eight regions in the country. Table 1.1 reveals that about 53% of patients younger than 20 years in KZN reported alcohol as their primary substance of abuse. In comparison to 2012, the population under treatment for alcohol abuse had more than doubled in KZN. Furthermore, over 50% of injury related deaths and 80% of murders in the Western Cape Province were linked to alcohol abuse in 2013 [57].

	Age	WC	KZN	EC	GT	NR	CR
Number of centres		32	4	5	18	4	4
Number of patients		3717	934	587	4026	941	472
Alcohol	All	20	51	37	27	22	51
	< 20	3	53	9	9	20	5
Cannabis	All	21	32	12	40	38	26
	< 20	70	31	34	75	52	81
Methaq (Mandrax)	All	30	15	5	1	1	2
	< 20	4	1	7	1	2	3
Cocaine	All	2	6	6	3	3	6
	< 20	< 1	6	2	1	1	0
Heroin	All	17	6	2	12	29	3
	< 20	4	7	3	6	13	0
Methamphetamine	All	28	< 1	19	3	< 1	2
	< 20	16	0	42	1	0	0

Table 1.1: Primary drug of abuse (%) for all patients and patients under 20 years for selected drugs (2013a) in South Africa. Data by SACENDU [66].

Other than the associated disease burden, alcohol abuse is linked to numerous financial, social and and developmental costs. In South Africa, the fiscal costs accrued to alcohol abuse in relation to violence, decreased productivity, high job turnover, absenteeism in workplace and road traffic accidents are estimated to be about R9 billion per annum [1]. This is equivalent to 1% of the countries GDP. Treatment for alcohol addiction is often a complicated process as withdrawal from alcoholism is associated with anxiety, tremors, irregular heartbeats, seizures and hallucinations. Alcohol has been identified as a risk factor for partner violence leading to coerced sex and rape. Thus, the impact of the harmful use of alcohol reaches deep into society [90].

A cross-sectional analysis in sub-Saharan Africa have demonstrated that heavy alcohol drinking is associated with risky sexual behaviours [25, 50, 77]. The implications of alcohol abuse on risks for HIV/AIDS infection are greatest in the Southern Africa because the region has the highest HIV prevalence in the world [18]. South Africa experiences a 12% HIV prevalence according to report by UNAIDS [83]. Sex under the influence of alcohol is associated with both increased STIs prevalence and a greater likelihood of paying for sex [61]. Heavy alcohol drinking is also associated with a greater likelihood of improper use of condoms due to drunkenness [77]. This results into unsafe sex and sexual promiscuity which enhances transmission of sexually transmitted diseases (STDs) and HIV/AIDS pandemic. Other consequences include foetal alcohol syndrome and school truancy.

Short term effects of alcohol addiction may feature slowed down activity of the brain causing speech to slow and the irregular drift in body temperatures. Some of the long term effects include the following: Major body organs can be permanently damaged as they fight to cope with the constant flow of alcohol around the circulatory system. The brain shrinks as exposure to alcohol deforms neurons and diminishes the cells. The heart is slowly weakened as it pumps contaminated blood around the body. The overworked pancreas is sent to overdrive as it struggles to cope with both food and toxic alcohol. Alcohol abusers experience poor eating habits owing to extreme pain as the digestive organs become inflammable. The liver is repeatedly scourge which can lead to total breakdown in its ability to function. According to the Independent Scientific Committee on Drugs (ISCD), alcohol is considered as the most harmful substance both to the consumer and to others. See Table 1.2.

Although achievable, the process of rehabilitation from alcohol abuse and alcoholism is both complicated and difficult. While the success of the process has been shown in numerous cases, only about 1 in 5 addicts is able to successfully beat addiction. Most of the addicts relapse to alcohol abuse after treatment. The high cases of relapse by addicts could be attributed to the fact that while in rehabilitation facility, withdrawal is slightly controlled by medication. This is never the case while the addict is at home

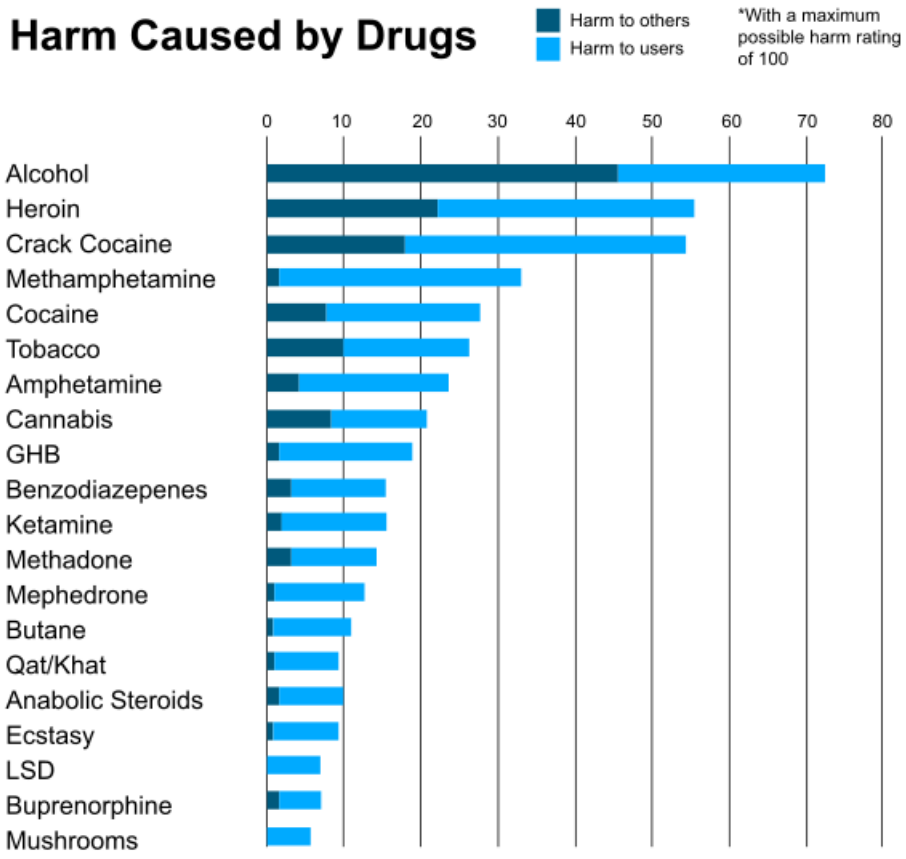


Table 1.2: Results of the ISCD 2010 study ranking the levels of damage caused by drugs, in the opinion of drug-harm experts. When harm to self and others is summed, alcohol was the most harmful of all drugs considered, scoring 72%.

with family and friends.

Clearly, the fight against alcohol abuse and alcoholism isn't an ordinary activity. It requires tireless effort by everybody from families to governments. The problem of alcohol abuse has unfortunately persisted and even continued to blossom in SA despite the numerous educational and legal initiatives set out by both the South African governmental and non-governmental organisations [69]. Some of the globally proven measures for minimizing harm related to alcohol abuse include: increased taxation on alcohol; reducing availability through allowing fewer outlets to sell alcohol, raising age limits for those buying, using effective drink-driving measures, promotion of screening and brief interventions (SBIRT) in healthcare settings, treatment of alcohol use disorders, regulating or banning marketing of alcoholic beverages and conducting information and educational campaigns in support of effective policy measures [89]. However, alcohol abuse still remains the major challenge to the South African government as far as the fight against drug and substance abuse is concerned. Insightful understanding of its combination with other psychoactive substances is therefore

paramount.

1.3 Methamphetamine abuse in South Africa

Methamphetamine is a powerful addictive stimulant that gives an intense sensation of pleasure. With numerous forms and street names, the bitter white crystalline powder can be manufactured locally from commonly available household ingredients. The demand, spread and abuse of the vicious stimulant has increased dramatically in the recent past [42]. Internationally, methamphetamine abuse remains a major global health and social problem. In South Africa, the abuse of methamphetamine has tremendously grown to epidemic levels, especially in the Western Cape Province [66]. Locally known as 'tik' in the streets of Cape Town in South Africa, methamphetamine is a relatively cheap drug and costs as little as R20 per 'straw' [64].

The global increase in methamphetamine-abuse has been documented to have reached epidemic proportions [51]. In 2012, the United Nations Office on Drug and Crime (UNODC) described methamphetamine epidemic as the greatest tragedy of all drugs. Globally, it is estimated that there are about 25 million users of methamphetamine. 'Speed' or 'crystal meth' as it is known in other countries such as USA, is easily administered through oral ingestion, smoking, snorting or injected intravenously by means of a needle [62]. Figures 1.2 and 1.3 show an increasing trend in the number of methamphetamine seizures and quantity in the European Union (EU) countries for the period 2001-2011. The growing trend is alarming.

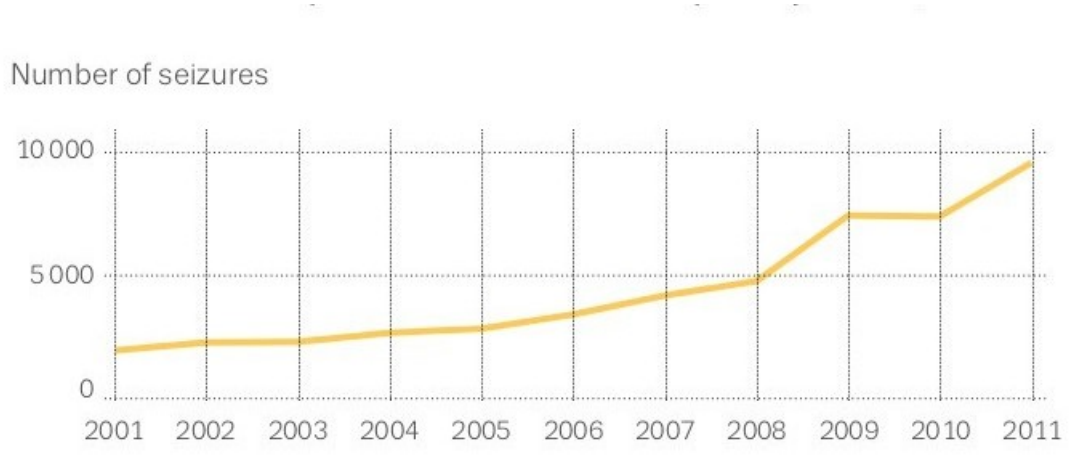


Figure 1.2: Number of methamphetamine seizures in EU, 2001-2011.

The motivation and crave for methamphetamine stems from several arguments by its lovers. Some of its extreme effects include a quick 'rush' accompanied by intense feeling of desirability, prolonged sense of euphoria, alertness, confidence, heightened

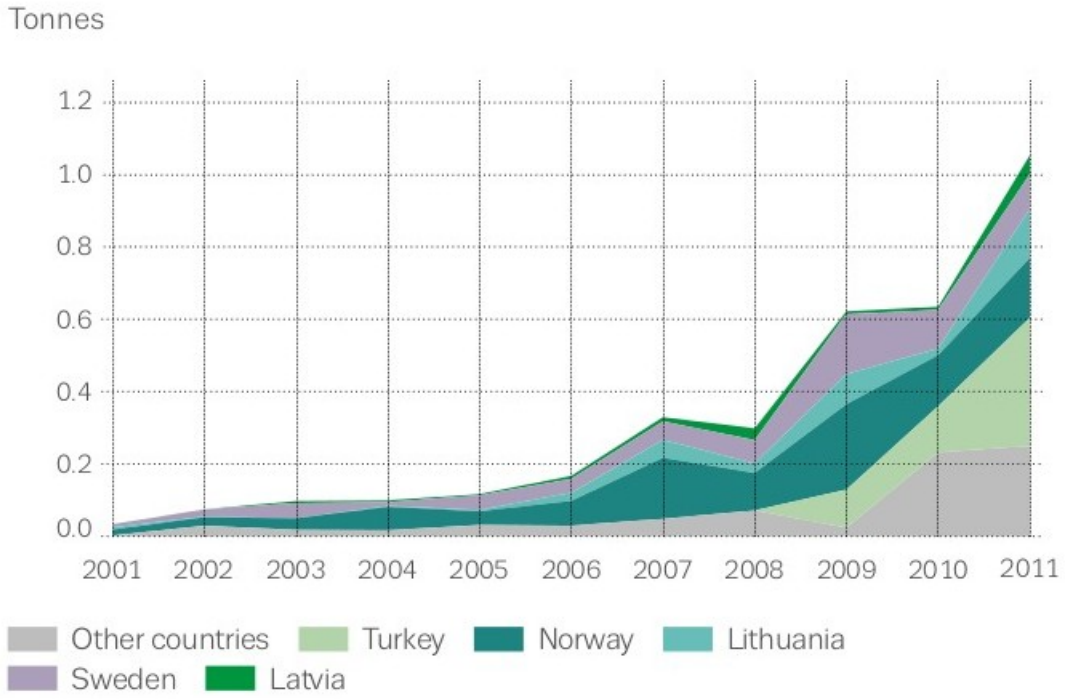


Figure 1.3: Quantity of methamphetamine seized in EU, 2001-2011.

desire for sex, increased energy and suppressed appetite for food. The drug is likened by women owing to its ability to cut weight and cure depression [26].

1.3.1 Methamphetamine and the human brain

Upon intake of methamphetamine, the human brain release dopamine, a chemical substance that causes an intense 'rush' of pleasure and prolonged sense of euphoria among methamphetamine users. After prolonged use, the dopamine receptors eventually get depleted and destroyed. Hence limiting feelings of pleasure. Although the pleasure centres may recover with time, the effects of methamphetamine on the cognitive abilities of the user is simply irreversible. Intake of methamphetamine also triggers the brain to release adrenaline, a hormone produced by the adrenal glands during high stress or exciting situations. Adrenaline hormone increases blood flow to the body muscles and oxygen to the lungs by stimulating the heart rate, contracting blood vessels, and dilating air passages. The excitement that accompany the release of these chemical hormones greatly contribute to the popularity of methamphetamine among its users.

Low dosages of methamphetamine is accompanied by such effects as increased alertness, concentration, and energy. Higher dosages arouses excessive excitement, enthusiasm, increased blood pressure, paranoia, aggression, extreme mood swing, lack of sleep and occasionally hallucination. Such individual bear increased self esteem and

intense desire for sexual intercourse. Excessive dosage of methamphetamine results into abuse and addiction; robbing users their looks, sexual desires, physical health and cognitive abilities. Chronic cases witness physical damage such as cardiovascular damage as a result of overdose and severe psychological harm such as impaired concentration and memory, paranoia, insomnia, extreme aggression and withdrawal; as a consequence of methamphetamine induced neurotoxicity [65]. Moreover, withdrawal often results into depression, abdominal cramps and increased appetite.

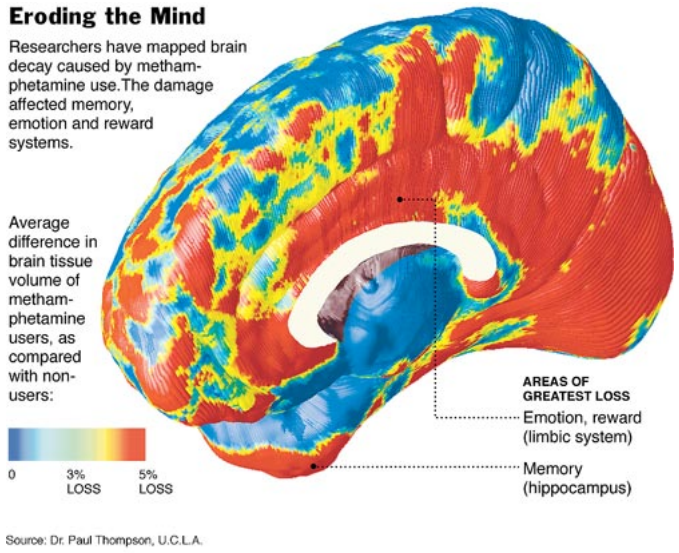


Figure 1.4: Shows the effects of methamphetamine on the human brain. Source [23].

Research evidence indicates that long term use of methamphetamine may increase risk of contracting HIV/AIDS [76]. As a consequence of drug injection and increased libido, users of methamphetamine are more likely to indulge in risky sexual behaviours coupled with impaired judgement stemming from abuse of methamphetamine. Addicted users are most likely to engage in unprotected sex, or engaging in sex with several partners or even exchange sex for drug, which is prevalent among prostitutes and sex workers. Chemicals in the brain such as dopamine and adrenaline which are triggered by methamphetamine not only provide the users with the required sense of desirability, confidence and stamina during sexual intercourse, but also impair judgement centres and leads to more aggressive sex for even longer periods of time, increasing chances of injury and the danger of spreading infections. Many users take the drug intravenously, thereby enhancing their chances of contracting diseases such as HIV/AIDS and Hepatitis B and C. Some of the physical damages resulting from methamphetamine abuse include discoloured and rotten teeth, popularly known as 'meth mouth'. Other effects include older skin, as it easily looses its lustre and elasticity, making the users appear older than they should be.

In South Africa, methamphetamine abuse is not only popular among adult population but also with the youth. Research by Pluddenum et al. in [67] shows a strong positive correlation between methamphetamine abuse and risky sexual behaviour among adolescents in Cape Town. Their results reveal that the youths who abuse methamphetamine were more likely to engage in unprotected sex in relation to those that never used the drug. Furthermore, the young methamphetamine users reported to having had several sex partners as compared to non-users [62]. Like elsewhere, the use of methamphetamine among commercial sex workers is also rampant in South Africa. Similar to cannabis and cocaine, methamphetamine abuse is popular among commercial sex workers and homosexuals [44].

The population of methamphetamine users in South Africa has been on a continuous rise since 1997. Data collected and presented by SACENDU shown in Table 3.3, reveals a growing number of patients seeking treatment for methamphetamine abuse in the Cape Town and Western Cape Province (WC) [67]. This dramatic increase in treatment demand for methamphetamine in the province, is a reflection of the increased population of methamphetamine users among residents of the WC and South Africa. An alarming report in [64] indicates that about 44% of patients who reported methamphetamine addiction were youths younger than 25 years of age. From Table 1.1, we observe that the treatment admissions for methamphetamine were low in the first half of 2013 in all regions except in the WC, which was at 28%. However, among those under 20 years of age, the proportion reporting methamphetamine abuse dropped from 32% to 29% in 2012b and 2013a respectively.

Although the collected data are indicative of a slight decline in the prevalence of methamphetamine in the WC, we strongly feel this may not be the true reflection of the drug situations in the province. Our argument is guided by the understanding that not all of the rehabilitation centres are covered by SACENDU program of monitoring the trends of alcohol and drug abuse in the province. The SACENDU programme to the best of our knowledge, only collects data from 23 rehabilitation centres, thereby, leaving out other centres whose statistics would be very crucial in the overall prevalence of methamphetamine abuse in the province and the country.

1.4 Multiple substance/drug abuse

There is no unitary definition of multiple substance abuse. However, the following definitions are useful for our case. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) defines multiple (or poly) drug abuse as the use of two or more drugs in combinations to achieve a particular effect. In many cases, one drug is used as a primary drug, with additional drugs to compensate for the side effects of the primary drug and make the experience more enjoyable or to supplement for

primary drug when supply is low [21].

Secondly, the United Nations Office on Drugs and Crime (UNODC), defines multiple substance abuse as the use of more than one psychoactive drug either simultaneously or at different times [84]. In the DSM-IV, a 'poly-substance dependence' refers to repeated use of at least three groups of (psychoactive) substances (not including caffeine and nicotine) but with no single substance predominating [59]. In this thesis project, we shall consider multiple substance abuse as the use of more than one illicit/licit substance simultaneous or at different times of the day.

The urge to use multiple drugs is a functionality of drug availability, desire to have and to prolong pleasurable experiences or to avoid negative experiences. Poly drug use:

1. Maximizes drug effect. For example, combined abuse of alcohol and cannabis and the intravenous injection of cocaine and heroin produces a greater profound effect than when each drugs are used independently.
2. Balances or controls negative effects of used drugs. Benzodiazapines are often following administration of stimulant drugs so as to cope with sleeping difficulty or depressed mood. Also, cannabis is taken to counteract withdrawal symptoms associated with abuse of opioid.
3. Substitute sort-after effects. Readily available drugs can always be used as substitute for drugs that aren't easily obtainable. For example, substituting cocaine with alternative stimulant such as amphetamine.

Users of psychoactive substances usually not only latch onto one drug of choice but increasingly take several other drugs in combinations that pose serious health dangers and create hazards for detoxification programmes. The use of multiple substances has more devastating health and social consequences. It progressively worsens medical symptoms among their hosts.

It is paradoxical that despite the numerous and increasing negative effects on the hosts, multiple substance abuse is becoming the norm for people heavily involved in drugs/substance abuse. We observe that while most treatment programmes are tailored for specific drugs of abuse, most of the patients on drug abuse, disappointingly admit to abusing only one drug. This makes diagnosis for poly drug abuse even more difficult and complicated. Mark Gold in [11], argues that even with proper diagnosis, detoxification of multiple substance-abuse is still unresolved. For example, during withdrawals, individuals are shown be in danger of experiencing brain seizures upon multiple use of alcohol and tranquillizers unless the specific treatment is tailed to the individual's condition.

Scientifically, assessing the risk of multiple drug abuse is complicated owing to a wide range of competing factors involved. Several research work has indicated that there are many approaches to multiple drug treatment. However, owing to the dangerous reactions during withdrawal, the process of detoxification should take place both at the rehabilitation center and at homes. Worse still, drug abuse specialists are unprepared to deal with poly drug abuse. Treatment centres and the medical community in general are only experienced at treating single drug addiction [11].

The problem of multiple substance/drug abuse has simply not been well studied. Both theoretical and practical results reveal some effective relationships between alcohol and methamphetamine abuse. Research work by Matthew et al.[46], confirms the effects of alcohol intake by users of methamphetamine and vice versa. In comparison to single drug effects, methamphetamine-alcohol combination produced a greater elevations of heart rate which is arguably a motivation for the drug users who consider such effects as positive impacts of the drug combinations. Their data show that methamphetamine combined with alcohol produced a profile of effects that was different from the effects of either drug alone. The combination of alcohol and methamphetamine does not produce a new psychoactive substance, but does increase heart rate and blood pressure beyond that seen for methamphetamine use alone [49].

While the combination of methamphetamine with cannabis is prevalent, its combination with alcohol is the most common among multiple drug abusers. In addition, a few proportion of methamphetamine users prefer its combination with heroin and other psycho-stimulants [38, 48]. Although extensive use of multiple drugs have been associated with poorer medical conditions of the user, concomitant use of methamphetamine with other drugs such as cocaine, opiates or alcohol, increases its toxicity [4]. Studies in [60, 79] have also shown that the use of one psychoactive substance increases the likelihood of the use of another. For example, teenagers who have used ecstasy are more likely to have tried a range of other drugs than teenagers who have only used cannabis, tobacco or alcohol.

1.5 Motivation and objectives of the study

1.5.1 Motivation

Several research work on drug epidemic have focussed on single substances/drugs. See for example [52, 55, 56, 74, 87]. The glaring fact, however, is that most substance abusers struggle with more than one intoxicant [54]. Unlike individual substances, very minimal research work has been done on the mathematical modelling of multiple abuse of substances. The understanding of such dynamics has been complicated due to lack of data on multiple substance abuse. Treatment resulting from substances

abuse has been shown to be a little easier when only one drug is involved and that abuse of more than one substance only increases the cost of treatment and rates of relapses [24]. By treatment, we mean the process of rehabilitating a drug addict. The epidemiological study of multiple substance is thus an important issue in public health.

In this work, we shall only consider a scenario in which an individual uses two different kinds of substances of abuse, in particular alcohol and methamphetamine for illustrative purposes. We ask: Can we model the dynamics of co-abuse of alcohol and methamphetamine in Western Cape Province of South Africa? Can we use the available data on primary substances of abuse to estimate the number of individuals who co-abuse alcohol and methamphetamine? Based on the available data, can we project of the future population under treatment for alcohol and methamohetamine? The co-abuse model is an amalgamation of two sub-models, one for alcohol abuse and the other for methamphetamine abuse. The sub-models are then fitted to data for person's seeking treatment services on alcohol and methamphetamine addiction. The data is obtained from different treatment centres within the Western Cape Province of South Africa by SACENDU [67]. Once each sub-model is fitted to data, the corresponding model parameters are obtained. These are then used in the co-abuse model to estimate the population under co-abuse of alcohol and methamphetamine in the province.

1.5.2 Objectives

The main objective of this thesis project is to model the dynamics of co-abuse in substance/drug abuse epidemic.

Specific objectives includes:

- To carry out a detailed mathematical analysis of the co-abuse model and its sub-models, so as to gain the understanding of the model behaviour based on the computed model reproduction numbers, equilibrium points and their corresponding stability analysis.
- To carry out sensitivity analysis so as to establish vital parameters in the co-abuse model and in the individual sub-models.
- To carry out numerical simulations of the described co-abuse model and establish the conditions necessary for epidemic persistence.
- To fit the alcohol sub-model to data on individuals under treatment for alcoholism in the Western Cape Province.

- To fit the methamphetamine sub-model to data on individuals under treatment for methamphetamine abuse in the Western Cape Province.
- To investigate the conditions under which the alcohol and /or methamphetamine epidemic would persist or die out.
- To project the population under treatment for methamphetamine and alcohol abuse in the next five years in the Western Cape Province, based on the fit to data curve for individuals under treatment.
- To use the data on individuals seeking treatment for alcohol and methamphetamine addiction to estimate the population of individuals who would be under treatment as a result of co-abuse of alcohol and methamphetamine in the Western Cape Province.
- To investigate the effects time-dependent controls (policies) on the dynamics of alcohol-methamphetamine co-abuse epidemic.

1.6 Mathematical preliminaries

1.6.1 Equilibrium analysis of a dynamic system

We first begin by giving the basic ideas and methodology of determining the stability of model equilibrium points as discussed in [37]. Consider an n coupled ordinary differential equations with n variables, $(X_i, 1 = 1, 2, \ldots, n)$.

$$\frac{\mathrm{d}X_i}{\mathrm{d}t} = f_i(X_1, X_2, \ldots X_n), \quad i = 1, 2, \ldots, n. \tag{1.6.1}$$

In order to explore the equilibrium dynamics, we first establish equilibrium state(s) of the system. This is done by setting equations in system (1.6.1) to zero and solving for the solutions $(X_1^*, X_2^*, \ldots, X_n^*)$. Unless perturbed, the system at equilibrium will remain in that state. The consequences of the small perturbations are achieved by looking at the rates of change of these variables when each of the variable is slightly shifted away from its equilibrium value. This is done by making the substitutions $X_i = X_i + \epsilon_i$ in equations of system (1.6.1) and exploring the growth and decline of the perturbation term, ϵ_i over time.

However, a more generic methodology for establishing stability of equilibrium points of system (1.6.1) is by determining the n eigenvalues $(\lambda_i, i = 1, 2, \ldots, n)$ associated with the system's Jacobian matrix J at specific equilibrium points. The equilibrium point $(X_1^*, X_2^*, \ldots, X_n^*)$ is said to be stable when the real parts of all the eigenvalues of J at that point are negative or have negative real parts. Otherwise it is unstable.

The Jacobian matrix J is given by:

$$J = \begin{pmatrix} \frac{\partial f_1^*}{\partial X_1} & \frac{\partial f_1^*}{\partial X_2} & \cdots & \frac{\partial f_1^*}{\partial X_n} \\ \frac{\partial f_2^*}{\partial X_1} & \frac{\partial f_2^*}{\partial X_2} & \cdots & \frac{\partial f_2^*}{\partial X_n} \\ \vdots & & \ddots & \vdots \\ \frac{\partial f_n^*}{\partial X_1} & \frac{\partial f_n^*}{\partial X_2} & \cdots & \frac{\partial f_n^*}{\partial X_n} \end{pmatrix} \tag{1.6.2}$$

The terms f_i^* refer to the function $f_i(X_1, X_2, \ldots, X_n)$ calculated at equilibrium points, i.e. $f_i(X_1^*, X_2^*, \ldots, X_n^*)$. The eigenvalues $\lambda_i (i = 1, 2, \ldots, n)$ are the solutions of determinant of the matrix $(J - \lambda I)$ set to zero; where I is the corresponding identity matrix. This will give rise to a polynomial in λ of order n. This is called characteristic polynomial which when set to zero and solved, gives rise to eigenvalues $(\lambda_1, \lambda_2, \ldots \lambda_n)$.

1.6.2 Reproduction number

Anderson and May [5] defines a disease reproduction number as a threshold quantity which represents on average the number of secondary cases that can be produced by a single 'infectious' individual in a completely susceptible population. Mathematically, reproduction number is a rate at which new cases are produced by an infectious individual (when the entire population is susceptible) multiplied by the average infectious period.

The concept of reproduction number is fundamental to the study of epidemiology of substance abuse and infectious diseases. It is useful in predicting factors and parameters that enhance the growth of an epidemic or those that help reduce or stop the growth of the epidemic. Its value is very useful in prevention strategies and management plans in both disease and drug abuse epidemics. If the reproduction number is greater than one, then then epidemic persists or becomes endemic in the community. On the other hand, when the reproduction number is less than one, the epidemic is often assumed but not always to die out. In this work, we shall adopt the method of next generation operator approach in computing the model reproduction number as is described by Van den Driessche and Watmough [86].

1.7 Project outline

The research project is organized into five chapters. In Chapter 1, an introduction on substance abuse, multiple substance abuse, alcohol abuse and methamphetamine abuse in South Africa are provided. In Chapter 2, we provide relevant literature reviews on mathematical models for single and multiple substances of abuse. The co-abuse model of alcohol and methamphetamine, together with its' sub-models (alcohol

model and methamphetamine model) are formulated and analysed in Chapter 3. In this chapter, the model and sub-model equilibrium points are established and their stabilities determined. Furthermore, the model parameters, numerical simulation, sensitivity analysis, alcohol and methamphetamine projection profiles and co-abuser populations are also estimated, discussed and analysed in Chapter 3. In chapter 4, we introduce time-dependent controls (policies) in the co-abuse model and discuss the effects of the controls on the dynamics of the co-abuse model. The paper is concluded in Chapter 5 with relevant discussions and recommendations.

Chapter 2

Literature review

2.1 Etiology of drug abuse

From the early works of Ross [70], social and health researchers who deal with data that are very scarce have often relied on simple deterministic models to generate insight and understanding on the relative role of various mechanisms of disease spread. This practice has been extended to substance abuse research where data availability remains the biggest challenge. The epidemiological study of substance/drug abuse is both challenging and rewarding. The study provides insightful information and understanding of both the local and global nature of the drug abuse problem and its impacts on health, social, economic and political situations of communities, countries and regions. The results from drug abuse study are very handy to policy makers, social scientists and epidemiologists. Contrary to infectious disease epidemics, the spread of drug abuse is influenced by social factors rather than the usual biological factors. Nevertheless, upon abuse, the biological and physiological factors often dominate the drug using career [78].

Like many other social behaviours, drug abuse is characterised by both demographic and geographical features. The underlying causes of drug abuse are numerous and varied. Some of the common causes include but not limited to peer pressure, which is most common among the youth; curiosity, which encompasses the desire to taste or discover the actual feelings associated with drug and drug abuse; depression, individuals take drugs so as to kill depression tendencies; during sexual intercourse, individuals may use such drugs as methamphetamine, cocaine among others to boost their libido and sexual performances. This is most common among commercial sex workers. Some drug users merely use them for purposes of rebellion and alienation tendencies.

The drug abusers not only suffer the usual social consequences of drug abuse such as personal and family neglect, but also expose their lives to numerous and adverse

health consequences. For example, the intravenous drug abusers are exposed to a high risk for contracting HIV/AIDS as well as a host of other diseases [76]. Drugs and drug abuse has evolved and changed substantially over time from patterns of abuse to modes of administration. Drug users have continued to indulge in more perilous modes of drug administration such as injection methods, and excessive dosages coupled with combinations of two or more substances. Clinical results have shown that the habit of using drugs in combinations increases victim's vulnerability to toxic effect, and offers greater consequences in relation to single drug abuse [27].

2.2 Multiple drug/substance abuse

The scientific definition of multiple drug/substance abuse is not unique. It is dependent on both the time and the effects to the users. Time category defines multiple drug/substance abuse on the basis of time frame in which the drugs are used. They include a case in which more than one substance is used on the same occasion called the Simultaneous Poly drug Use (SPU) and a scenario in which different drugs are used by drug user during his/her drug using career, called the Concurrent Poly drug Use (CPU). Effect category on the other hand, defines multiple drug/substance use in terms of the effects of mixing drugs. Mixing of drugs is likely to increase or decrease the effects of each drug; or a case in which drugs are combined to generate new effects [30].

Multiple drug/substance abuse in South Africa, like most other parts of the world, is viewed as a 'positive' step to satisfaction by drug abusers. Data from SACENDU [65], illustrates continued use of multiple drugs/substances by patients seeking rehabilitation services in the different rehab centres in the country. Patients not only reported their primary drug of abuse but also the secondary drug of choice. Some of the substances used in combinations in South Africa include combinations of alcohol and cocaine, marijuana, methamphetamine, tranquillizers, prescription narcotics and sleeping pills. It is important to observe that the users of multiple drugs are often addicted to two or more such drugs [35]. Treatment services should therefore be broad enough to cater for the secondary and even tertiary drugs of abuse consumed by the patient.

Abuse of drugs in combinations apparently leads to increased health problems [54]. Data collected by the National Institute on Drug Abuse indicate that about two-thirds of hospital emergency room cases admitted for drug abuse involve combinations of drugs. The diagnosis of poly-drug abuse is however a difficult and more challenging process. During intoxication and withdrawal, multiple substance abusers may exhibit symptoms that mimic psychiatric disorders. In addition, since most treatment programs require patients to be drug free, poly-drug abusers often admit sadly to using

only one kind of drug/substance [54].

Gold in [11] further argues that even with the proper diagnosis, the detoxification of multiple-substance abusers is even more complicated owing to lack of uniform approach to poly drug abuse treatment. For example, individuals who use alcohol in combination with tranquillizers; drugs that are used to reduce anxiety, fear, tension, agitation, and related states of mental disturbances, are at a high risk of experiencing brain seizures during withdrawal unless treatment is tailored to the individual's condition. In order to avoid withdrawal tendencies, detoxification procedures need continue both in hospitals and at homes during rehabilitation procedures.

Multiple drug abuse among adolescents is of great concern. Some of the problems associated with multiple drug abuse and especially among the adolescents are well documented in [19] by Czechowcz and his colleagues. Their research work highlights some of the merits of concern for multiple abuse of alcohol and other drugs among adolescents. Other researchers such as Kandel [35] and Bailey [7] share the argument that alcohol abuse is very instrumental in contributing to multiple substance abuse epidemic. According to Kandel *et al*., indulgence into multiple substance abuse is sequential and not random. They argue that adolescents typically use alcohol and then graduate to marijuana before progressing to other illegal drugs such as cocaine and methamphetamine. Bailey also observed in [7] that adolescents do not progress to marijuana and other drugs until they are alcohol users. Also, they observed that fewer young students use drugs such as hallucinogens, amphetamines or cocaine without initially using alcohol and marijuana [34]. Hesselbrock in [28] observes that unlike other substances, most alcohol abusers frequently abuse other drugs in dangerous combinations. Statistics from multiple drug abuse combinations shows for example that about 30-60% of alcoholics abuse cocaine [82], 20-50% of alcoholics abuse marijuana [13], 12-20% of alcoholics abuse benzodiasepines [16] and approximately 7-10% of alcoholics abuse heroin [13]. This view is also supported by research work by the National Institute of Drug Authority, which indicates that the majority of drug related energy room visits involve combinations of alcohol and other illicit drug use [54].

Some of the consequences associated with multiple drug abuse include low self-esteem, emotional distress, physical and sexual abuse. The specific consequences are however quite numerous. Multiple substance abuse therefore presents a range of problems to treatment and public health institutions. It also increases the likelihood of overdose and suicide among its users [72]. This is common in cases where, in an effort to balance the side effects of one drug of abuse, a drug abuser uses the secondary drug in excessive doses. Sex enhancing drugs such as methamphetamine which increases sexual energy, are taken in combination with other substances such as alcohol before indulging in sexual escapades. Such individuals exhibit a high likelihood to

indulge in unprotected sex or be unable to control themselves during sexual intercourse, creating a better opportunity for infections from other STDs and HIV/AIDS [63]. Patients of drug abuse have very minimal chance of full recovery owing to other secondary substances, resulting into poor treatment outcome [75].

2.3 General models on substance abuse

Unlike infectious diseases, data on substance abuse is very scarce. This could be attributed to the fact that drug abuse and possession is considered illegal in most countries. The challenge in estimating the actual population of drug users is further compounded by the fact that the behaviour of drug users do not exactly mirror that of individuals infected with infectious diseases. Despite these short falls, the technique of mathematical modelling has become handy in providing the necessary insight and understanding towards drug abuse epidemic. Deterministic and stochastic models have been helpful in the understanding of the various aspects of the substance/drug abuse dynamics from initiation, treatment to prevention measures.

Several researchers in [5, 9, 55, 87] have formulated and analysed mathematical models on substance abuse. They have attempted to answer such questions as: the type and amount of drug abused, trends of drug abuse, consequences of abuse, effectiveness of available policies and their corresponding costs. Policy makers on the other, have been faced with such challenges as understanding the problem of drug abuse, designing robust intervention strategies and constructing better evaluation tools to test on the effectiveness of the designed strategies [71].

Unlike infectious disease epidemic model with biological parameters, drug abuse epidemic is mainly characterised by social parameters which are often transitory [71]. It is assumed that the rate of new 'infections' in drug abuse epidemic is regulated by the law of mass-action which states that new cases of drug abuse are reliant on the population of drug users and the population of individuals who have never used drugs before but are at risk of being initiated into drug abuse [43].

Compartmental model is a powerful and well-established tool that can be applied not only in modelling the spread of diseases but also the spread of drug/substance abuse in a population of interest [71]. The compartments are constructed such that the flow mirrors the usual dynamics and interactions in disease epidemics. Upon sub-diving the population into distinct and homogeneous compartments. Based on provided hypotheses and assumptions, suitable mathematical equations are derived that represents the change in population in each compartment over time. Rossi in [71] categorised the susceptible population into 'Stayers' (those who cannot be initiated into drug abuse for one reason or another, and hence are never at risk) and 'Movers'

(those who are at risk always). Upon initiation, drug users undergone a process of latency, a period of hidden drug use. During the latency phase, the drug users may die, quit or continue using the drug. The hidden phase can further be split into several compartments depending on the interest of the modeller. For example, the hidden phase may be split into 'light drug use', representing initial stages of drug use and 'hard drug use', which marks the problematic stage of drug abuse. Addicts are further taken through rehabilitation which may be a success or not.

Some of the substance abuse models have been formulated and discussed in [9, 17, 56, 87]. In 2006, Emma White and Catherine Comiskey [87] developed the first ordinary differential equation model for opiate addiction. While relying on information in [5, 7, 17], the results from their study was vital to policy makers in targeting prevention and treatment in heroin epidemic. The original model, see Figure 2.1, has three compartments each representing a stage in the drug using career of a drug user. Those individuals who have never used drugs before but stand a chance of using them, are called susceptibles (S). Drug users not under treatment are denoted by U_1 while those that have reached the problematic phase of drug abuse and are under treatment are denoted by U_2.

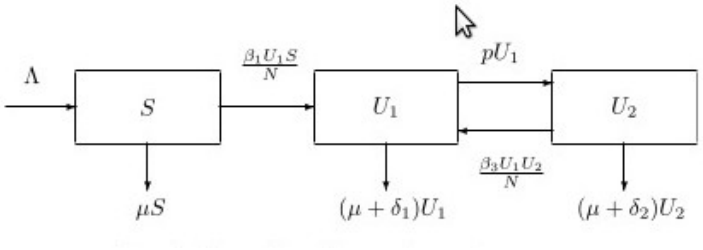


Figure 2.1: A simple substance abuse model. Source [87].

Results from the sensitivity analysis identified the probability of becoming a drug user as the most influential parameter for target in the reduction of secondary cases of heroin abuse. Secondly, preventive therapy was more effective as compared to treatment for maximum and effective eradication of opiate addiction and abuse. More efforts and resources should therefore be put to prevention as it was shown to be more effective in controlling the spread of habitual drug use as opposed to enhancing progression of drug addicts to treatment [87].

Mathematical modelling is a predictive tool. It enables epidemiologists to follow consistently the behaviour of different classes of drug users at different stages of their drug using career. It is also instrumental in developing robust intervention strategies in drug abuse epidemic [52]. Mulone and Straughan in 2009 [52] proved

the stabilities of the equilibria in the heroin epidemic model by Emma White and Comisky in [87] without making assumption of a constant recruitment rate for new users and those that had relapsed into drug abuse after treatment. They showed that the equilibrium solution of the Heroin epidemic model is stable both linearly and non-linearly under the realistic conditions that the relapse rate of those in treatment returning to untreated drug use (β_3) is greater than the prevalence rate of susceptibles becoming drug users (β_1), see the figure in [87] for parameter descriptions.

2.4 Methamphetamine (MA) abuse models

Mathematical model on methamphetamine abuse in South Africa was first studied by Nyabadza and Hove Musekwa in [55]. In their work, they argued that drug users cannot get to the problematic stage of addiction upon initiation and that it is only while still at the light use stage (concealed stage of drug use) that a drug user can easily quit drug use. Once addicted, drug users must undergo treatment to survive drug abuse epidemic. Their model which was an extension of the Heroin epidemic model by Emma White and Comisky [87], had the compartment of drug users not in treatment further subdivided into compartments of light users and hard users (drug users who are addicted to the drug of abuse).

Although recovery from substance abuse epidemic is often expected upon treatment, cases of relapse have been dominant. A compartment of recovered drug users is created in the model in [55]. The relapsed individuals are assumed to relapse to the class of hard drug use and not to the light use stage owing to their earlier experience with the drug. The analysis of the model which is done in terms of the model threshold parameter R_0 indicates that the model has multiple equilibria, and exhibits backward bifurcation. The five compartmental model is shown in Figure 2.2, with variables S, I_1, I_2, T and R representing the classes of susceptible, light MA users, hard MA users, MA users under treatment, and recovered individuals respectively.

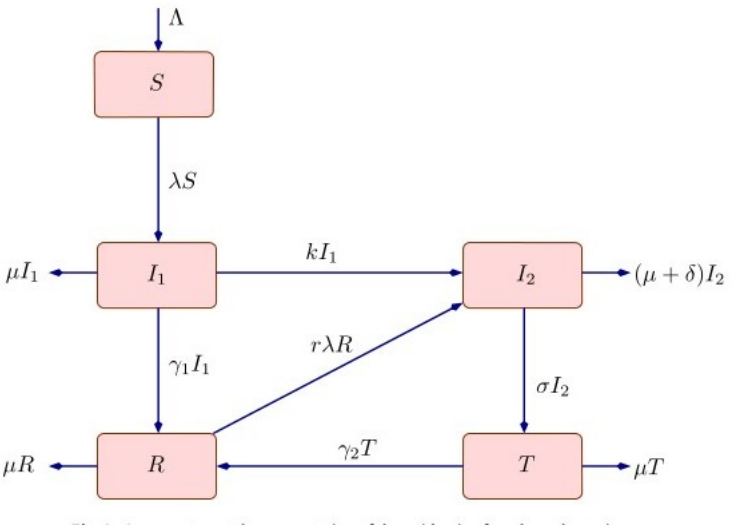


Figure 2.2: A compartmental representation of the epidemic of MA use

In addition to the bilinear interaction that generate new users, the contributions made by drug-supply chains is vital in drug abuse epidemic. Compartmental model described in [55] provides a structure in which individuals in each compartment can be tracked in time as relationships between compartments described in mathematical terms. Deterministic model described in [56], which is an expansion of the model in [55] incorporates not only the density of drugs in the supply chains but also a recovery process that is ameliorative. Important aspects of policing that are important in controlling supply of drugs in the market is considered in this model. Their analysis reveal that prevention of drug abuse and addiction can best be achieved through cutting out any initial use.

2.5 Alcohol abuse models

Problem drinking is modelled as an acquired state. It is the result of regular interactions between individuals in three drinking states (susceptibles, problem drinkers and temporary recovered) within a specified drinking environment [74]. The dynamics of drinking problem has been considered in the context of classic SIR model epidemiological framework by Chavez in [15]. We observe that the classification of individuals into distinct homogeneous classes for modelling of alcoholism is varied and never universal. However, individual move from one class to another subject to changes in his/her drinking habits. In [74] the general population is subdivided into occasional and moderate drinkers (S); problem drinkers (D) and temporarily recovered (R). The dynamics of alcoholism model is dependent on the original population of problem drinkers, the time they spend in the drinking environment and the intensity of interaction with the susceptibles.

We observe in [74] that ineffective treatment program with high relapse rates may actually promote the spread of alcoholism, because they create a group of recovered drinkers who could easily relapse. Robust treatment strategy for curbing the spread of alcoholism should limit the amount of time a recovered alcoholic spends in places where drinking occurs such as in bars and pubs.

Benedict in [8] categorised individuals into three homogeneous compartments of susceptible drinkers, S (those who consume alcohol in moderation but may one day develop problems with alcohol; alcoholics, A (those who have drinking problems or addiction); and recovered individuals, R (former alcoholics who have entered treatment and are abstaining from alcohol). When a moderate drinker develops drinking problem, he/she moves from class S to A. Secondly, an alcoholic can give up drinking upon treatment and move from A to R. Owing to treatment failure, the recovered individuals may relapse into alcoholism and move from compartment R to A. A set of non-linear ordinary differential equations are used to describe the changes in population within the modelling time in each of the three compartments.

Bhunu in [9] improved the alcohol model in [8] by subdivided further the population that drink alcohol into moderate drinkers (individuals who may be consuming alcohol but are yet to graduate to the more problematic stage of alcohol dependent) and alcoholics (persons that are fully dependent on alcohol abuse). The results of his model reveals the need to encourage more moderate drinkers to quit alcohol use. We also observe that enhanced quitting process at early stages of moderate drinking is much easier and beneficial in the fight against alcoholism relative to enhanced treatment rates from alcoholism. Thus, a lot more focus should be on moderate drinkers and not necessarily visible victims of alcoholism as is often the case.

For effective management of alcoholism, both categories of alcohol drinkers should be targeted. Further, there is a need to improve the educational campaigns in public places such as schools and health centres while targeting specific alcohol abusers. Since alcohol drinking is a social activity, it is mainly a product of peer pressure. The introduction of an anti-alcoholism peer groups as proposed by Bhunu could in some way directly thwart recruitment in alcohol abuse epidemic.

2.6 Models on multiple substance abuse

Lack of data on multiple substance abuse has ensured minimal research in this area. Most of the treatment/rehabilitation centres in Western Cape Province like the rest of South Africa only has minimal data on population of patients seeking treatment services for a specific drug/substance of abuse. However, this does not exclude the possibility of drug users taking multiple drugs to achieve certain objectives. Often,

only the more virulent drug (whose side effects or consequences are felt the most) is reported for treatment. The less virulent drug (whose negative effects are less pronounced or felt) is often ignored or given minimal attention despite the fact that it could greatly influence cases of relapse. It is worth noting that the substances/drugs taken by the user, have a symbiotic relationship with the effects of each other. The use and abuse of one substance, is dependent on the use and availability of the other. Research work in [60, 79] reveals the sequential abuse of such substances by their users

Some of the research work on multiple substance/drug abuse include the following: In 2011, Bhunu and Mushayabasa in [53] modelled the effects of heavy alcohol consumption on the transmission dynamics of gonorrhoea. They categorised alcohol users into social drinkers and heavy drinkers. Unlike social drinkers, heavy consumers of alcohol were more likely to engage in risky sexual behaviour which unfortunately, enhanced their chances of contracting sexually transmitted infections such as gonorrhoea. Results from their study indicated that disease prevalence increased with increasing alcohol consumption, see Figure 2.3. That is, communities with higher population of heavy alcohol drinkers were more likely to experience increased disease incidences and prevalences.

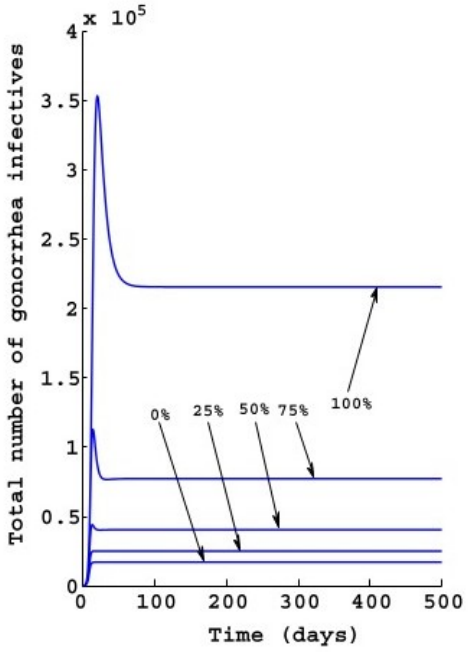


Figure 2.3: Simulations showing the influence of increased heavy alcohol drinkers on gonorrhoea cases. Source [53].

In their analysis of the growing health and social problems associated with alcoholism and smoking, Bhunu and Mushayabasa in [9] formulated and analysed a mathemati-

cal model for alcoholism and smoking. Results of their study emphasised the need to support and encourage moderate alcohol drinkers and moderate smokers to quit alcoholism and smoking respectively. This according to the study was shown to be much more effective in controlling the prevalence of alcoholism and smoking epidemics than the usual support and encouragement given to addicts.

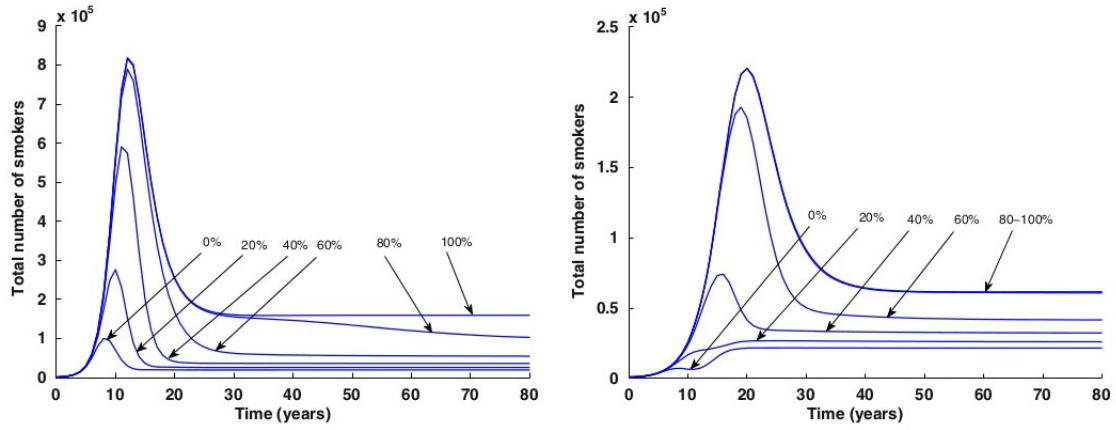


Figure 2.4: Simulations showing the effects of varying the percentage of alcohol drinkers on the population on smokers in the absence and presence of quitting smoking. Source [9].

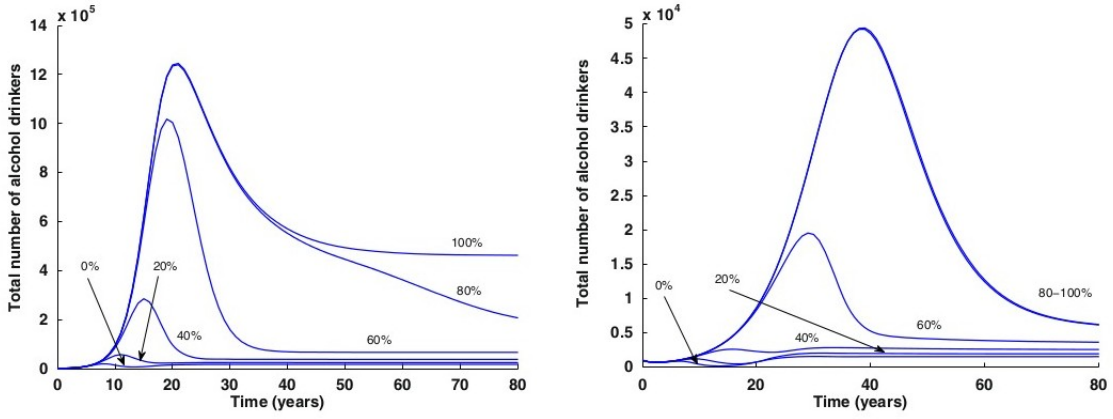


Figure 2.5: Simulations showing the effects of varying the percentage of smokers on the population on alcohol drinkers in the absence and presence of quitting alcohol drinking. Source [9].

Unlike moderate drinkers or smokers, allowing addicts to quit has instant benefits that are related to both personal, health and social problems. They noted that smoking

highly influences alcoholism and that the converse was equally true. That is, smoking fuels alcoholism and vice versa. As the percentage of smokers increase, so does the percentage of drinkers as shown in Figure 2.5. If smoking can be stopped, then the levels or cases of alcoholism would equally decline in a community, see Figure 2.5. The process of quitting alcoholism and smoking is too complex and required several spirited efforts [9].

Regular educational campaigns against drug abuse coupled with constant motivation to quit, persuasion and frequent counselling are some of the recommendations for effective management of alcoholism and smoking epidemics.

Lawi and his colleagues in [39], modelled the co-infection of paediatric malaria and pneumonia. Their results from the sensitivity analysis emphasised the need to enhance treatment services for individuals suffering from the two diseases. The model reproduction numbers were observed to be most sensitive to the treatment rates in the co-infection model. Improved treatment services would significantly result into in the expected decline of new disease incidences.

2.7 Our Research

It is against this background that we endeavour to model the dynamics of multiple substance abuse: a scenario in which an individual uses two different kinds of drugs/substance of abuse. In this thesis, we shall however focus on the simultaneous abuse of alcohol and methamphetamine. We shall apply our individual sub-models to data of persons seeking treatment services resulting from alcohol and methamphetanine abuse from the different rehabilitation centre within the Western Cape Province as is presented in the bi-annual report by SACENDU. We propose a co-abuse drug epidemic model in which initiation, addiction, treatment, recovery and relapse form part of the drug abuse dynamics. Feasible equilibrium states of the model and its sub-models are established and their stabilities determined through the Lyapunov method. Owing to the non-linearity of differential equations in the system that forms the co-abuse model, we carry out numerical simulations as analytic solutions become elusive. We apply theorems in epidemics to establish local stabilities of the steady states from the sub-models. Using data from SACENDU and the Least Squares Method, we determine the prevalence of co-abuse of alcohol and methamphetamine in the Western Cape Province of South Africa.

Chapter 3

Co-abuse model

3.1 Model formulation

We describe the dynamics of the co-abuse of alcohol and methamphetamine within the context of a classical Susceptible-Infected-Recovered (SIR) epidemiological framework [14]. Our modelling of substance abuse is based on the premise that the dynamics of substance abuse epidemic mirrors that of infectious diseases [87]. The total population is partitioned into seven compartments: the susceptible compartment denoted by S, which refers to individuals who have never used or abused alcohol (moderate or occasional drinkers) and/or methamphetamine before, but are at risk of using both substances, the compartment of alcohol abusers U_a, which refers to problem drinkers who are not under rehabilitation (taking of pills or any other forms of treatment), compartment of alcohol abusers under rehabilitation R_a, that of methamphetamine users who are not under rehabilitation U_t, the compartment of methamphetamine users under rehabilitation R_t, the compartment of users of both alcohol and methamphetamine (co-users) who are not under rehabilitation U_{at}, and that of co-users of alcohol and methamphetanime under rehabilitation R_{at}.

Individuals move from one compartment to another upon changes in their status with regards to co-abuse of alcohol and methamphetamine. In this work, we shall focus on a specific closed population. We therefore assume that within the modelling period, the overall population size denoted by N is not constant; that is, N undergoes subtle changes over the study period. Therefore, at any modelling time t, the total human population is given by:

$$N(t) = U_a(t) + R_a(t) + U_t(t) + R_t(t) + U_{at}(t) + R_{at}(t). \tag{3.1.1}$$

The population under study is also assumed to be large enough to be modelled deterministically. The susceptible population is increased by a constant inflow into the population at a rate Λ through births and immigration processes. Through homogeneous mixing, they acquire alcohol drinking and or methamphetamine habits that

lead to abuse following effective contacts with those that use alcohol and/or methamphetamine. We argue that the rapid contact is mainly driven by peer pressure.

The fact that some susceptibles spend time with people who drink alcohol and or use methamphetamine enhances their propensity to drinking alcohol and or to using methamphetamine. Without minimizing the fact that environmental, social and behavioural factors tend to contribute to variation in individual susceptibility to substance abuse, we shall assume here that individuals under study mixes homogeneously so that those at risk of substance abuse are equally susceptible. The dynamics of the co-abuse model is characterised by two non-linear interactions between susceptibles and abusers of alcohol and/or methamphetamine. Assuming a frequency-dependent force of initiation, the susceptibles acquire alcohol abuse through their interactions with those in classes; U_a, R_a, U_{at} and R_{at} at a rate denoted by λ_1, where

$$\lambda_1 = \beta_1 \left(\frac{U_a + \zeta_1 R_a + \zeta_2 U_{at} + \zeta_3 R_{at}}{N} \right). \tag{3.1.2}$$

The parameter β_1 denotes the effective alcohol transmission rate. The transmission parameter represent an effective contact by an alcohol drinker that will result into non-alcohol user beginning to use alcohol. We nevertheless recognize that complex initiation into substance abuse may not only be through effective contact. Other processes such as self-initiation may influence a non-alcohol user to start using it.

The parameters ζ_1, ζ_2 and ζ_3 are called modification parameters. They capture the relative ability to initiate new users of alcohol and methamphetamine by alcohol users under treatment, co-abusers of alcohol and methamphetamine without treatment and the co-abusers under treatment. We assume here that substance users under treatment have a slightly lower probability to initiate new users owing to 'negative' advertisement of the consequences of substance abuse. Thus, $\zeta_1, \zeta_3 < 1$ while $\zeta_2 > 1$.

As a consequence of close contact with methamphetamine users in bars and pubs, alcoholics in the class U_a begin to abuse methamphetamine at a rate $\eta_a \lambda_2$ $(\eta_a \geq 1)$ to join the class of co-abusers of alcohol and methamphetamine, $U_{at}(t)$. Alcoholics in the class $U_a(t)$ seek treatment at a rate σ_1 and join the class R_a. Upon successful treatment, individuals in R_a may permanently quit alcoholism at a rate ρ_4 and move into class $Q(t)$. In this model, we assume relapse in the form of rehabilitation failure. Individuals under treatment, relapse into alcoholism at a rate γ_1. We also recognize that some alcoholics may permanently quit early at a rate ρ_3 before rehabilitation. Furthermore, we assume a constant natural mortality rate in each population class denoted by μ. Alcohol addiction often results in deaths associated with its abuse. We thus assume a mortality rate associated with alcohol abuse denoted by δ_1.

Similarly, susceptible individuals get recruited into methamphetamine abuse at a rate

λ_2 given by

$$\lambda_2 = \beta_2 \left(\frac{U_t + \epsilon_1 R_t + \epsilon_2 U_{at} + \epsilon_3 R_{at}}{N} \right), \tag{3.1.3}$$

where the parameter β_2 is the transmission rate of methamphetamine abuse and ϵ_i ,$i = 1, 2, 3$ are the modification parameters. Like the case of alcohol abuse, the modification parameters ϵ_1 and ϵ_3 are both assumed to be less than unity while $\epsilon_2 > 1$.

Some individuals in $U_t(t)$ acquire alcohol drinking habits at the rate $\eta_t \lambda_1$ and move into the class $U_{at}(t)$ with $\eta_t \geq 1$ accounting for the increased chances of drinking alcohol for methamphetamine users when compared to those that are not using methamphetamine. Methamphetamine addicted individuals seek treatment at a rate σ_3. Such addicts may permanently quit methamphetamine upon successful treatment or relapse later into methamphetamine abuse at the rates ρ_6 and γ_3 respectively. Moreover, we allow for permanent quitting of individuals in the class $U_t(t)$ at a rate ρ_7. Individuals under abuse of methamphetamine may die due to methamphetamine-related causes and naturally at the rates δ_3 and μ respectively.

On quitting combined abuse of alcohol and methamphetamine, co-abusers in the class U_{at}, may revert to alcohol abuse only or methamphetamine abuse only at the rates ρ_1 and ρ_2 respectively. The co-abusers may also progress into treatment for combined effects at a rate σ_2 and join the class R_{at}. Total treatment failure may cause relapse into U_{at} at a rate γ_2. In the same breadth, partial treatment success may imply quitting only one substance of abuse. If co-abusers quit alcohol only after treatment, then they are assumed to have relapsed into their earlier status of methamphetamine abuse and retreat to class U_t at the rate γ_5. Similarly, they may quit methamphetamine and relapse back to U_a at a rate γ_4. Successfully treated co-abusers quit the combined use of alcohol and methamphetamine at a rate ρ_5. Other than the constant natural death, co-abusers may be removed due to death related to co-abuse of alcohol and methamphetamine at a rate δ_2. The possible transitions of users and co-abusers of alcohol and methamphetamine are represented by the schematic diagram, Figure 3.1.

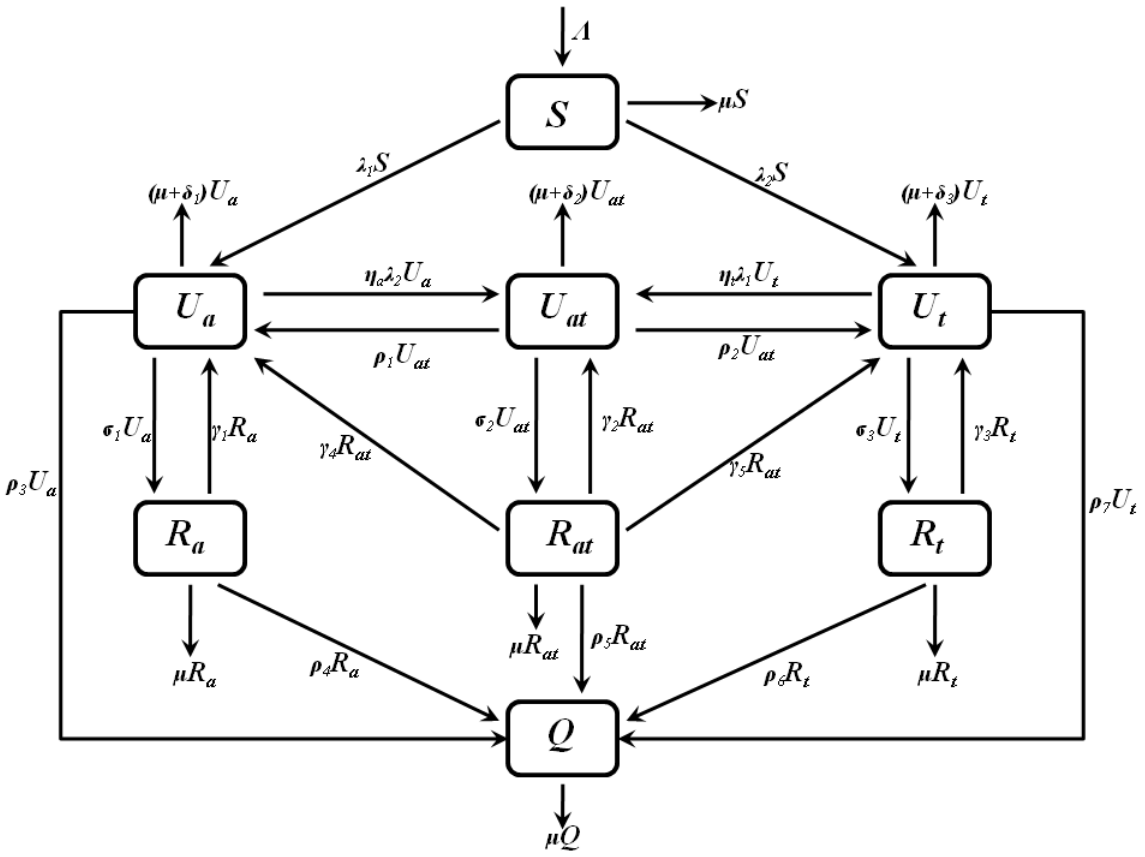


Figure 3.1: A compartmental representation of the epidemic of the alcohol-methamphetamine co-abuse

Additional assumptions are that;

- Individuals under treatment can initiate non users as the rehabilitation process is taken to be outpatient.
- We allow permanent quitting of alcohol and or methamphetamine abuse upon treatment.
- Although quitting both substances at the same time is unlikely, in this model, we allow permanent quitting by individuals in rehabilitation for both alcohol and methamphetamine.

The aforementioned assumptions, variables and parameter descriptions shown in Figure 3.1 gives rise to the following system of non-linear ordinary differential equations, with non-negative initial conditions that describe the dynamics of alcohol and methamphetamine co-abuse epidemic. It is important to observe that the equation in the compartment Q is redundant, hence omitted (since the other differential equations are independent of Q). The alcohol-methamphetamine co-abuse model is thus

represented by the following system of non-linear ordinary differential equations.

$$\left.\begin{aligned}
\frac{dS}{dt} &= \Lambda - (\mu + \lambda_1 + \lambda_2)S, \\
\frac{dU_a}{dt} &= \lambda_1 S + \rho_1 U_{at} + \gamma_1 R_a + \gamma_4 R_{at} - \eta_a \lambda_2 U_a - (\mu + \sigma_1 + \delta_1 + \rho_3)U_a, \\
\frac{dR_a}{dt} &= \sigma_1 U_a - (\mu + \gamma_1 + \rho_4)R_a, \\
\frac{dU_t}{dt} &= \lambda_2 S + \rho_2 U_{at} + \gamma_3 R_t + \gamma_5 R_{at} - \eta_t \lambda_1 U_t - (\mu + \sigma_3 + \delta_3 + \rho_7)U_t, \\
\frac{dR_t}{dt} &= \sigma_3 U_t - (\mu + \gamma_3 + \rho_6)R_t, \\
\frac{dU_{at}}{dt} &= \eta_a \lambda_2 U_a + \eta_t \lambda_1 U_t + \gamma_2 R_{at} - (\mu + \rho_1 + \rho_2 + \delta_2 + \sigma_2)U_{at}, \\
\frac{dR_{at}}{dt} &= \sigma_2 U_{at} - (\mu + \gamma_2 + \gamma_4 + \gamma_5 + \rho_5)R_{at},
\end{aligned}\right\} \tag{3.1.4}$$

where

$S_0 > 0, U_{a0} \geq 0, R_{a0} \geq 0, U_{t0} \geq 0, R_{t0} \geq 0, U_{at0} \geq 0, R_{at0} \geq 0.$

A description of parameters used in the co-abuse model and its sub-models are defined in Table 3.1.

Table 3.1: Descriptions of co-abuse model parameters

Parameter	Description
Λ	Recruitment rate for susceptible persons
μ	Natural mortality rate
β_1	Alcohol transmission rate
β_2	Methamphetamine transmission rate
γ_1	Relapse rate for alcohol abusers
γ_2	Relapse rate for co-abuser
γ_3	Relapse rate for methamphetamine abusers
γ_4	Co-abusers' relapse rate into alcohol only abuse
γ_5	Co-abusers' relapse rate into methamphetamine only abuse
δ_1	Alcohol-induced mortality rate
δ_2	Co-abuse-induced mortality rate
δ_3	Methamphetamine-induced mortality rate
σ_1	Recovery rate for alcohol abusers
σ_2	Recovery rate for co-abusers of alcohol and methamphetamine
σ_3	Recovery rate for methamphetamine abusers
ρ_1	Rate at which co-abusers revert to methamphetamine abuse only without treatment
ρ_2	Rate at which co-abusers revert to alcoholism only without treatment
ρ_3	Quitting rate for alcohol abusers without treatment
ρ_4	Quitting rate for alcohol abusers upon success treatment
ρ_5	Quitting rate for co-abusers upon successful treatment
ρ_6	Quitting rate for methamphetamine abusers upon successful treatment
ρ_7	Quitting rate for methamphetamine abusers without treatment
η_a, η_t, ϵ_1, ϵ_2	Modification parameters
ζ_1, ζ_2, ζ_3, ϵ_3	Modification parameters

3.2 Basic properties of the co-abuse model

In this section, we study the basic results of solutions of model system (3.1.4). These results are essential in the proofs of stability results. We begin by identifying our region of interest. The domain of biological significance is denoted by Ω and is defined as:

$$\Omega = \left\{ (S(t), U_a(t), R_a(t), U_t(t), R_t(t), U_{at}(t), R_{at}(t)) \in \mathbb{R}^7_+ | 0 \leq N \leq \frac{\Lambda}{\mu} \right\}, \qquad (3.2.1)$$

with initial conditions defined in (3.1.4).

3.2.1 Positivity of solutions of the model

For every dynamic system, it is quite important to establish the long term behaviour of its solutions. The formulated model system (3.1.4) monitors changes in human population. We therefore show that all solutions of the system (3.1.4) with non-negative initial data will remain non-negative for all times $t \geq 0$. We make the following claim.

Lemma 3.2.1. *Given that the initial conditions of the system* (3.1.4), $S_0 > 0$, $U_{a0} \geq 0$, $R_{a0} \geq 0$, $U_{t0} \geq 0$, $R_{t0} \geq 0$, $U_{at0} \geq 0$, $R_{at0} \geq 0$, *the resulting solutions* $S, U_a, R_a, U_t, R_t, U_{at}, R_{at}$ *are all non-negative for all time* $t \geq 0$.

Proof. For the equations in model system (3.1.4), let us assume that T is the maximum time for the epidemic. That is, $T = \sup\{t > 0, S > 0, U_a \geq 0, R_a \geq 0, U_t \geq 0, R_t \geq 0, U_{at} \geq 0 \quad and \quad R_{at} \geq 0\} \in [0, t]$.

Therefore, $T \geq 0$ and from the first equation of model system (3.1.4), we obtain

$$\frac{\mathrm{d}}{\mathrm{d}t}\left[S(t)\exp\left\{\mu t + \int_0^t (\lambda_1(s) + \lambda_2(s))\mathrm{d}s\right\}\right] = \Lambda \exp\left[\mu t + \int_0^t (\lambda_1(s) + \lambda_2(2))\mathrm{d}s\right],$$

So that

$$S(T) = S(0)\exp\left[-\left\{\mu T + \int_0^T (\lambda_1(s) + \lambda_2(s))\mathrm{d}s\right\}\right]$$
$$+ \exp\left[-\left\{\mu T + \int_0^T (\lambda_1(s) + \lambda_2(s))\mathrm{d}s\right\}\right]\left(\int_0^T \Lambda \exp\left[\mu\widehat{T} + \int_0^{\widehat{T}} ((\lambda_1(w) + \lambda_2(w))\mathrm{d}w\right]\mathrm{d}\widehat{T}\right)$$
$$\geq 0.$$

Hence, $S(T) \geq 0$ for $\forall T \geq 0$.

Now, for the second equation (3.1.4), we have;

$$\begin{aligned}\frac{dU_a}{dt} &= \lambda_1 S + \rho_1 U_{at} + \gamma_1 R_a + \gamma_4 R_{at} - \eta_a \lambda_2 U_a - (\mu + \sigma_1 + \delta_1 + \rho_3) U_a, \\ &\geq -(\eta_a \lambda_2 - \mu + \sigma_1 + \delta_1 + \rho_3) U_a, \\ U_a(t) &= U_{a0} \exp\left[(\mu + \sigma_1 + \delta_1 + \rho_3)t + \int_0^t \eta_a \lambda_2(s) ds\right]. \end{aligned} \tag{3.2.2}$$

This implies that $U_a(t) \geq 0$ for all time $t \geq 0$.

The above method can be applied to all the other equations in the system (3.1.4) to show that all the population variables ($U_t \geq 0$, $R_t \geq 0$, $U_{at} \geq 0$ and $R_{at} \geq 0$) are non-negative for all time $t \geq 0$. We will have

$$\begin{aligned} R_a(t) &\geq R_{a0} \exp\left[-(\mu + \gamma_1 + \rho_4)t\right] > 0, \\ U_t(t) &\geq U_{t0} \exp\left\{(\mu + \sigma_3 + \delta_3 + \rho_7)t + \int_0^t \eta_t \lambda_2(s) ds\right\} > 0, \\ R_t(t) &\geq R_{t0} \exp\{-(\mu + \gamma_3 + \rho_6)t\} > 0, \\ U_{at}(t) &\geq U_{at0} \exp\left\{-(\mu + \sigma_2 + \delta_2 + \rho_1 + \rho_2)t\right\} > 0 \quad \text{and} \\ R_{at}(t) &\geq R_{at0} \exp\{-(\mu + \gamma_3 + \gamma_4 + \gamma_5 + \rho_5)t\} > 0. \end{aligned}$$

Therefore, all the solutions of the system (3.1.4) with non-negative initial conditions will remain non-negative for all time $t \geq 0$. This marks the end of the proof. □

3.2.2 Boundedness of solutions of the co-abuse model

We show that the total population is bounded for all time $t \geq 0$.

The total populations in this model is clearly not constant. Therefore, the evolution of the population over time is given by

$$\frac{dN}{dt} = \Lambda - \mu N - (\delta_1 U_a + \delta_2 U_{at} + \delta_3 U_t) - (\rho_3 U_a + \rho_4 R_a + \rho_5 R_{at} + \rho_6 R_t + \rho_7 U_t). \tag{3.2.3}$$

In the absence of substance abuse, we obtain:

$$\frac{dN}{dt} \leq \Lambda - \mu N. \tag{3.2.4}$$

Upon solving for N in the differential equation (3.2.4), we have:

$$N(t) \leq \frac{\Lambda}{\mu} + \left(N_0 - \frac{\Lambda}{\mu}\right) \exp(-\mu t). \tag{3.2.5}$$

From equation (3.2.5), it is clear that the total population $N(t)$ will approach the threshold $\frac{\Lambda}{\mu}$ as $t \to \infty$. This therefore implies that if our initial total population, N_0 is less than $\frac{\Lambda}{\mu}$ i.e. if $N_0 \leq \frac{\Lambda}{\mu}$ then $\lim_{t\to\infty} N(t) = \frac{\Lambda}{\mu}$. Clearly $\frac{\Lambda}{\mu}$ is the upper bound of N.

On the other hand, if $N_0 > \frac{\Lambda}{\mu}$, then $N(t)$ will decrease to $\frac{\Lambda}{\mu}$ as $t \to \infty$. This means that if $N_0 > \frac{\Lambda}{\mu}$, then the solution $(S(t), U_a(t), R_a(t), U_t(t), R_t(t), U_{at}(t), R_{at}(t))$ enters Ω or approaches it asymptotically. We thus conclude that the region Ω is positively invariant under the flow induced by system (3.1.4).

The described model system (3.1.4) is thus both mathematically and epidemiologically well-posed in the region Ω. It is therefore sufficient to study the dynamics of model system (3.1.4) in Ω.

3.3 Co-abuse model analysis

In this section, we give the mathematical analysis of the co-abuse model. We derive the model equilibria (where possible) and investigate their stability.

3.3.1 Equilibrium points of the co-abuse model

Since the rate of change in populations in each compartment is constant at equilibrium, we set the right hand side of equations (3.1.4) to zero as follows:

$$\left.\begin{aligned}
0 =& \Lambda - (\mu + \lambda_1 + \lambda_2)S^*, \\
0 =& \lambda_1 S^* + \rho_1 U_{at}^* + \gamma_1 R_a^* + \gamma_4 R_{at}^* - \eta_a \lambda_2 U_a^* - (\mu + \sigma_1 + \delta_1 + \rho_3)U_a^*, \\
0 =& \sigma_1 U_a^* - (\mu + \gamma_1 + \rho_4)R_a^*, \\
0 =& \lambda_2 S^* + \rho_2 U_{at}^* + \gamma_3 R_t^* + \gamma_5 R_{at}^* - \eta_t \lambda_1 U_t^* - (\mu + \sigma_3 + \delta_3 + \rho_7)U_t^*, \\
0 =& \sigma_3 U_t^* - (\mu + \gamma_3 + \rho_6)R_t^*, \\
0 =& \eta_a \lambda_2 U_a^* + \eta_t \lambda_1 U_t^* + \gamma_2 R_{at}^* - (\mu + \rho_1 + \rho_2 + \delta_2 + \sigma_2)U_{at}^*, \\
0 =& \sigma_2 U_{at}^* - (\mu + \gamma_2 + \gamma_4 + \gamma_5 + \rho_5)R_{at}^*,
\end{aligned}\right\} \tag{3.3.1}$$

We next solve for $S^*, U_a^*, R_a^*, U_t^*, R_t^*, U_{at}^*$ and R_{at}^* from the equations (3.3.1). Expressing in terms of the forces of infections λ_1 and λ_2 we have,

$$\left.\begin{aligned}
S^* =& \frac{\Lambda}{\mu + \lambda_1 + \lambda_2}, \\
R_{at}^* =& \frac{\Lambda\lambda_1\lambda_2\left[-J_3\zeta_1\eta_a + \zeta_2\eta_t\{-J_1 + \zeta_1\eta_a(\lambda_1 + \lambda_2)\}\right]}{\Theta}, \\
R_a^* =& \frac{1}{\zeta_1\eta_a\lambda_2 - J_1}\{J_2 R_{at}^* + S^*\lambda_1\}, \\
U_a^* =& \frac{b_2}{\sigma_1}R_a^*, \\
R_t^* =& \frac{1}{\zeta_3\eta_t\lambda_1 - J_3}\{J_4 R_{at}^* + S^*\lambda_1\}, \\
U_t^* =& \frac{b_4}{\sigma_3}R_t^*, \\
U_{at}^* =& \frac{b_6}{\sigma_2}R_{at}^*.
\end{aligned}\right\} \tag{3.3.2}$$

where

$$\Theta = (\mu+\lambda_1+\lambda_2)(J_1(J_3K-\zeta_2(J_4+K)\eta_t\lambda_1)+\zeta_1\eta_a(-J_3(J_2+K)+\zeta_2(J_2+J_4+K)\eta_t\lambda_1)\lambda_2),$$

$$J_1 = \gamma_1(1-\frac{\gamma_1\sigma_1}{b_1b_2}), \quad J_2 = \gamma_4+\frac{\rho_1b_6}{\sigma_2}, \quad J_3 = \gamma_3(1-\frac{\gamma_3\sigma_3}{b_3b_4}),$$
$$J_4 = \gamma_5+\frac{\rho_2b_4}{\sigma_3}, \quad K = \gamma_2-b_5\zeta_3, \quad b_1 = \mu+\sigma_1+\delta_1+\rho_3,$$
$$b_2 = \mu+\gamma_1+\rho_4, \quad b_3 = \mu+\sigma_3+\delta_3+\rho_7, \quad b_4 = \mu+\gamma_3+\rho_6,$$
$$b_5 = \mu+\rho_1+\rho_2+\delta_2+\sigma_2, \quad b_6 = \mu+\gamma_2+\gamma_4+\gamma_5+\rho_5.$$

When the equations in state variables, R_a, R_t and R_{at} in equation (3.3.2) are substituted into the expressions for the forces of infection, λ_1 and λ_2 and into the total population, N, we obtain the following expressions

$$\lambda_1 = \frac{\beta_1(\phi_1R_a+\phi_2R_{at})}{N_1}, \quad \lambda_2 = \frac{\beta_2(\phi_3R_t+\phi_4R_{at})}{N_1} \quad \text{and} \quad N_1 = S+\phi_5R_a+\phi_6R_t+\phi_7R_{at},$$

where

$$\phi_1 = \zeta_1+\frac{b_2}{\sigma_1}, \quad \phi_2 = \zeta_3+\frac{b_6}{\sigma_2}, \quad \phi_3 = \epsilon_1+\frac{b_4}{\sigma_3}, \quad \phi_4 = \epsilon_3+\frac{\epsilon_2b_6}{\sigma_1},$$
$$\phi_5 = \frac{b_2}{\sigma_2}+1, \quad \phi_6 = \frac{b_4}{\sigma_3}+1, \quad \phi_7 = \frac{b_6}{\sigma_2}+1.$$

Upon diving and simplifying the two expressions for λ_1 and λ_2, we obtain the polynomial

$$h(\lambda_1,\lambda_2) = \lambda_1(C_0+C_1\lambda_1+C_2\lambda_2+C_3\lambda_1\lambda_2+C_4\lambda_1^{*2}+C_5\lambda_2^{*2}), \tag{3.3.3}$$

where

$$\begin{aligned}
C_0 =& -(\gamma_2-b_5\zeta_3)(J_3\beta_1\phi_1-J_1\beta_2\phi_3),\\
C_1 =& \beta_1\zeta_3(\gamma_2-b_5\zeta_3)\eta_t\phi_1+J_4(\beta_1\zeta_2\eta_t\phi_1+\beta_2\zeta_1\eta_a\phi_3)-\beta_2(J_3\zeta_1\eta_a+J_1\zeta_2\eta_t)\phi_4,\\
C_2 =& \beta_1(J_3\zeta_1\eta_a\phi_2+\zeta_2\eta_t(-J_2\phi_1+J_1\phi_2))-\beta_2\zeta_1(J_2+\gamma_2-b_5\zeta_3)\eta_a\phi_3,\\
C_3 =& -[\zeta_1\eta_a\eta_t(\beta_1\zeta_3\phi_2+\beta_2\zeta_2\phi_4)],\\
C_4 =& \beta_2\zeta_1\zeta_3\eta_a\eta_t\phi_4, \quad \text{and} \quad C_5 = -\beta_1\zeta_1\zeta_3\eta_a\eta_t\phi_2.
\end{aligned}$$

Note that if $\lambda_1 = 0$, then clearly $\lambda_2 = 0$. This gives the substance-free equilibrium (SFE). The SFE denoted by $\mathcal{E}_{at}^0$ represents a scenario in which alcohol and or methamphetamine abuse do not exist in the community. Mathematically, $\mathcal{E}_{at}^0$ is expressed as

$$\mathcal{E}_{at}^0 = (S^*, U_a^*, R_a^*, U_t^*, R_t^*, U_{at}^*, R_{at}^*) = (\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0). \tag{3.3.4}$$

The solutions to the remaining part of the polynomial (3.3.3), described by equation (3.3.5) defines the possible endemic states of the model system (3.1.4). A scenario in

which the co-abuse of alcohol and methamphetamine persists in the society. We thus have

$$p(\lambda_1, \lambda_2) = C_0 + C_1\lambda_1 + C_2\lambda_2 + C_3\lambda_1\lambda_2 + C_4\lambda_1^2 + C_5\lambda_2^2. \tag{3.3.5}$$

Although the existence of the endemic equilibrium points for the co-abuse epidemic model depend on the solutions of the polynomial in equation (3.3.5), the roots of the polynomial must be real and positive to guarantee existence of the endemic equilibrium point(s). Due to mathematical complexity, we are not able to express explicitly the endemic steady states of the co-abuse model. We shall however represent the polynomial in equation (3.3.5) graphically as shown in Figure 3.2 for illustrative purposes using the parameters given in the caption.

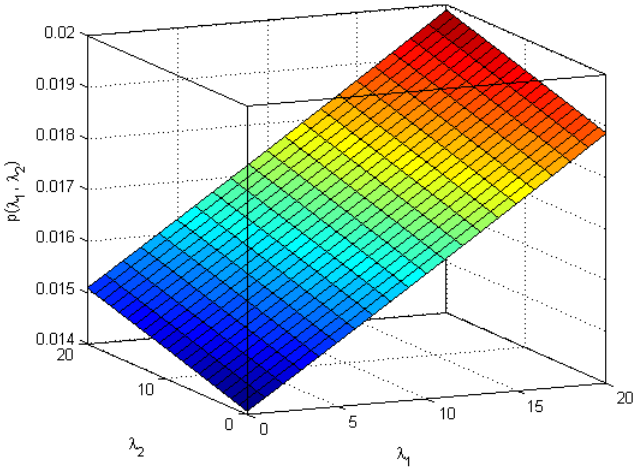


Figure 3.2: Endemic equilibrium points of the co-abuse model for the parameters values: μ = 0.02, β_1 = 0.25, β_2 = 0.45, γ_1 = 0.5, γ_2 = 0.4, γ_3 = 0.23, γ_4 = 0.1, γ_5 = 0.12, δ_1 = 0.03, δ_2 = 0.04, δ_3 = 0.04, σ_1 = 0.53, σ_2 = 0.3, σ_3 = 0.421, ρ_1 = 0.2, ρ_2 = 0.03, ρ_3= 0.35, ρ_4 = 0.45, ρ_5 = 0.35, ρ_6 = 0.78 ρ_7 = 0.4, η_a = 1.005, η_t = 1.005, ζ_1 = 0.85, ζ_2 = 1.05, ζ_3 = 0.805, ϵ_1 = 0.05, ϵ_2 = 1.003, ϵ_3 = 0.04, Λ = 0.29

From the surface plot in Figure 3.2, we notice that there exists endemic steady states for the co-abuse epidemic model based on the chosen parameter values. Such steady states only exists for positive values of $p(\lambda_1, \lambda_2)$. Based on the general structure of the co-abuse model, there is therefore at most three possible endemic equilibrium points. The endemic equilibria exists for the case in which only alcohol abuse is present, the case where only methamphetamine abuse exists or both alcohol and methamphetamine abuse co-exist.

3.3.2 Reproduction number due to alcohol-methamphetamine co-abuse model

We consider a vector, $X = (S, U_a, R_a, U_t, R_t, U_{at}, R_{at})^T$, so that the co-abuse model system (3.1.4) can be rewritten as;

$$\frac{\mathrm{d}X}{\mathrm{d}t} = \mathcal{F}(X) - \mathcal{V}(X), \tag{3.3.6}$$

where matrices $\mathcal{F}$ and $\mathcal{V}$ denotes the rates of appearance of new infections and transfers of infections into and out of any compartment respectively.

The two matrices are given as follows:

$$\mathcal{F} = \begin{pmatrix} \lambda_1 S \\ 0 \\ \lambda_2 S \\ 0 \\ 0 \\ 0 \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} -\rho_1 U_{at} - \gamma_1 R_a - \gamma_4 R_{at} + \eta_a \lambda_2 U_a + (\mu + \sigma_1 + \delta_1 + \rho_3) U_a \\ -\sigma_1 U_a + (\mu + \gamma_1 + \rho_4) R_a \\ -\rho_2 U_{at} - \gamma_3 R_t - \gamma_5 R_{at} + \eta_t \lambda_1 U_t + (\mu + \sigma_3 + \delta_3 + \rho_7) U_t \\ -\sigma_3 U_t + (\mu + \gamma_3 + \rho_6) R_t \\ -\eta_a \lambda_2 U_a - \eta_t \lambda_1 U_t - \gamma_2 R_{at} + (\mu + \rho_1 + \rho_2 + \delta_2 + \sigma_2) U_{at} \\ \sigma_2 U_{at} - (\mu + \gamma_2 + \gamma_4 + \gamma_5 + \rho_5) R_{at} \end{pmatrix}.$$

By taking the partial derivatives of the terms in matrices $\mathcal{F}$ and $\mathcal{V}$, at the substance-free equilibrium (3.3.4), we obtain a non-negative square matrix F and a non-singular square matrix V given by:

$$\mathrm{F} = \begin{pmatrix} \beta_1 & \beta_1\zeta_1 & 0 & 0 & \beta_1\zeta_2 & \beta_1\zeta_3 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & \epsilon_1\beta_2 & \epsilon_2\beta_2 & \epsilon_3\beta_2 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad \mathrm{V} = \begin{pmatrix} b_1 & -\gamma_1 & 0 & 0 & -\rho_1 & -\gamma_4 \\ -\sigma_1 & b_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & b_3 & -\gamma_3 & -\rho_2 & -\gamma_5 \\ 0 & 0 & -\sigma_3 & b_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & b_5 & -\gamma_2 \\ 0 & 0 & 0 & 0 & -\sigma_2 & b_6 \end{pmatrix}, \tag{3.3.7}$$

where $b_1 = \mu + \sigma_1 + \delta_1 + \rho_3$, $b_2 = \mu + \gamma_1 + \rho_4$, $b_3 = \mu + \sigma_3 + \delta_3 + \rho_7$, $b_4 = \mu + \gamma_3 + \rho_6$, $b_5 = \mu + \rho_1 + \rho_2 + \delta_2 + \sigma_2$, and $b_6 = \mu + \gamma_2 + \gamma_4 + \gamma_5 + \rho_5$.

The reproduction number of the co-abuse model system (3.1.4), denoted by R_{at0}, is therefore given by

$$\mathcal{R}_{at0} = \rho(\mathrm{FV}^{-1}) = \max\{\mathcal{R}_{a0}, \mathcal{R}_{t0}\}, \tag{3.3.8}$$

where

$$\mathcal{R}_{a0} = \frac{\beta_1(b_2 + \zeta_1\sigma_1)}{b_1 b_2(1 - \Phi_1)}, \quad \mathcal{R}_{t0} = \frac{\beta_2(b_4 + \epsilon_1\sigma_3)}{b_3 b_4(1 - \Phi_2)}, \tag{3.3.9}$$

$$\Phi_1 = \frac{\gamma_1\sigma_1}{b_1 b_2} \quad \text{and} \quad \Phi_2 = \frac{\gamma_3\sigma_3}{b_3 b_4}.$$

Notice that $\mathcal{R}_{a0}$ are the average number of secondary alcohol abusers produced as a result of associating with an individual who abuse alcohol during his or her entire drinking life and $\mathcal{R}_{t0}$ being the average number of new methamphetamine users produced as a result of associating with an individual who uses methamphetamine, during his or her entire methamphetamine-using career. We can easily conclude that the existence of co-abuse of alcohol and methamphetamine is dependent on the dynamics of individual substances of abuse (alcohol and methamphetamine). Control efforts should therefore focus on both substances and not either of the substances as is often the case.

The stability of the substance free equilibrium (SFE); a scenario in which substance abuse do not exist in the community is stated as follows.

Theorem 3.3.1. *The substance free equilibrium $\mathcal{E}^0_{at}$ expressed in equation* (3.3.4) *is locally asymptotically stable if $\mathcal{R}_{at0} < 1$ (that is; if $\mathcal{R}_{a0} < 1$ and $\mathcal{R}_{t0} < 1$) and unstable if $\mathcal{R}_{at0} > 1$ (if $\mathcal{R}_{a0} > 1$ and $\mathcal{R}_{t0} > 1$).*

Since the endemic equilibria of the co-abuse model could not be obtained explicitly, we shall comprehensively analyse the steady states of the respective sub-models derived from the co-abuse model. We assume without loss of generality that the co-abuse model share similar characteristics with its sub-models. We begin by analysing the alcohol model in the following section.

3.4 Alcohol abuse model

In this section, we discuss the first sub-model, the alcohol model. The model with alcohol only but no methamphetamine consists of only three compartments (S, U_a, R_a) satisfying equations in system (3.4.1). This occurs when $U_t = R_t = U_{at} = R_{at} = 0$ so that the total population becomes $N_a = S + U_a + R_a$. We derive the model based on the provided variables, parameters and assumptions in model system (3.1.4). Unlike the co-abuse model, we analyse the alcohol model, evaluate its equilibrium points and establish their corresponding stabilities. The sub-model is tested for its usefulness using alcohol data as provided in [66].

3.4.1 Model formulation

The system of ordinary differential equations that describe the dynamics in alcohol epidemic is given as follows:

$$\left.\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= \Lambda - (\mu + \bar{\lambda}_1)S,\\ \frac{\mathrm{d}U_a}{\mathrm{d}t} &= \bar{\lambda}_1 S + \gamma_1 R_a - (\mu + \sigma_1 + \delta_1 + \rho_3)U_a,\\ \frac{\mathrm{d}R_a}{\mathrm{d}t} &= \sigma_1 U_a - (\mu + \gamma_1 + \rho_4)R_a,\end{aligned}\right\} \tag{3.4.1}$$

where

$$\bar{\lambda}_1 = \frac{\beta_1(U_a + \zeta_1 R_a)}{N_a}. \tag{3.4.2}$$

Next, we determine the equilibrium states of the alcohol model and analyse their stability.

3.4.2 Alcohol-free equilibrium state $(\mathcal{E}_0^a)$

The alcohol-free equilibrium state describes a scenario in which a drinking culture cease to exist in the community. We thus have:

$$\mathcal{E}_0^a = (S^*, U_a^*, R_a^*) = \left(\frac{\Lambda}{\mu}, 0, 0\right). \tag{3.4.3}$$

Next, we shall briefly discuss reproduction number as used in epidemiology and then compute the reproduction number due to the alcohol abuse sub-model.

3.4.3 Reproduction number due to the alcohol sub-model

The reproduction number due to alcohol model, denoted by $\mathcal{R}_{a0}$, provides a measure of the resilience of the alcohol-free equilibrium state $\mathcal{E}_0^a$ to invasion by problem drinkers. $\mathcal{R}_{a0}$ represents on average, the number of secondary cases generated by a 'typical' problem drinker in a completely susceptible population (i.e., where the population of problem drinkers is originally insignificant).

Following the descriptions in [86], the rate of appearance of new infections, $\mathcal{F}$ and the rate of transfer into and out of any class, $\mathcal{V}$ are respectively given as follows:

$$\mathcal{F} = \begin{pmatrix} \frac{\beta_1(U_a + \zeta_1 R_a)}{N} \\ 0 \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} (\mu + \sigma_1 + \delta_1 + \rho_3)U_a - \gamma_1 R_a \\ -\sigma_1 U_a + (\mu + \gamma_1 + \rho_4)R_a \end{pmatrix}. \tag{3.4.4}$$

So that,

$$\mathrm{F} = \begin{pmatrix} \beta_1 & \beta_1\zeta_1 \\ 0 & 0 \end{pmatrix} \quad \text{and} \quad \mathrm{V} = \begin{pmatrix} (\mu + \delta_1 + \rho_3 + \sigma_1) & -\gamma_1 \\ -\sigma_1 & (\mu + \gamma_1 + \rho_4) \end{pmatrix}. \tag{3.4.5}$$

Following Watmough and Driessche in [86], the reproduction number due to the alcohol model system (3.4.1), and denoted by $\mathcal{R}_{a0}$ is the spectral radius (the dominant eigenvalue) of the next generation matrix (FV^{-1}), and is given by:

$$\mathcal{R}_{a0} = \frac{\beta_1[b_2 + \zeta_1\sigma_1]}{b_1 b_2[1 - \Phi_1]}, \tag{3.4.6}$$

where $b_1 = \mu + \delta_1 + \rho_3 + \sigma_1$, $b_2 = \mu + \gamma_1 + \rho_4$ and $\Phi_1 = \frac{\gamma_1\sigma_1}{b_1 b_2}$.

Next, we analyse the stability of the equilibrium points established from the alcohol abuse model (3.4.1). Here, we argue that the stability of the sub-models are a true representation or are a reflection of the stability of the co-abuse model whose endemic equilibrium points we were not able to obtain explicitly due to mathematical intractability. We briefly discuss stability properties and then apply these properties in the subsequent subsections.

3.4.4 Stability properties

Having derived the substance-free equilibrium point and the endemic equilibrium point(s) of the model (1.6.1), and taken into consideration the restrictions on the parameter values for the equilibria to be biological feasible, the next step is to evaluate the chance that we are likely to observe these equilibria points. Mathematically, this calls for 'stability analysis' of each equilibrium point. Stability analysis provide the conditions on the parameter values necessary for the equilibrium to be (asymptotically) stable to small perturbations [37].

3.4.5 Local stability of alcohol-free equilibrium

Theorem 3.4.1. *The alcohol free equilibrium, $\mathcal{E}_0^a$ is locally asymptotically stable if $\mathcal{R}_{a0} < 1$ and unstable if $\mathcal{R}_{a0} > 1$.*

Proof. $\mathcal{E}_0^a$ is said to be locally asymptotically stable if the eigenvalues of the Jacobian matrix at $\mathcal{E}_0^a$ have negative real parts.

The Jacobian matrix evaluated at the alcohol-free steady state $(S^*, U_a^*, R_a^*) = (\frac{\Lambda}{\mu}, 0, 0)$ is given by:

$$J\left(\frac{\Lambda}{\mu}, 0, 0\right) = \begin{pmatrix} -\mu & -\beta_1 & -\beta_1\zeta_1 \\ 0 & \beta_1 - b_1 & \gamma_1 + \beta_1\zeta_1 \\ 0 & \sigma_1 & -b_2 \end{pmatrix}. \tag{3.4.7}$$

To obtain the characteristic polynomial, we subtract λ from the diagonal elements and calculate the determinant.

$$\begin{vmatrix} -\mu-\lambda & -\beta_1 & -\beta_1\zeta_1 \\ 0 & \beta_1-b_1-\lambda & \gamma_1+\beta_1\zeta_1 \\ 0 & \sigma_1 & -b_2-\lambda \end{vmatrix} = 0. \tag{3.4.8}$$

This gives:

$$(-\lambda-\mu)\{(\beta_1-b_1-\lambda)(-b_2-\lambda)-\sigma_1(\gamma_1+\beta_1\zeta_1)\}=0. \tag{3.4.9}$$

Notice that $(-\lambda-\mu)$ can be factored straight away, giving the eigenvalue $\lambda_1=-\mu$ that is negative. The other two remaining eigenvalues are obtained by solving the quadratic equation:

$$(\beta_1-b_1-\lambda)(-b_2-\lambda)-\sigma_1(\gamma_1+\beta_1\zeta_1)=0. \tag{3.4.10}$$

After making some simplifications the quadratic equation (3.4.10) in λ, can be re-expressed in terms of R_{a0} as follows:

$$\lambda^2+\lambda(b_1+b_2-\beta_1)+b_1b_2(1-\Phi_1)(1-R_{a0})=0. \tag{3.4.11}$$

It can easily be seen from equation (3.4.11) that when $\mathcal{R}_{a0}<1$ then the constant terms $(b_1b_2(1-\Phi_1)(1-\mathcal{R}_{a0}))$ and $(b_1+b_2-\beta_1)$ become positive. Upon solving such a quadratic equation (with positive coefficients), we obtain two negative real roots or complex roots with negative real parts. Therefore, the alcohol free equilibrium, $\mathcal{E}_0^a$ is locally asymptotically stable for $\mathcal{R}_{a0}<1$ and unstable when $\mathcal{R}_{a0}>1$. □

Notice that the reproduction number ($\mathcal{R}_{a0}$) measures on average the number of new alcoholics generated by a single alcoholic in a completely susceptible population. Thus, Theorem 3.4.1 implies that alcoholism can be eliminated from the community whenever $\mathcal{R}_{a0}<1$ if the initial sizes of the sub-populations of the model system (3.4.1) are in the basin of attraction of the alcohol free equilibrium ($\mathcal{E}_0^a$). To ensure that the elimination of alcoholism is independent of the initial sizes of the sub-populations, it is necessary to show that the alcohol free equilibrium is globally stable.

Using a theorem by Castillo-Chavez in [15], we now show the global stability of the alcohol free equilibrium in the case that the effective reproduction number is less than unity.

3.4.6 Global stability of the alcohol-free equilibrium

Theorem 3.4.2. *The alcohol free-equilibrium $\mathcal{E}_0^a$ of system* (3.4.1) *is globally asymptotically stable if $\mathcal{R}_{a0}\leq 1$ and unstable if $\mathcal{R}_{a0}>1$.*

Proof. Let $V(U_a, R_a) = \alpha_1 U_a + \alpha_2 R_a$, be a candidate Lyapunov function for some positive parameters, α_1 and α_2.

Taking time derivative of V, we obtain

$$\frac{dV}{dt} = \alpha_1(\lambda_1 S + \gamma_1 R_a - b_1 U_a) + \alpha_2(\sigma_1 U_a - b_2 R_a), \tag{3.4.12}$$

$$= [\alpha_1(\beta_1 - b_1) + \alpha_2\sigma_1]U_a + [\alpha_1(\beta_1\zeta_1 + \gamma_1) - \alpha_2 b_2]R_a. \tag{3.4.13}$$

Equating the coefficients of U_a to zero, we obtain, $\alpha_1 = \sigma_1$ and $\alpha_2 = b_1 - \beta_1$ so that our Lyapunov function becomes

$$V = \sigma_1 U_a + (b_1 - \beta_1)R_a. \tag{3.4.14}$$

On taking the derivative of (3.4.14) and subsequently substituting for $\dot{U}_a$ and $\dot{R}_a$, we obtain

$$\frac{dV}{dt} = \left(\sigma_1 \frac{\beta_1(U_a + \zeta_1 R_a)S}{N_a} + \gamma_1 R_a - b_1 U_a\right) + (b_1 - \beta_1)(\sigma_1 U_a - b_2 R_a), \tag{3.4.15}$$

$$= b_1 b_2 (1 - \frac{\gamma_1\sigma_1}{b_1 b_2})(\mathcal{R}_{a0} - 1)R_a < 0 \quad \text{for} \quad \mathcal{R}_{a0} < 1. \tag{3.4.16}$$

Noting that all the model parameters are positive, it follows that $\dot{V} \leq 0$ for $R_{ao} < 1$ with $V = 0$ only if $R_a = 0$ or $R_{ao} = 1$. Hence, V is a Lyapunov function on $\Omega = (S, U_a, R_a)$. Since Ω is invariant and attracting, it follows that the largest possible invariant set in $\{(S, U_a, R_a) \in \Omega : \dot{V} = 0\}$ is the singleton $\{\mathcal{E}_0^a\}$. Therefore, by the La-Salle's invariance principle [73], every solution to the equation in the alcohol-only model in system (3.4.1) with initial conditions in Ω approaches E_0^a as time approaches infinity. That is, as $t \to \infty$, $(U_a(t), R_a(t)) \to (0, 0)$.

Substituting for $U_a = R_a = 0$ into the model system (3.4.1), gives $S \to \frac{\Lambda}{\mu}$ as $t \to \infty$. Thus $(S(t), U_a(t), R_a(t)) \to \left(\frac{\Lambda}{\mu}, 0, 0\right)$ as $t \to \infty$ for $\mathcal{R}_{ao} < 1$ so that $\mathcal{E}_0^a$ is globally asymptotically stable in Ω if $\mathcal{R}_{a0} < 1$. □

3.4.7 Existence of endemic equilibria and stability analysis

Upon equating model system (3.4.1) to zero and solving for S^*, U_a^* and R_a^* in terms of the force of infection $\bar{\lambda}_1^*$, we obtain the following expressions.

$$S^* = \frac{\Lambda}{\mu + \bar{\lambda}_1^*}, \quad U_a^* = \frac{\Lambda\bar{\lambda}_1^* b_2}{(\mu + \bar{\lambda}_1^*)(b_1 b_2 - \gamma_1\sigma_1)}, \quad R_a^* = \frac{\Lambda\bar{\lambda}_1^*\sigma_1}{(\mu + \bar{\lambda}_1^*)(b_1 b_2 - \gamma_1\sigma_1)}. \tag{3.4.17}$$

On substituting equations in (3.4.17) into (3.4.2), we obtain the polynomial

$$\bar{\lambda}_1^* \left\{(1 - \mathcal{R}_{a0}) + \bar{\lambda}_1^* \left(\frac{b_2 + \sigma_1}{b_1 b_2[1 - \phi_1]}\right)\right\} = 0. \tag{3.4.18}$$

We observe from polynomial (3.4.18) that $\bar{\lambda}_1^* = 0$ corresponds to the alcohol free-equilibrium. A scenario in which there is no alcohol abuse in the community.

Similarly, $\bar{\lambda}_1^* = \left\{(\mathcal{R}_{a0} - 1)\frac{b_1 b_2(1-\phi_1)}{b_2+\gamma_1}\right\}$ which exists for $\mathcal{R}_{a0} > 1$ corresponds to the endemic equilibrium, a state in which alcohol abuse persists in the society. Thus, system (3.4.1) has a unique endemic equilibrium point $\mathcal{E}_1^a = (S^*, U_a^*, R_a^*)$ which makes biological sense only when $R_{a0} > 1$.

3.4.8 Local stability of the alcohol endemic equilibrium point, $\mathcal{E}_1^a$

Theorem 3.4.3. *The alcohol endemic steady state, $\mathcal{E}_1^a$ is locally asymptotically stable if $\mathcal{R}_a > 1$ but close to 1.*

Proof. Since the explicit endemic equilibrium is cumbersome to obtain, the evaluation of the eigenvalues of the Jacobian matrix of system (3.4.1) at the endemic steady states is thus complicated. We shall thus apply the center manifold theory as presented in [15], to establish the stability of the endemic alcohol equilibrium, $\mathcal{E}_1^a$.

The stability of equilibrium points as defined by the Center manifold theory is given by the Theorem 3.4.4. We shall begin the proof by re-stating the theorem as presented in [15].

Theorem 3.4.4. *Consider the following general system of ordinary differential equations with a parameter φ:*

$$\frac{\mathrm{d}x}{\mathrm{d}t} = g(x, \varphi), \quad g : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \quad \text{and} \quad g \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}), \tag{3.4.19}$$

and $g(0, \varphi) = 0$ for all φ, where 0 is the steady states of the system (3.4.19).

Assume

1. *$M = D_x g(0,0) = (\frac{\partial g}{\partial x_j}(0,0))$ is the linearisation matrix of system* (3.4.19) *around the equilibrium 0 with bifurcation parameter φ evaluated at 0. Zero is a simple eigenvalue of matrix M and all the other eigenvalues of M have negative real parts;*

2. *Matrix M has a non-negative right eigenvector w and a left eigenvector v that corresponds to the zero eigenvalue. Let g_k be the k^{th} component of g and*

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 g_k}{\partial x_i \partial x_j}(0,0), \quad b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 g_k}{\partial x_i \partial \varphi}(0,0). \tag{3.4.20}$$

The local dynamics of system (3.4.19) *around 0 is totally determined by the signs of a and b [15].*

(i) *If $a > 0, b > 0$. When $\varphi < 0$ such that $|\varphi| \leq 1$, 0 is locally asymptotically stable and a positive unstable equilibrium exists. when $0 < \varphi \leq 1$, 0 is unstable and negative and locally asymptotically stable equilibrium exists.*

(ii) *If $a < 0, b < 0$. When $\varphi < 0$ such that $|\varphi| \leq 1$, 0 is unstable; similarly, when $0 < \varphi \leq 1$, 0 is locally asymptotically stable and a positive unstable equilibrium exists;*

(iii) *If $a > 0$, $b < 0$. When $\varphi < 0$ such that $|\varphi| \leq 1$, 0 is unstable and a locally asymptotically stable negative equilibrium exists; similarly, when $0 < \varphi \leq 1$, 0 is stable and a positive unstable equilibrium exists.*

(iv) *If $a < 0$, $b > 0$. When the sign of φ changes from negative to positive, the stability of 0 changes from stable to unstable. Accordingly, a negative unstable equilibrium changes to a positive and locally asymptotically stable equilibrium.*

In order to apply the center manifold theory, it is necessary to make the following changes to the state variables.

Let $S = x_1, U_a = x_2, R_a = x_3, U_t = R_t = U_{at} = R_{at} = 0$, so that the total population N_a, becomes $N_a^* = x_1 + x_2 + x_3$.

The model system (3.4.1) can now be written in the form $\frac{dx}{dt} = f(x)$ where $x = (x_1, x_2, x_3)$. System (3.4.1) thus becomes

$$\left.\begin{aligned} \frac{dx_1}{dt} &= \Lambda - \left(\mu + \frac{\beta_1(x_2 + \zeta_1 x_3)}{x_1 + x_2 + x_3}\right) x_1, \\ \frac{dx_2}{dt} &= \frac{\beta_1(x_2 + \zeta_1 x_3)}{x_1 + x_2 + x_3} x_1 + \gamma_1 x_3 - b_1 x_2, \\ \frac{dx_3}{dt} &= \sigma_1 x_2 - b_2 x_3. \end{aligned}\right\} \tag{3.4.21}$$

We let $\mathcal{R}_{a0} = 1$ and choose $\varphi = \beta_1$ as the bifurcation parameter.

$$\varphi = \frac{b_1(1 - \phi_1)}{1 + \frac{\zeta_1 \sigma_1}{b_2}}.$$

The Jacobian matrix of system (3.4.21) at the alcohol free equilibrium, $\mathcal{E}_0^a$, when $\varphi = \beta_1$ is given by

$$J(\varphi) = \begin{pmatrix} -\mu & -\varphi & -\varphi\zeta_1 \\ 0 & \varphi - b_1 & \gamma_1 + \varphi\zeta_1 \\ 0 & \sigma_1 & -b_2 \end{pmatrix}. \tag{3.4.22}$$

Since the second and the third rows of the Jacobian matrix in (3.4.22), can be expressed as a scalar multiple of the other, the Jacobian matrix can be row-reduced into an echelon form (upper triangular matrix) with one of the eigenvalues being zero.

The transformed system (3.4.21) with the bifurcation point φ has a simple zero eigenvalue. This allows us to apply the center manifold theory to analyse the stability of the model system (3.4.1) near $\beta_1 = \varphi$.

The right eigenvector of the Jacobian of the model system (3.4.1), at $\beta = \varphi$ associated with the zero eigenvalue is $w = [w_1, w_2, w_3]$ where

$$w_1 = -(\frac{\beta_1 b_2 + \beta_1 \zeta_1 \sigma_1}{\mu \sigma_1}) w_3 < 0,$$
$$w_2 = \frac{b_2}{\sigma_1} w_3 > 0, \quad \text{and} \quad w_3 = w_3 > 0.$$

Similarly, the expression for the corresponding left eigenvector $v = [v_1, v_2, v_3]^T$, is given as follows.

$$v_1 = 0, v_2 = \frac{\sigma_1}{b_1 - \beta_1} v_3 \quad \text{and} \quad v_3 = v_3 > 0.$$

We now compute a and b as outlined in Theorem 3.4.4. From system (3.4.21), the non-zero partial derivatives of $f(x)$ associated with a are

$$\frac{\partial^2 f_2}{\partial x_2^2} = \frac{-2\mu\beta_1}{\Lambda}, \quad \frac{\partial^2 f_2}{\partial x_2 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = -\frac{\mu\beta_1(1+\zeta_1)}{\Lambda}. \tag{3.4.23}$$

The expression for a in equations (3.4.20) becomes

$$a = \frac{-2\mu\beta_1}{\Lambda(b_1 - \beta_1)} \left\{ b_2^2 v_3 w_3^2 + (1+\zeta_1) b_2 v_3 w_3 \right\} < 0 \quad \text{since} \quad b_1 - \beta_1 > 0, R_{a0} > 1. \tag{3.4.24}$$

For the sign of b, it can be shown that the associated non-zero partial derivatives of f are

$$\frac{\partial^2 f_1}{\partial x_2 \partial \varphi} = -1, \quad \frac{\partial^2 f_1}{\partial x_3 \partial \varphi} = -\zeta_1, \quad \frac{\partial^2 f_2}{\partial x_3 \partial \varphi} = \zeta_1, \quad \text{and} \quad \frac{\partial^2 f_2}{\partial x_2 \partial \varphi} = 1. \tag{3.4.25}$$

It follows from equation (3.4.26) that

$$b = \frac{1}{b_1 - \beta_1}(b_2 v_3 w_3 + \zeta_1 \sigma_1 w_3) > 0. \tag{3.4.26}$$

Thus, $a < 0$ and $b > 0$. We therefore conclude from Theorem 3.4.4 , item (iv) that the established alcohol endemic equilibrium E_1^a is locally asymptotically stable for $R_{a0} > 1$ but close to 1. □

3.4.9 Global stability of the alcohol-endemic equilibrium point, $\mathcal{E}_1^a$

In order to show that the unique endemic steady state $\mathcal{E}_1^a$, is globally asymptotically stable, we shall assume among other stated assumptions that

$$\Lambda = \mu N_a + (\delta_1 + \rho_3) U_a + \rho_4 R_a. \tag{3.4.27}$$

The above assumption, ensures that the total population N_a remains a constant. The differential equations in system (3.4.1), thus becomes

$$\left.\begin{aligned}\frac{dS}{dt} &= (\mu+\delta_1+\rho_3)U_a + (\mu+\rho_4)R_a - \lambda_1 S,\\ \frac{dU_a}{dt} &= \lambda_1 S + \gamma_1 R_a - (\mu+\delta_1+\rho_3+\sigma_1)U_a,\\ \frac{dR_a}{dt} &= \sigma_1 U_a - (\mu+\gamma_1+\rho_4)R.\end{aligned}\right\} \tag{3.4.28}$$

Since $N_a = S + U_a + R_a$, is a constant, we introduce the fractions of S, U_a and R_a:

$$s = \frac{S}{N_a}, v = \frac{U_a}{N_a} \quad \text{and} \quad w = \frac{R_a}{N_a}.$$

Our new system therefore becomes:

$$\left.\begin{aligned}\dot{s} &= (\mu+\delta_1+\rho_3)v + (\mu+\rho_4)w - \beta_1(v+\zeta_1 w)s,\\ \dot{v} &= \beta_1(v+\zeta_1 w)s + \gamma_1 w - (\mu+\delta_1+\rho_3+\sigma_1)v,\\ \dot{w} &= \sigma_1 v - (\gamma_1+\rho_4+\mu)w.\end{aligned}\right\} \tag{3.4.29}$$

Remark 3.4.5. *System* (3.4.29) *has a unique endemic equilibrium following the analysis of the original model. Thus leads to Theorem 3.4.6.*

Theorem 3.4.6. *The alcohol-endemic equilibrium $\mathcal{E}_1^a$ is globally asymptotically stable whenever $\mathcal{R}_{a0}$ is greater than unity.*

Proof. We propose a suitable Lyapunov function $\mathcal{V}$ such that

$$\mathcal{V} = \left(s - s^* - s^* \ln\frac{s}{s^*}\right) + A\left(v - v^* - v^* \ln\frac{v}{v^*}\right) + B\left(w - w^* - w^* \ln\frac{w}{w^*}\right). \tag{3.4.30}$$

The positive constants A and B are to be determined. We observe that from the proposed Lyapunov function in equation (3.4.30), the first partial derivatives with respect to any of the state variables is given by

$$\frac{\partial \mathcal{V}}{\partial s} = \left(1 - \frac{s^*}{s}\right), \quad \frac{\partial \mathcal{V}}{\partial v} = A\left(1 - \frac{v^*}{v}\right), \quad \frac{\partial \mathcal{V}}{\partial w} = B\left(1 - \frac{w^*}{w}\right), \tag{3.4.31}$$

are all zero at the corresponding alcohol-endemic steady state. That is, at the endemic steady states, $s = s^*$, $v = v^*$ and $w = w^*$.

In addition, the second partial derivatives of $\mathcal{V}$ with respect to any of the three state variables are given as follows;

$$\frac{\partial^2 \mathcal{V}}{\partial s^2} = \frac{s^*}{s^2}, \quad \frac{\partial^2 \mathcal{V}}{\partial v^2} = A\frac{v^*}{v^2} \quad \text{and} \quad \frac{\partial^2 \mathcal{V}}{\partial w^2} = B\frac{w^*}{w^2}. \tag{3.4.32}$$

We observe from equation (3.4.32) that all the second partial derivatives are positive. This indicates that the alcohol endemic equilibrium is the minimum of each of the state variables.

The time derivative of the Lyapunov function in (3.4.30) is given by

$$\dot{\mathcal{V}} = \left(1 - \frac{s^*}{s}\right)\dot{s} + A\left(1 - \frac{v^*}{v}\right)\dot{v} + B\left(1 - \frac{w^*}{w}\right)\dot{w}. \tag{3.4.33}$$

Substituting for $\dot{s}$, $\dot{v}$ and $\dot{w}$ from system (3.4.29), we have

$$\begin{aligned}\dot{\mathcal{V}} = \left(1 - \frac{s^*}{s}\right)[av + (\mu+\rho_4)w - \beta_1(v+\zeta_1 w)s] + A\left(1 - \frac{v^*}{v}\right)[\beta_1(v+\zeta_1 w)s \\ + \gamma_1 w - b_1 v] + B\left(1 - \frac{w^*}{w}[\sigma_1 v - b_2 w]\right),\end{aligned} \tag{3.4.34}$$

where $a = \mu + \delta_1 + \rho_3$, $\quad b_1 = \mu + \gamma_1 + \rho_4$ and $b_2 = \mu + \delta_1 + \rho_3 + \sigma_1$.

We now use the system of equation (3.4.29) at $\mathcal{E}_1^a$ to obtain:

$$a = \frac{\beta_1(v^* + \zeta_1 w^*)s^* - (\mu+\rho_4)w^*}{v^*}, \quad b_1 = \frac{\beta_1(v^* + \zeta_1 w^*)s^* + \gamma_1 w^*}{v^*} \quad \text{and} \quad b_2 = \frac{\sigma_1 v^*}{w^*}. \tag{3.4.35}$$

Substituting the terms in (3.4.35) into (3.4.33) we obtain

$$\begin{aligned}\dot{\mathcal{V}} = \left(1 - \frac{s^*}{s}\right)\left[\beta_1 v^* s^*\left(\frac{v}{v^*} - \frac{vs}{v^* s^*}\right) + \beta_1\zeta_1 w^* s^*\left(\frac{v}{v^*} - \frac{ws}{w^* s^*}\right) + (\mu+\rho_4)w^*\left(\frac{v}{v^*} + \frac{w}{w^*}\right)\right] \\ + A\left(1 - \frac{v^*}{v}\right)\left[\beta_1 v^* s^*\left(-\frac{v}{v^*} - \frac{vs}{v^* s^*}\right) + \beta_1\zeta_1 w^* s^*\left(-\frac{v}{v^*} + \frac{ws}{w^* s^*}\right) + \gamma_1 w^*\left(\frac{v}{v^*} + \frac{w}{w^*}\right)\right] \\ + B\left(1 - \frac{w^*}{w}\right)\left[\sigma_1 v^*\left(\frac{v}{v^*} - \frac{w}{w^*}\right)\right].\end{aligned} \tag{3.4.36}$$

Let $\frac{s}{s^*} = x$, $\quad \frac{v}{v^*} = y$, $\quad$ and $\quad \frac{w}{w^*} = t$.

Therefore, $\dot{\mathcal{V}}$ becomes

$$\begin{aligned}\dot{\mathcal{V}} = \beta_1 v^* s^*\left[\left(2y - xy - \frac{y}{x}\right) + A(1 + xy - (y+x))\right] \\ + (\mu+\rho_4)\left[(t+y) - \left(\frac{t}{x} + \frac{y}{x}\right)\right]w^* \\ + \beta_1\zeta_1 w^* s^*\left[(y+t) - \left(xt + \frac{y}{x}\right) + A(1+xt) - \left(y + \frac{xt}{y}\right)\right] \\ + A\gamma_1 w^*\left[(t+y) - \left(1 + \frac{t}{y}\right)\right] + B\sigma_1 v^*\left[(1+y) - \left(t + \frac{y}{t}\right)\right].\end{aligned} \tag{3.4.37}$$

Setting the coefficients of y, xy, xt, $\frac{y}{x}$ to zero, we obtain

$$A = 1 \quad \text{and} \quad B = \frac{\beta_1\zeta_1 w^* s^* + (\mu+\rho_4)w^*}{\sigma_1 v^*} > 0. \tag{3.4.38}$$

Upon substituting the expressions in equation (3.4.38) back into (3.4.33), we obtain

$$\dot{\mathcal{V}} = \left(1 - \frac{s^*}{s}\right)\dot{s} + \left(1 - \frac{v^*}{v}\right)\dot{v} + \left(1 - \frac{w^*}{w}\right)\left(\frac{\beta_1\zeta_1 w^* s^* + (\mu+\rho_4)w^*}{\sigma_1 v^*}\right)\dot{w}. \tag{3.4.39}$$

Further, we substitute the values of A and B in equations (3.4.38) into (3.4.39) so that

$$\dot{\mathcal{V}} = \beta_1 v^* s^* \left[(y-x)\left(1-\frac{1}{x}\right)\right] + \beta_1 \zeta_1 w^* s^* \left[2+y-\left(\frac{y}{x}+\frac{y}{t}+\frac{xt}{y}\right)\right] + (\mu+\rho_4) w^* \left[1+2y-\left(\frac{t}{x}+\frac{y}{x}+\frac{y}{t}\right)\right] + \gamma_1 w^* \left(t-\frac{t}{y}+y-1\right). \tag{3.4.40}$$

From equation (3.4.40), we observe that the expression $(y-x)\left(1-\frac{1}{x}\right)$ is less than or equal to zero with equality holding if and only if $x = 1$ or $y = x$.

Also, the expression $(t-y)\left(1-\frac{1}{y}\right) \leq 0$ with the equality holding if and only if $y = 1$ or $t = y$.

We can draw similar conclusions from the remaining expressions $\left(2+y-\left(\frac{y}{x}+\frac{y}{t}+\frac{xt}{y}\right)\right)$ and $\left(1+2y-\left(\frac{t}{x}+\frac{y}{x}+\frac{y}{t}\right)\right)$. In the two cases, equality holds if and only if $y = x = t$.

Therefore, $\dot{\mathcal{V}} \leq 0$ with equality holding if and only if $y = x = t$. Since $\dot{\mathcal{V}} = 0$ only when $y = x = t$, which corresponds to $s = s^*$, $v = v^*$, and $w = w^*$ and Subsequently, to $S = S^*$, $U_a = U_a^*$ and $R_a = R_a^*$, the largest invariant set in $\{(S, U_a, R_a) \in \Omega : \dot{\mathcal{V}} = 0$ is the singleton $\{\mathcal{E}_1^a\}$. By LaSalle's invariance principle [73], we therefore conclude that the endemic equilibrium $\mathcal{E}_1^a$ is globally asymptotically stable in the interior of Ω. This shows that every solution in Ω or that intersects Ω, would approach the endemic equilibrium $\mathcal{E}_1^a$. □

3.5 Methamphetamine abuse model

Just like alcohol, we formulate a dynamic model due to methamphetamine abuse only. In the absence of alcohol, population in the compartments classes $U_a = R_a = U_{at} = R_{at} = 0$. The co-abuse model (3.1.4) therefore reduces to the following model due to methamphetamine abuse.

$$\left.\begin{aligned} \frac{dS}{dt} &= \Lambda - (\mu + \bar{\lambda}_2) S, \\ \frac{dU_t}{dt} &= \bar{\lambda}_2 S + \gamma_3 R_t - (\mu + \sigma_3 + \delta_3 + \rho_7) U_t, \\ \frac{dR_t}{dt} &= \sigma_3 U_t - (\mu + \gamma_3 + \rho_6) R_t, \end{aligned}\right\} \tag{3.5.1}$$

where

$$\bar{\lambda}_2 = \frac{\beta_2 (U_t + \epsilon_1 R_t)}{N}.$$

3.5.1 Equilibrium point(s) of methamphetamine abuse model

Setting the right hand side of equations in model system (3.5.1) to zero, and solving for S, U_t and R_t, we obtain the polynomial

$$\bar{\lambda}_2^{**}\left\{(1-R_t^{**})+\bar{\lambda}_2^{**}\left(\frac{\bar{\lambda}_2^{**}(\sigma_3+b_4)}{b_1b_2[1-\Phi_2]}\right)\right\}=0. \tag{3.5.2}$$

From equation (3.5.2), $\bar{\lambda}_2^{**}=0$ corresponds to the methamphetamine-free equilibrium, denoted by $\mathcal{E}_0^t$ and this is a scenario in which the community is free of methamphetamine abuse.

$$\mathcal{E}_0^t=(S^{**},U_t^{**},R_t^{**})=\left(\frac{\Lambda}{\mu},0,0\right).$$

3.5.2 Reproduction number due to methamphetamine abuse ($\mathcal{R}_{t0}$)

$\mathcal{R}_{t0}$ is similarly obtained by the method of next generation matrix as illustrated in [86]. Adopting the notations in [86], we obtain the matrices for new infections terms (F) and the transfer terms (V) at the methamphetamine-free equilibrium as follows.

$$\mathrm{F}=\begin{pmatrix}\beta_2 & \beta_2\epsilon_1\\ 0 & 0\end{pmatrix},\quad\text{and}\quad \mathrm{V}=\begin{pmatrix}(\mu+\delta_3+\rho_7+\sigma_3) & -\gamma_3\\ -\sigma_3 & (\mu+\gamma_3+\rho_6)\end{pmatrix}. \tag{3.5.3}$$

Thus, the methamphetamine epidemic reproduction number is given by

$$\mathcal{R}_{t0}=\frac{\beta_2[b_4+\epsilon_1\sigma_3]}{b_3b_4[1-\Phi_2]}, \tag{3.5.4}$$

where $b_3=\mu+\delta_3+\rho_7+\sigma_3$, $b_4=\mu+\gamma_3+\rho_6$ and $\Phi_2=\frac{\gamma_3\sigma_3}{b_3b_4}$.

3.5.3 Endemic equilibrium of the methamphetamine model

From polynomial equation given in (3.5.2), $\bar{\lambda}_2^{**}=\left\{(R_{t0}-1)\left(\frac{b_3b_4(1-\phi_2)}{\sigma_3+b_4}\right)\right\}$ which exists for $\mathcal{R}_{t0}>1$, and corresponds to the methamphetamine-endemic equilibrium, denoted by $\mathcal{E}_1^t$. Such that $\mathcal{E}_1^t=(S^{**},U_t^{**},R_t^{**})$ where,

$$S^{**}=\frac{\Lambda}{\mu+\bar{\lambda}_2^{**}},\quad U_t^{**}=\frac{\Lambda\bar{\lambda}_2^{**}b_4}{(\mu+\bar{\lambda}_2^{**})(b_3b_4-\gamma_3\sigma_3)},\quad R_t^{**}=\frac{\Lambda\bar{\lambda}_2^{**}\sigma_3}{(\mu+\bar{\lambda}_2^{**})(b_3b_4-\gamma_3\sigma_3)}. \tag{3.5.5}$$

3.5.4 Stability analysis of the methamphetamine abuse model

We observe that structures of the two sub-models (alcohol and methamphetamine models) are quite similar. The mathematical analysis of the two models would equally be similar. Having done the analysis for the alcohol model, we can safely state the stability theorems with regards to the methamphetamine abuse epidemic.

Theorem 3.5.1. *The unique methamphetamine-free equilibrium point, $\mathcal{E}_0^t$ is locally asymptotically stable for $\mathcal{R}_{t0} < 1$ and unstable for $\mathcal{R}_{t0} > 1$.*

Theorem 3.5.2. *The unique endemic equilibrium, $\mathcal{E}_1^t$ is locally asymptotically stable for $\mathcal{R}_{t0} > 1$ but close to 1.*

3.6 Numerical simulation

In this section, we carry-out parameters estimation, sensitivity of the model parameters and numerical simulation of the co-abuse model system (3.1.4). We solve numerically model system (3.1.4) based on the chosen parameter space. The simulations are carried out using Matlab programming language and the set of parameter values are given in Table 3.2. Lack of data on co-abuse of alcohol and methamphetamine in Western Cape Province is however detrimental in our quest to make precise calibrations. Nevertheless, for purposes of illustration, we shall assume some of the parameters in some realistic range with guidance from past literature on alcohol and methamphetamine abuse epidemics.

3.6.1 Sensitivity analysis

We perform sensitivity analysis to establish parameters that have significant influences on the reproduction numbers R_a, R_t and R_{at}; and hence on the co-abuse epidemic. In this work, of the numerous sensitivity methodologies, we choose the Latin Hypercube Sampling (LHS) methodology. We perform the sensitivity analysis by computing the Partial Rank Correlation Coefficients (PRCC) for each parameter value; sampled by the LHS scheme, and the outcome values of the reproduction number R_{at} derived from uncertainty analysis [10]. Using 1000 simulations per run we examine the sensitivity of the methamphetamine reproduction number $\mathcal{R}_{t0}$, the alcohol reproduction number $\mathcal{R}_{a0}$ and the reproduction number due to co-abuse of alcohol and methamphetamine $\mathcal{R}_{at0}$ to variation in parameters.

According to Mckay in [47], sensitivity analysis is the study of how the uncertainty in the output of a model can be allocated to different sources of uncertainty in the model output. It is a technique for systematically changing parameters in a model to determine the effects of such changes. Results of sensitivity analysis facilitates model development, verification and validation. The technique helps to build confidence in the model by studying the uncertainty associated with parameters in the model. Our preference for LHS is based on the following discussions on LHS.

3.6.2 Latin Hypercube Sampling (LHS)

Latin Hypercube Sampling is a stratified Monte Carlo sampling technique which was first proposed by McKay *et al*. [47]. LHS is a powerful technique for achieving equitable sampling of all predictors simultaneously. Introduced to the field of disease modelling by Blower in 1994, LHS is currently the most efficient and refined statistical techniques [10].

LHS allows for an efficient analysis of parameter variations across simultaneous uncertainty ranges in each parameter. For each parameter, a probability density function is defined and stratified into N equiproportional serial intervals. A single value is then selected randomly from every interval and this is done for every parameter. In this way, an input value from each sampling interval is used only once in the analysis but the entire parameter space is equitably sampled in an efficient manner [10].

3.6.3 Results of our analysis

The PRCCs illustrates the degree of the effect that each parameter has on the outcome variable (reproduction number). Parameters with positive PRCCs will increase the defined reproduction number when they are increased; that is, the number of new 'infections' increases. On the other side, parameters with negative PRCCs values will decrease the reproduction number, when they are increased (necessary mechanisms to eliminate the epidemic). The PRCC results are presented as follows.

Figure 3.3, reveals that the transmission rate due to methamphetamine abuse, β_2 together with the relapse rate γ_3 have the highest positive influences on the sub-model reproduction numbers $\mathcal{R}_{t0}$; that is, an increase (or a decrease) in the magnitude of these parameters will result in an increase (or decrease) in methamphetamine abuse in the community. On the other hand, the treatment parameter, σ_3 is shown to have the greatest potential to considerably minimize the epidemic. An increase in σ_3 results into a corresponding decreases in $\mathcal{R}_{t0}$ and hence decreased population of methamphetamine abusers. Effective treatment measures should therefore be enhanced in order to manage the epidemic due to methamphetamine abuse.

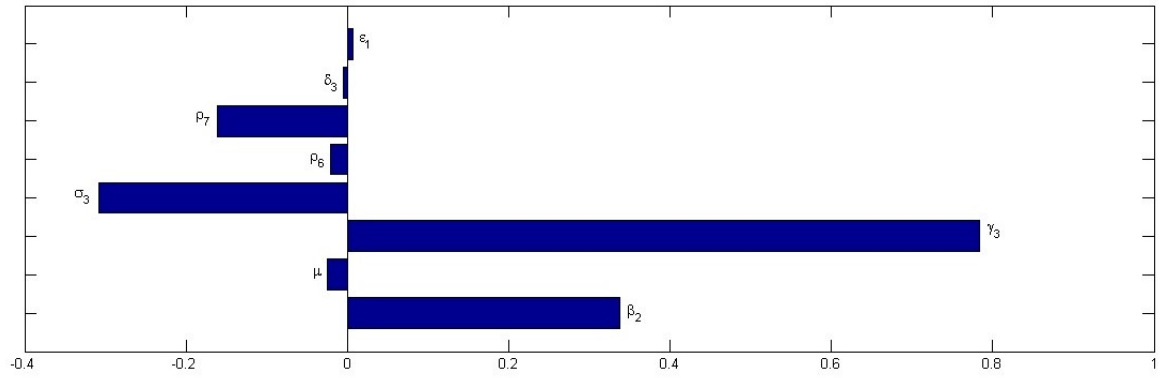


Figure 3.3: PRCC values showing the effects of parameter variations on $\mathcal{R}_{t0}$.

It is clear from Figure 3.4 that transmission parameter β_1 and relapse constant γ_1 have the highest positive influence on the magnitude of the reproduction number $\mathcal{R}_{t0}$; that is, an increase (or decrease) in the magnitude of these parameters will result in an increase (or decrease) in the magnitude of $\mathcal{R}_{t0}$. On the contrary, the parameters; σ_1, ρ_3 and ρ_4 are shown to negatively affect the alcohol reproduction number. It is similarly clear that other than other useful strategies aimed at eliminating alcohol abuse, a lot more effort should focus on new users. The transmission rate from abusers to the susceptibles, should be minimised the most. Secondly, educational campaigns would be very helpful in reducing recruitment into alcohol abuse.

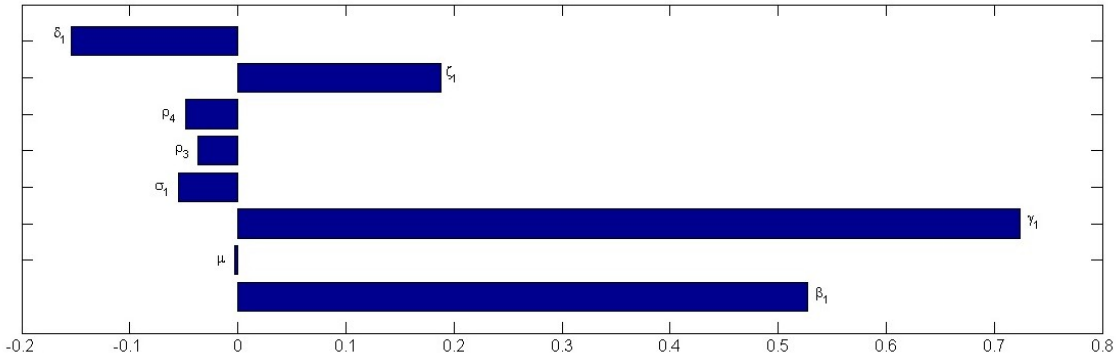


Figure 3.4: PRCCs showing the effects of parameter variations on $\mathcal{R}_{a0}$.

3.6.4 PRCCs for the parameters in the alcohol-methamphetamine co-abuse model

Figure 3.3 shows that the transmission rates, β_1 and β_2 exhibit the highest positive influences on the co-abuse model reproduction numbers, $\mathcal{R}_{t0}$ and $\mathcal{R}_{t0}$; that is, an increase (or a decrease) in the magnitude of these parameters will result in an increase (or decrease) in the prevalence of co-abuse of alcohol and methamphetamine

in Western Cape province. On the other hand, the quitting parameters ρ_3 and ρ_6 are shown to have the greatest potential to reduce the epidemic when they are maximised. This calls for the need to enhance quitting processes through improved treatment programmes, constant educational campaigns on the dangers of multiple substance abuse and strict implementation and adherence to the laws regarding substance abuse. Campaigns targeting the susceptibles ensures that abusers of the individual psychoactive substances or both do not have the opportunity to recruit them into the dangerous epidemic of multiple substance abuse.

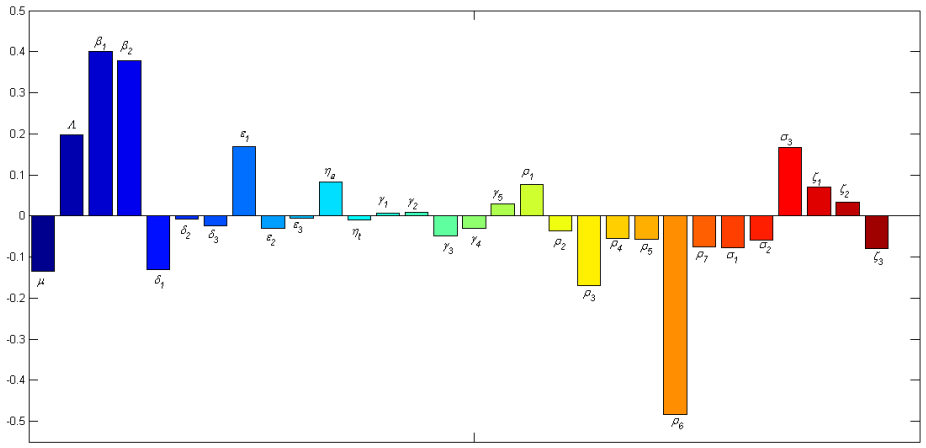
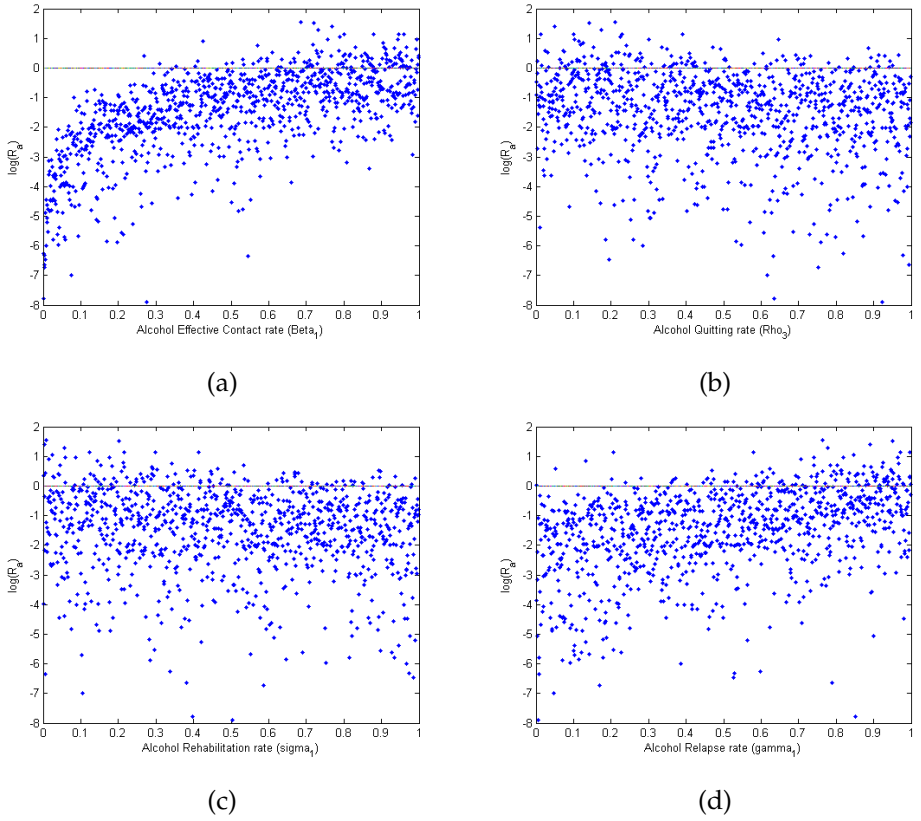


Figure 3.5: PRCCs showing the effects of parameter variations on the population of co-abusers of alcohol and methamphetamine U_{at}.

We conclude from the sensitivity analysis that more attention should be paid to reducing contact between susceptibles and the alcohol and/or methamphetamine users in order to control co-abuse epidemic. Secondly, improved rehabilitation programmes is key to enhancing the dificult process of quitting substance abuse.

In order to verify the satisfaction of the assumption of monotonicity, we further produced PRCC scatter plots of the sampled parameters with the greatest influence on the reproduction numbers $\mathcal{R}_{a0}$ or $\mathcal{R}_{t0}$. See Figure 3.6 and Figure 3.7. Observe that each dot (point) represents the output values of either $\mathcal{R}_{a0}$ or $\mathcal{R}_{t0}$ for a specific sampled value of the input parameter.



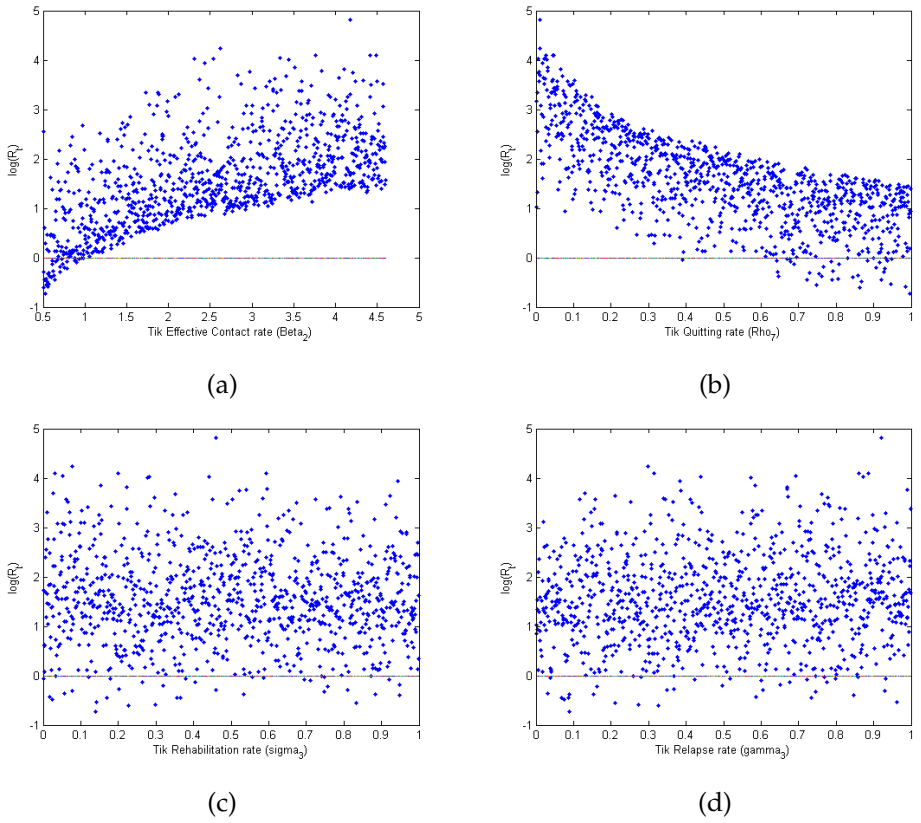
(a) (b)

(c) (d)

Figure 3.6: Graphs (a), (b), (c) and (d) show the Monte Carlo simulations for the four paremeters with the greatest PRCC magnitude in the alcohol model. Parameter values in Table (3.2) and 1,000 simulations per run were used.

The PRCC scatter plots clearly show that the alcohol reproduction number $\mathcal{R}_{a0}$ is mainly influenced by the transmission parameter β_1 and the relapse rate γ_1. Control measures should similarly focus on these two parameters.

Similarly, from Figure 3.7, it is clear that the parameters with greater influence on methamphetamine abuse epidemic (or on $\mathcal{R}_{t0}$) are the recruitment and relapse rates denoted by β_2 and γ_3 respectively. With increased cases of relapse, the population of co-abusers of alcohol and methamphetamine U_{at} increases. Increased cases of relapse ensures that the epidemic remains endemic within a community. Improved rehabilitation strategies are helpful in limiting relapse cases.



(a) (b)

(c) (d)

Figure 3.7: Graphs (a), (b), (c) and (d) show the Monte Carlo simulations for the four parameters with the greatest PRCC magnitude in the methamphetamine (Tik) model. Parameter values in Table (3.2) and 1,000 simulations per run were used.

Summary

The parameters with the greatest potential to make the co-abuse epidemic worse when they it are increased are the alcohol and methamphetamine transmission parameters β_1 and β_2 respectively. Control efforts for alcohol-methamphetamine co-abuse should thus focus on reducing new cases. Secondly, the quitting process should be enhanced especially for those alcohol users who are not yet addicted. As shown from the PRCC figures, relapse into substance abuse, just like transmission rate is a major contributor to the growth of the co-abuse epidemic. Control mechanisms should therefore equally emphasise the need to reduce rampant cases of relapse upon or during treatment services.

3.6.5 Parameter estimation

In this subsection, we estimate the co-abuse model parameters to be used in the simulations. While most parameters are obtained from the fitting of the sub-models to alcohol and methamphetamine data collected by SACENDU in the Western Province

of South Africa [66], some parameters were simply estimated based on available literature, see [9, 55, 84]].

Some of the demographic parameters used for our model simulation are derived as follows: The 2014 demographic data released by Statistics South Africa, estimates the life expectancy at birth to be 59.1 years for the males and 63.1 years for the females [3]. Epidemiologically, this is equivalent to an average natural mortality rate of 0.02 per annum, assuming only users of alcohol and or methamphetamine are older than 10 years of age. We thus assume a natural mortality rate, $\mu = 0.02$ for the co-abuse model (3.1.4). Secondly, the average birth rate in South Africa has been estimated to be about 0.028 per annum [31] . Owing to unchecked immigration from neighbouring countries like Zimbabwe, we shall set our recruitment rate Λ to be greater than 0.028. Substance induced mortality rate is however quite difficult to estimate, and especially in the absence of such data. Some of the reasons for this challenge is the variation in time of involvement in high risk behaviours by individuals while under the influence of substances of abuse [12]. This variation also extends within and among a population. The mortality rate for example among injecting crank-cocaine users in [12] is 0.018 per year.

According to a report in [54], a smokers life expectancy is increased by about 14% if he/she quits smoking at about age 35. Since treatment impacts positively on the quality of our lives, we assume that it reduces mortality rate related to substance abuse by at least 50%. Thus, we choose $\zeta_1 = 0.756$, $\zeta_3 = 0.87$, $\epsilon_1 = 0.67$ and $\epsilon_3 = 0.77$ per year. The observed treatment demand for methamphetamine users was 17% in [55]. Here, we choose the average treatment demand of 30% as the corresponding treatment rate of 0.3. In [40], recovery rate due to alcohol abuse is given as 0.20 while the rate of relapse upon treatment from alcohol abuse is given as 0.21. We shall therefore consider alcohol recovery and relapse rates in the range (0.15-0.22).

Using the fourth order Runge-Kutta integration scheme, we solve model system (3.1.4) numerically. Owing to lack of data on co-abuse epidemic, transmission and progression rates for the co-abuse model are estimated based on available literature. We shall use methamphetamine only and alcohol only epidemic data for the Cape Town and Western Cape Province (WC) for the period 1997-2013. The alcohol and methamphetamine data are used to model the growth in the population of alcohol users under rehabilitation (R_a) and methamphetamine users under rehabilitation (R_t) respectively.

The setting of an appropriate initial conditions was one of our greatest challenge. However, for purposes of simulation and illustrating the usefulness of the co-abuse model, we assumed a fractional population whose total sum was one at the start of the epidemics. The alcohol and methamphetamine data shown in Table 3.3 and 3.4 respectively, is used to estimate co-abuse model parameter values. We employed the

least squares curve fit routine in Matlab with optimisation to estimate the parameter values. Unless otherwise stated, the parameter values used in the numerical simulations is given in Table 3.2.

Table 3.2: Parameter values used in model simulation and their sources

Symbol	Value	Source	Symbol	Value	Source
Λ	0.03	Estimated	σ_1	0.2 (0.15-0.22)	[40]
μ	0.02 (0.02-0.05)	[55],[12]	σ_2	0.3	Estimated
β_1	0.25(0-1)	[40]	σ_3	0.3 (0.09-0.3)	[55]
β_2	0.2 (0-1)	[55]	ρ_1	0.01	Estimated
γ_1	0.15 (0.15-0.22)	[40]	ρ_2	0.01	Estimated
γ_2	0.1	Estimated	ρ_3	0.35	Estimated
γ_3	0.3 (0-10)	Estimated	ρ_4	0.25	Estimated
γ_4	0.3	Estimated	ρ_5	0.25	Estimated
γ_5	0.3	Estimated	ρ_6	0.78	Estimated
δ_1	0.03	Estimated	ρ_7	0.4	Estimated
δ_2	0.04	Estimated	η_a	1.05	Estimated
δ_3	0.03 (0.02-0.033)	[12]	η_t	1.03	Estimated
ζ_1	0.756	Estimated	ζ_2	1.01	Estimated
ζ_3	0.87	Estimated	ϵ_1	0.67	Estimated
ϵ_2	1.105	Estimated	ϵ_3	0.77	Estimated

3.6.6 Numerical results

From Figure 3.8, we observe that when $R_{at0} < 1$, the populations of alcohol and methamphetamine abusers with and without treatment decline to zero. However, the susceptibles population approaches a constant, $\frac{\Lambda}{\mu}$. This shows that when $R_{at0} < 1$; that is $(R_{a0} < 1$ and $R_{t0} < 1)$, the alcohol-methamphetamine co-abuse epidemic dies out and only the susceptible population remains. The given system approaches the substance-free equilibrium (SFE) which is consistent with Theorem 3.3.1 in Chapter 3. On the other hand, Figure 3.9, shows that the populations of susceptibles, methamphetamine and alcohol abusers in treatment and those without treatment initially increase and later level off at different heights when $R_{at0} > 1$, which implies that the system stabilizes at endemic equilibria for $R_{at0} > 1$. The co-abuse epidemic would persists when $R_{at0} > 1$.

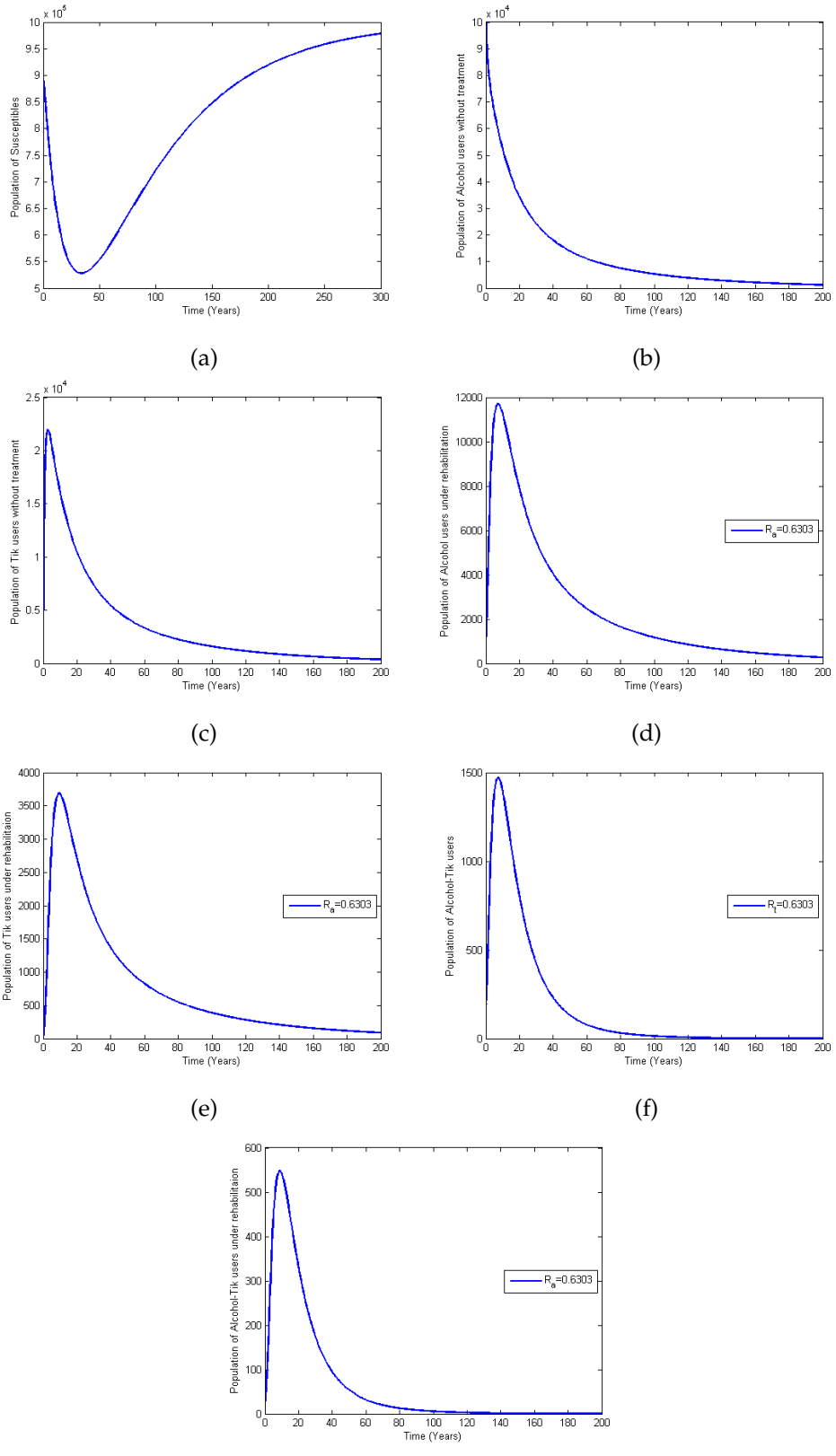


Figure 3.8: Graphs showing the population dynamics of methamphetamine users under treatment, alcohol-methamphetamine users and alcohol-methamphetamine users under treatment respectively. Parameter values: $R_{at} = 0.6303, \mu = 0.02, \Lambda = 20000, \beta_1 = 0.288, \beta_2 = 0.05, \delta_1 = 0.03, \delta_2 = 0.04, \delta_3 = 0.04, \epsilon_1 = 0.65, \epsilon_2 = 1.05, \epsilon_3 = 0.65, \eta_a = 1.05, \eta_t = 1.05, \gamma_1 = 0.45, \gamma_2 = 0.4; \gamma_3 = 0.525; \gamma_4 = 0.4, \gamma_5 = 0.42, \rho_1 = 0.1, \rho_2 = 0.03, \rho_3 = 0.35, \rho_4 = 0.45, \rho_5 = 0.35, \rho_6 = 0.38, \rho_7 = 0.24, \sigma_1 = 0.3, \sigma_2 = 0.3, \sigma_3 = 0.21, \zeta_1 = 0.65, \zeta_2 = 1.05, \zeta_3 = 0.65.$

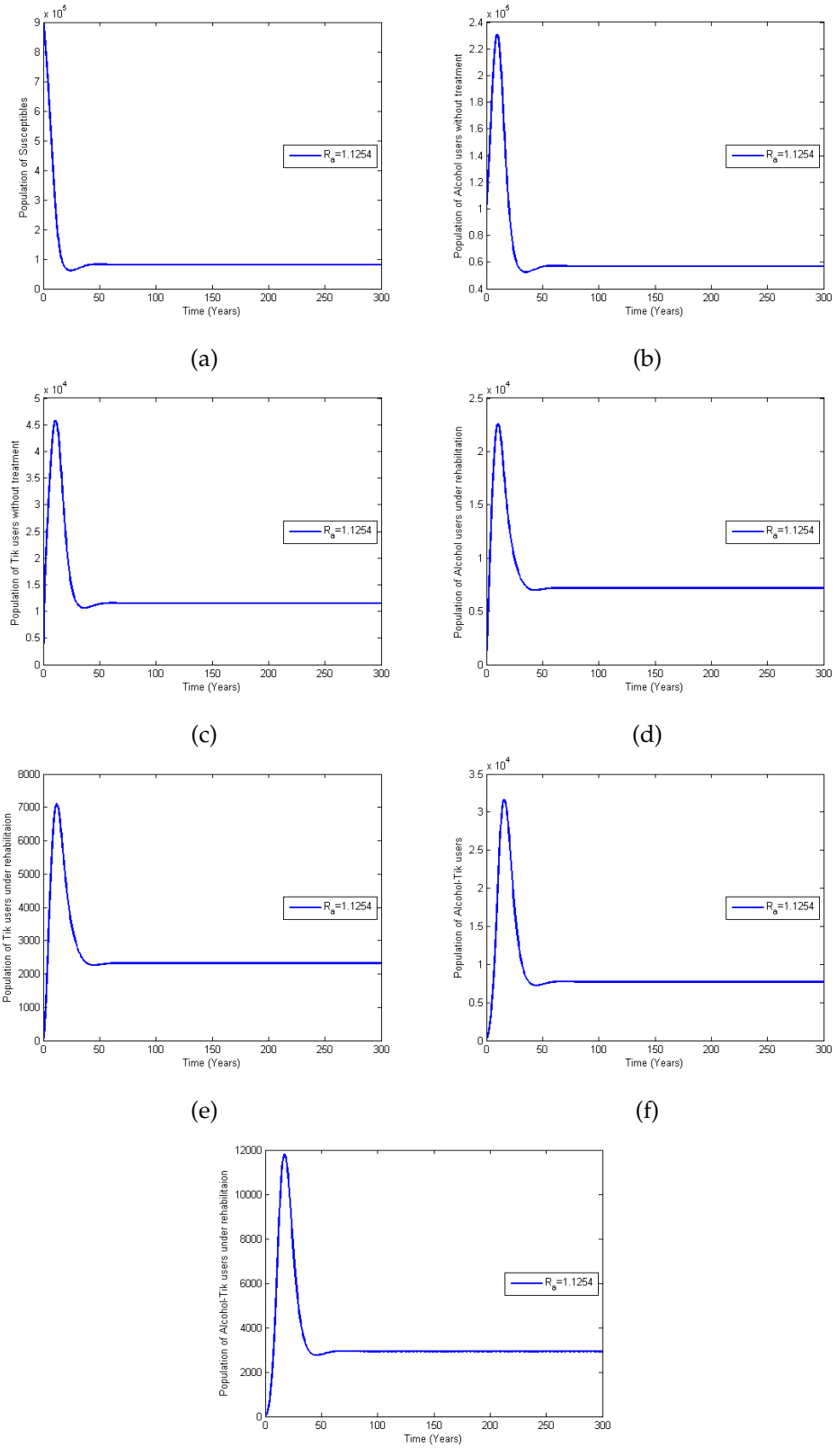


Figure 3.9: Graphs showing the population dynamics of susceptible, alcohol users, alcohol users under treatment, methamphetamine (Tik) users, methamphetamine users in treatment, alcohol-methamphetamine co-abusers and alcohol-methamphetamine co-abusers in treatment. Parameter values: $R_{at} = 1.1254, \mu = 0.02, \Lambda = 20000, \beta_1 = 0.45, \beta_2 = 0.15, \delta_1 = 0.0013, \delta_2 = 0.004, \delta_3 = 0.006, \epsilon_1 = 0.45, \epsilon_2 = 1.005, \epsilon_3 = 0.45, \eta_a = 1.05, \eta_t = 1.05, \gamma_1 = 0.5, \gamma_2 = 0.4; \gamma_3 = 0.526; \gamma_4 = 0.4, \gamma_5 = 0.42, \rho_1 = 0.3, \rho_2 = 0.3, \rho_3 = 0.3, \rho_4 = 0.3, \rho_5 = 0.21, \rho_6 = 0.01, \rho_7 = 0.34, \sigma_1 = 0.16, \sigma_2 = 0.3, \sigma_3 = 0.31, \zeta_1 = 0.45, \zeta_2 = 1.005, \zeta_3 = 0.45.$

3.6.7 Model fitting

Curve fitting is a process of curve construction or the building of a mathematical function that has the best fit to a series of data points. The process of curve fitting encompasses two techniques: 1) Smoothing, in which a smooth continuous function is constructed and 2) Interpolation, in which an exact fit to data is required. The results of the fitting process is useful in estimating the values of the model parameters and validation of the constructed model.

In this work, we are primarily interested in the construction of a smooth curve that best fit the provided data points. Some of the techniques of model fitting methods includes the Least Squares (LS) method, the Maximum Likelihood (ML) method and the method of Moments. The method of moments is useful in estimation of population parameters such as mean, median, variance, among others. The sample moments are equated to unobservable population moments from which, the resultant equations are solved to obtain the estimated parameter quantities.

It is however important to note that the method of moments is an insufficient technique that occasionally, fails to account for all the relevant information in the sample. Its also unreliable when big data samples are used. The method of maximum likelihood, chooses the values of the model parameters such that the likelihood function is maximised. Lastly, in the Least Squares method, unknown parameters are estimated by minimizing the sum of the squared deviations between the data and the model. It minimises the sum of squared distances between the observed values and the values provided by the model.

The LS method can be derived as the ML method estimator under the assumption that errors exists only in the response data and not in the predictor data. Secondly, the errors are random and follow a normal distribution with zero mean and a constant variance. Both the LSM and the MLM are residual square estimation. The residual of the i^{th} data point, r_i is defined as the difference between the observed response value y_i and the fitted response $\bar{y}_i$ and is identified as the error associated with the data.

$$r_i = y_i - \bar{y}_i \tag{3.6.1}$$

The sum of squares of the residuals is given by

$$S_n = \sum_{i=1}^{n} r_i^2 = \sum_{i=1}^{n} (y_i - \hat{y}_i)^2, \tag{3.6.2}$$

where n is the number of data points included in the fit and S_n is the sum of square error estimate. The least squares method can be derived as the maximum likelihood estimator under the assumption that the errors are normally distributed. The main disadvantage of least-squares fitting is its sensitivity to outliers. Outliers have a large

influence on the fit because squaring the residuals magnifies the effects of these extreme data points. To minimize the influence of outliers, you can fit your data using robust least-squares regression. In this work, we shall apply the superior technique of the least squares curve fitting method to fit our model to data on individuals under treatment for methamphetamine and alcohol abuse. Our choice is guided by advantages of the least squares fitting method vis a vis the short comings of the other curve fitting techniques.

3.6.8 Model fit to methamphetamine data

We fit the model system (3.5.1) to the data of individuals seeking treatment for methamphetamine as a primary substance of abuse at specialised treatment centres in Cape Town and Western Cape Province. The data was collected from 1997a to 2013a on a six month interval i.e. from January to June and from July to December by SACENDU and is given in Table 3.3. The letters a and b represents the first six months

Table 3.3: Primary methamphetamine (Tik) abuse from 1997a to 2013a in %. Source: [65].

Year	1997a	1997b	1998a	1998b	1999a	1999b	2000a	2000b	2001a
% Tik users	0.0	0.1	0.0	0.1	0.1	0.1	0.2	0.1	0.1
Year	2001b	2002a	2002b	2003a	2003b	2004a	2004b	2005a	2005b
% Tik users	0.3	0.3	0.8	2.3	2.3	10.7	19.3	26.1	34.7
Year	2006a	2006b	2007a	2007b	2008a	2008b	2009a	2009b	2010a
% Tik users	37.2	42.3	40.7	36.1	35.8	35.1	40.6	35.5	33.6
Year	2010b	2011a	2011b	2012a	2012b	2013a			
% Tik users	35.1	35.3	38.8	33.7	33.3	27.8			

(January-June) and the second six months (July-December) of the year respectively.

The estimation process attempts to find the best concordance between computed and observed data. A matlab code is used in which, the unknown parameter values are given a lower bound (LB) and an upper bound (UB) from which the set of parameter values that produce the best fit are obtained. The data on the demand for rehabilitation/treatment is used to model growth in the R_a class in our combined model. Figure 3.10 shows methamphetamine model (3.5.1) fitted to data for persons in treatment for methamphetamine abuse in Cape Town and Western Cape Province.

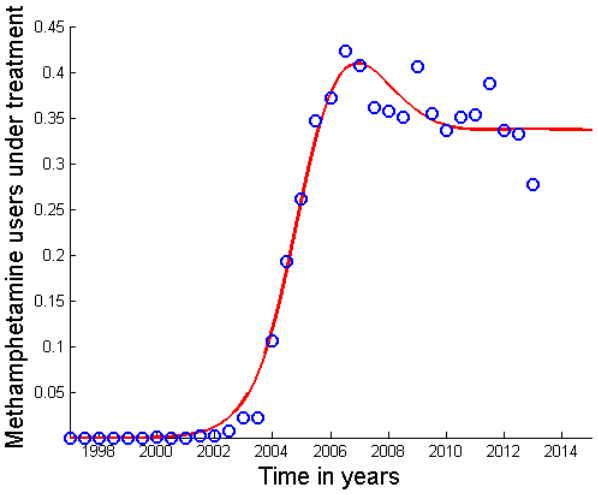


Figure 3.10: Model system (3.4.1) fitted to data for individuals seeking treatment for methamphetamine as a primary substance of abuse.

The black circles and the solid line in Figure 3.10 represent the actual data points and the model fit to the data. We observe that the model fits well with the data. Furthermore, we notice that according to the available data, there were no population of methamphetamine users before 1997. This does not however imply that there were no methamphetamine users before or during this period. It only shows that individuals on methamphetamine abuse may not have been progressing into treatment before 1997. Also, the number of drug users in treatment reached the peak between the second half of 2006 and the first half of 2009.

Our results are indicative of a short-term, fast growing methamphetamine epidemic in which there is a significant increase in the number of users between the year 2002 and 2005, followed by a significant slow down in the generation of new cases. The data shows an epidemic that is stabilizing at about 35% of the rehabilitants. The model also shows a steady state solution close to this value. The projected prevalence of methamphetamine abuse is shown in Figure 3.11. Using similar parameter values as shown in Table 3.2, we observe that there would be a constant prevalence rate for the next 5 years.

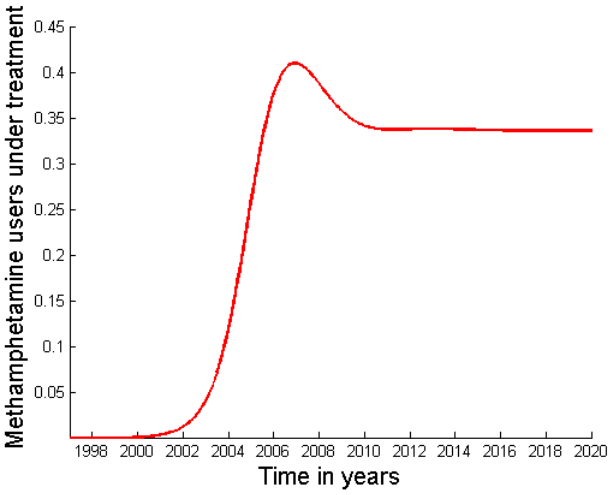


Figure 3.11: Projected population of methamphetamine users under treatment in Cape Town and Western Cape Province for the next 5 years.

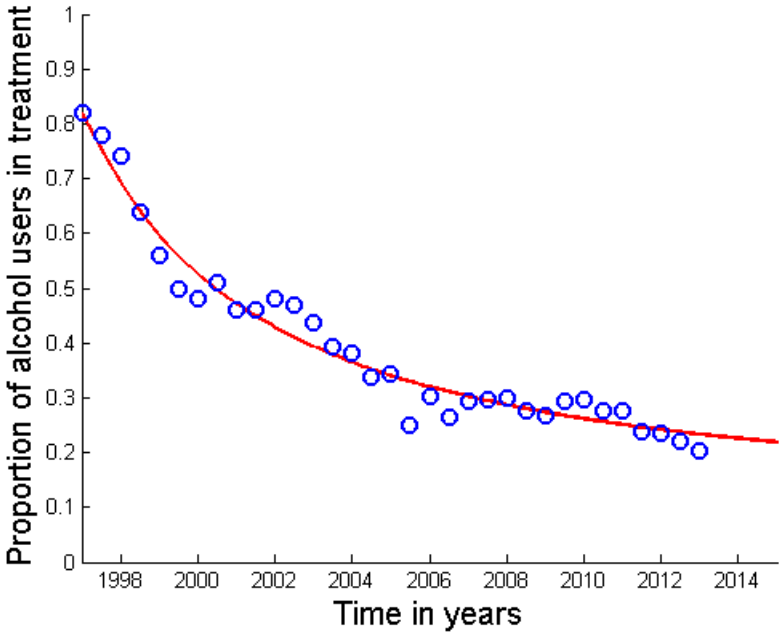
3.6.9 Model fit to alcohol data

The data showing the demand for treatment as a result of alcohol abuse is shown in Table 3.4. Just like methamphetamine, the alcohol data was similarly collected by SACENDU from 1997 to 2013 in time periods of six months.

Table 3.4: Primary alcohol abuse from 1997a to 2013a in %. Source [65].

Year	1997a	1997b	1998a	1998b	1999a	1999b	2000a	2000b	2001a
% Alcohol users	82.0	78.0	74.0	64.0	56.0	50.0	48.0	51.0	46.0
Year	2001b	2002a	2002b	2003a	2003b	2004a	2004b	2005a	2005b
% Alcohol users	46.0	48.0	47.0	43.6	39.4	38.3	33.7	34.4	25.1
Year	2006a	2006b	2007a	2007b	2008a	2008b	2009a	2009b	2010a
% Alcohol users	30.2	26.4	29.5	29.7	30.0	27.6	26.8	29.4	29.8
Year	2010b	2011a	2011b	2012a	2012b	2013a			
% Alcohol users	27.5	27.5	23.7	23.6	22.2	20.2			

Figure 3.12 reveals that the proportion of individuals seeking treatment for alcohol abuse has been on a steady decline. Although the data is presented in terms of proportions and not actual populations, the decline in the population seeking treatment for alcohol abuse could be attributed to the fact that some alcohol users may have found refuge in other substances of abuse such as bhang, cocaine, methamphetamine or uses it in combination with other psychoactive stimulants. Victims of drug/substance abuse, could as a result, be experiencing greater effects of other drugs as compared



H

Figure 3.12: Shows the model system (3.5.1) fitted to data for individuals seeking treatment for alcohol abuse as a primary substance of abuse in Cape Town and Western Cape Province.

to alcohol, hence increased prevalence of other drugs. The projected prevalence of alcohol abuse is shown to be on the decline, see Figure 3.13.

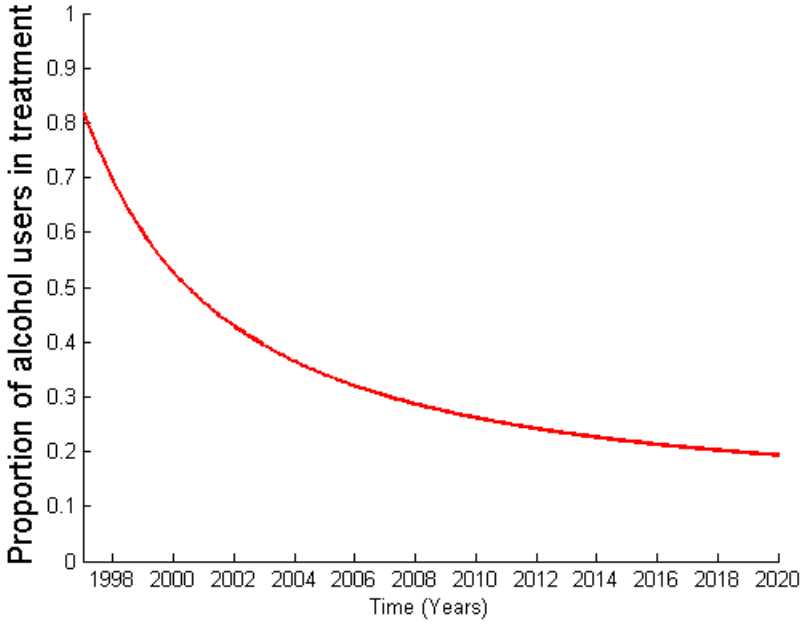


Figure 3.13: Shows the projected population of methamphetamine users under treatment in Cape Town and Western Cape Province for the next 5 years.

3.6.10 Estimated population of alcohol-methamphetamine co-abusers

Very little has been done to estimate the number of individuals who abuse multiple sub-stances in South Africa to the best of our knowledge. We argue that estimation can be done through the use of mathematical models. A sundry of research works on drug epidemic models have focussed on the abuse of a single substance, see for instance [9, 52, 55, 87]. The minimal research work on mathematical modelling of multiple substance abuse can be attributed to lack of data on multiple substances of abuse. We ask: can we use the available data on primary substances of abuse to estimate the number of individuals who use more than one substance? We shall use our combined model formulated and described in Chapter 3 to estimate the proportion of individuals using both alcohol and methamphetamine in Cape Town and Western Cape Province. Using the parameter values defined in Table 3.2, the population under co-abuse is estimated as shown in Figure 3.14. Figure 3.14 reveals that the popula-

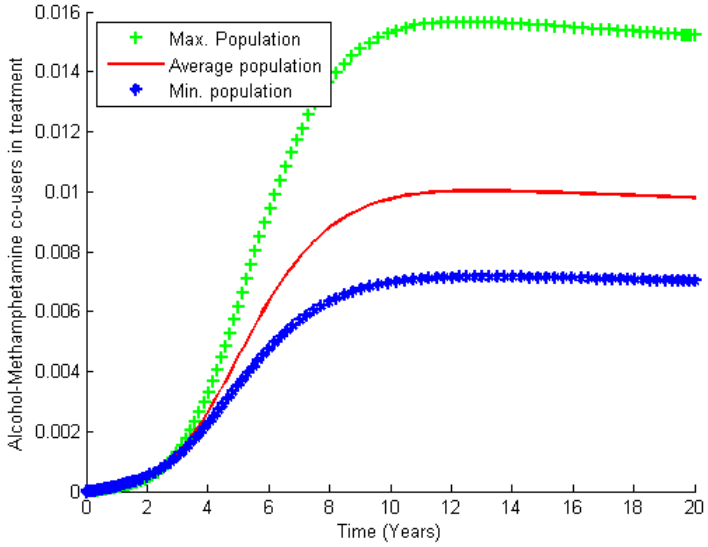


Figure 3.14: Graph showing the proportions of alcohol-methamphetamine users under treatment in Cape Town and Western Cape Province of South Africa.

tion estimate of alcohol-methamphetamine users in Cape Town and Western Cape Province has been growing in the recent past correspondingly to that of methamphetamine abuse in the province. Our results are also consistent with the clinical results which have shown a strong link between the two substances of abuse, see [46]. This trend is further consistent with the growing popularity of methamphetamine in the province in the last few years [61]. The two substances have been shown to influence intake and abuse of the other for varied and diverse reasons discussed in Chapter 1. Therefore, increased in-take and abuse of methamphetamine, enhances the use and abuse of alcohol and vice versa as described in [46]. The maximum (Max)

and minimum (Min) curves correspond to estimated proportion of co-users when transmission rates are doubled and halved respectively.

Furthermore, we observe from Figure 3.15 that the projected alcohol-methamphetamine co-abuse prevalence is about 1% in the Western Cape Province. This signifies that from a population of 1,000,000 people, about 10,000 would be seeking treatment or in need of treatment for co-abuse of alcohol and methamphetamine in the province. Comparison of the population values in Table 3.3 and 3.4 reveal that in the year 2011, the population of individuals under treatment for methamphetamine abuse (2093 individuals) was higher than that for persons under treatment for alcohol addiction (1553 individuals). Similarly, in reference to the approximation curve in Figure 3.14, we observe that there were approximately 40 individuals under treatment for abuse of both alcohol and methamphetamine. Since most substance abuse treatment centres in South Africa do not cater for individuals under addiction for multiple substances abuse, it is vital to observe that such population does in deed exist, and that they should not be ignored if the fight against drug abuse is to be successful. Nevertheless, treatment for multiple substance abuse is an expensive activity and will obviously require more resources as compared to those used in treatment of addicts of single substances.

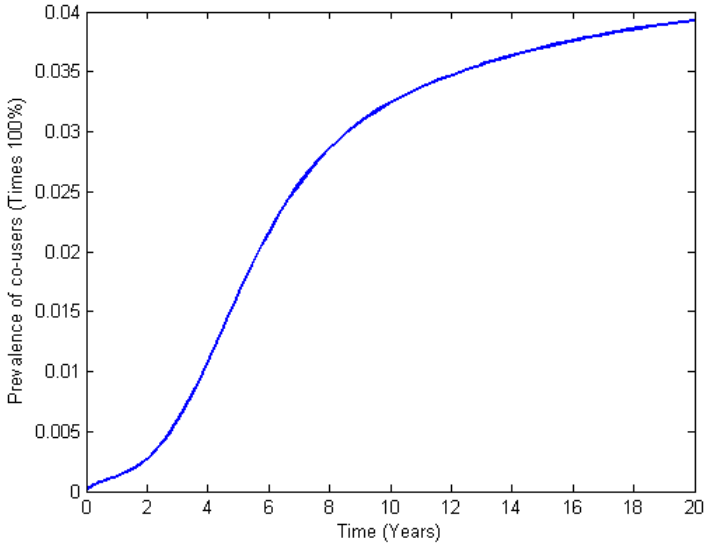


Figure 3.15: Shows the general prevalence of alcohol-methamphetamine abuse in the Western Cape Province of South Africa, for parameter values: $\mu = 0.02$, $\beta_1 = 2.8640$, $\beta_2 = 2.3525$, $\gamma_1 = 0.00047576$, $\gamma_2 = 0.2$, $\gamma_3 = 0.0863$, $\gamma_4 = 0.01$, $\gamma_5 = 0.02$, $\delta_1 = 0.6626$, $\delta_2 = 0.002$, $\delta_3 = 0.02$, $\sigma_1 = 0.3372$, $\sigma_2 = 0.1$, $\sigma_3 = 0.9693$, $\rho_1 = 0.6626$, $\rho_2 = 0.05$, ρ_3= 0.7292, $\rho_4 = 0.0118$, $\rho_5 = 0.01$, $\rho_6 = 0.68$, $\rho_7 = 0.9$, $\eta_a = 0.01$, $\eta_t = 0.02$, $\zeta_1 = 0.0780$, $\zeta_2 = 0.01$, $\zeta_3 = 0.01$, $\epsilon_1 = 0.00054933$, $\epsilon_2 = 0.1$, $\epsilon_3 = 0.02$, Λ =2.3.

Chapter 4

Application of optimal control to the co-abuse epidemic model

4.1 Introduction

The basis of epidemiological study of any kind is the need to improve existing control strategies and ultimately eradicate the epidemic from the affected population. The application of optical control is vital to decision making in terms of viable control strategies to be employed to eradicate the epidemic [36]. The inclusion of optimal control to epidemic modelling is therefore very instrumental in the understanding of multiple substance abuse epidemic. In order to identify optimal control policies that minimize the size of population of multiple substance abusers at a relative minimum cost, a mathematical optimal control problem is formulated and analysed numerically. In this chapter, the alcohol-methamphetamine co-abuse model (3.1.4) is extended to include control measures. We aim to assess the impact of the controls on relapse and recruitment in the epidemic dynamics. Both controls (aimed at initiation and treatment) are some form of preventive measures.

4.2 Co-abuse model with controls

We formulate a framework that minimizes the population of substance abusers (U_a, U_t, U_{at}). This is done by incorporating two control policies that minimizes the rate of recruitment into substance abuse; that is, alcohol abuse, methamphetamine abuse and co-abuse of alcohol and methamphetamine, and also the rampant relapse rates among rehabilitants (individuals under rehabilitation). We assume a function $\hat{u}_i(t)$ such that $\hat{u}_i = 1 - u_i, i = 1, 2, 3$. The time dependent controls $u_1(t)$ and $u_2(t)$ are tied to prevalence reduction through educational campaigns; that is, campaigns aimed at reducing social interactions between users and non-users and also providing relevant information on the dangers of drug/substance abuse. On the other hand, the control $u_3(t)$

is tied to efficacy of rehab centres. As the efficacy improves (as u_3 increases), the function $\hat{u}_3$ decreases, resulting into decreased cases of relapse. It is important to note that if $u_i = 1$ then the control measures are 100% effective in controlling substance abuse while if $u_i = 0$ then they are not effective at all. The forces of 'infection' λ_1 and λ_2 corresponding to alcohol abuse and methamphetamine abuse are respectively reduced by factors u_1 and u_2. We therefore have

$$\lambda_1 = \frac{\hat{u}_1\beta_1(U_a + \zeta_1 R_a + \zeta_2 U_{at} + \zeta_3 R_{at})}{N} \quad \text{and} \quad \lambda_2 = \frac{\hat{u}_2\beta_2(U_t + \epsilon_1 R_t + \epsilon_2 U_{at} + \epsilon_3 R_{at})}{N}. \tag{4.2.1}$$

The impact of relapse is minimised by improved treatment services while reducing the intensity of interactions between individuals in $U_a - R_a$, $U_t - R_t$, $U_{at} - R_{at}$, $U_{at} - R_a$, and $U_{at} - R_t$ classes. Here, we have assumed that effective treatment minimizes the rates of relapse denoted by γ_1, γ_2, γ_3, γ_4 and γ_5 by a common factor of $\hat{u}_3 = 1 - u_3$, where u_3 represents the optimal control on treatment efficacy .

As a result of lack of data, we are focused on achieving an optimal solution that minimizes the defined relative costs. To identify the required level of effort to control multiple substance abuse, we propose an objective functional denoted by J which aims to minimize the population under substance abuse (alcohol, methamphetamine or both) and the cost of employing the the suggested controls u_1, u_2, and u_3. We therefore endeavour to find the most-effective strategy that reduces the prevalence of co-abuse of alcohol and methamphetamine at a minimal cost (in the sense discussed in this chapter), subject to the state equations in (4.2.3) and the initial conditions therein. In view of this, our objective functional to be minimised is given by:

$$J = \min_{u_1,u_2,u_3} \int_0^T (A_1 U_a + A_2 U_t + A_3 U_{at} + \alpha_1 u_1^2 + \alpha_2 u_2^2 + \alpha_3 u_3^2)\mathrm{d}t. \tag{4.2.2}$$

subject to the differential system

$$\left.\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \Lambda - (\mu + \lambda_1 + \lambda_2)S, \\
\frac{\mathrm{d}U_a}{\mathrm{d}t} &= \lambda_1 S + \rho_1 U_{at} + u_3\gamma_1 R_a + u_3\gamma_4 R_{at} - \eta_a\lambda_2 U_a - (\mu + \sigma_1 + \delta_1 + \rho_3)U_a, \\
\frac{\mathrm{d}R_a}{\mathrm{d}t} &= \sigma_1 U_a - (\mu + u_3\gamma_1 + \rho_4)R_a, \\
\frac{\mathrm{d}U_t}{\mathrm{d}t} &= \lambda_2 S + \rho_2 U_{at} + u_3\gamma_3 R_t + u_3\gamma_5 R_{at} - \eta_t\lambda_1 U_t - (\mu + \sigma_3 + \delta_3 + \rho_7)U_t, \\
\frac{\mathrm{d}R_t}{\mathrm{d}t} &= \sigma_3 U_t - (\mu + u_3\gamma_3 + \rho_6)R_t, \\
\frac{\mathrm{d}U_{at}}{\mathrm{d}t} &= \eta_a\lambda_2 U_a + \eta_t\lambda_1 U_t + u_3\gamma_2 R_{at} - (\mu + \rho_1 + \rho_2 + \delta_2 + \sigma_2)U_{at}, \\
\frac{\mathrm{d}R_{at}}{\mathrm{d}t} &= \sigma_2 U_{at} - (\mu + u_3\gamma_2 + u_3\gamma_4 + u_3\gamma_5 + \rho_5)R_{at},
\end{aligned}\right\} \tag{4.2.3}$$

with initial conditions given by, $S(0) = S_0$, $U_a(0) = U_{a0}$, $R_a(0) = R_{a0}$, $U_t(0) = U_{t0}$, $R_t(0) = R_{t0}$, $U_{at}(0) = U_{at0}$, $R_{at}(0) = R_{at0}$.

The coefficients A_1, A_2 and A_3 are the costs associated with minimizing 'infectives', i.e. the number of alcohol abusers, methamphetamine abusers and the co-abusers of alcohol and methamphetamine respectively. Similarly, the parameters α_1, α_2 and α_3 are the weights constants associated with the controls u_1, u_2, and u_3 respectively. The weight constants accounts for the relative importance pre-assigned by the modeller to the contributing terms in the objective functional [40]. T is the time period of intervention. Following the work by Joshi in [33] and Kar in [36], we assume that the costs of 'infection', A_1U_a, A_2U_t and A_3U_{at} are linear functions whereas the cost on the controls $\alpha_1u_1^2$, $\alpha_2u_2^2$ and $\alpha_3u_3^2$ are non-linear and takes the quadratic forms.

Our objective of minimizing population of substance abusers is achievable through proper implementation of the policies u_1, u_2, and u_3 over a time interval given by $[0, T]$. Mathematically, this is equivalent to minimizing the objective functional over the given time as described below. We thus seek an optimal control set (u_1^*, u_2^*, u_3^*) such that

$$J(u_1^*, u_2^*, u_3^*) = \min_{u_1,u_2,u_3 \in \mathbf{U}} \{J(u_1, u_2, u_3) | u_1, u_2, u_3 \in \mathbf{U}\}. \tag{4.2.4}$$

where $\mathbf{U} = \{(u_1, u_2, u_3) | 0 \leq u_i(t) \leq 1, i = 1, 2, 3\}$ is the control set. These control functions u_1, u_2 and u_3 are bounded and Lebesgue integrable.

Using Pontryagin's Maximum Principle [68], the optimality system (4.2.2, 4.2.3, 4.2.4) is converted into an equivalent problem; that is, a problem of minimizing a pointwise Hamiltonian H, with respect to u_1, u_2 and u_3 and is given by

$$\begin{aligned} H =& A_1U_a + A_2U_t + A_3U_{at} + \alpha_1u_1^2 + \alpha_2u_2^2 + \alpha_3u_3^2 + p_1(t)\{\Lambda - (\mu + \lambda_1 + \lambda_2)S\} \\ &+ p_2(t)\{\lambda_1 S + \rho_1 U_{at} + u_1\gamma_1 R_a + u_3\gamma_4 R_{at} - \eta_a\lambda_2 U_a - (\mu + \sigma_1 + \delta_1 + \rho_3)U_a\} \\ &+ p_3(t)\{\sigma_1 U_a - (\mu + u_3\gamma_1 + \rho_4)R_a\} \\ &+ p_4(t)\{\lambda_2 S + \rho_2 U_{at} + u_3\gamma_3 R_t + u_3\gamma_5 R_{at} - \eta_t\lambda_1 U_t - (\mu + \sigma_3 + \delta_3 + \rho_7)U_t\} \\ &+ p_5(t)\{\sigma_3 U_t - (\mu + u_3\gamma_3 + \rho_6)R_t\} \\ &+ p_6(t)\{\eta_a\lambda_2 U_a + \eta_t\lambda_1 U_t + u_2\gamma_2 R_{at} - (\mu + \rho_1 + \rho_2 + \delta_2 + \sigma_2)U_{at}\} \\ &+ p_7(t)\{\sigma_2 U_{at} - (\mu + u_3\gamma_2 + u_3\gamma_4 + u_3\gamma_5 + \rho_5)R_{at}\}, \end{aligned} \tag{4.2.5}$$

where $(p_i, i = 1, \ldots, 7)$ are the corresponding adjoint or co-state variables, obtained directly from the application of Pontryagin's Maximum Principle in [68]. Given optimal control set (u_1, u_2, u_3) and solutions $S(t), U_a(t), R_a(t), U_t(t)R_t(t), U_{at}(t)$ and $R_{at}(t)$ of the corresponding state system (4.2.3), there exist adjoint variables $p_i, i = 1, \ldots 7$, such that

$$\frac{\mathrm{d}p_1}{\mathrm{d}t} = -\frac{\partial H}{\partial S}, \quad \frac{\mathrm{d}p_2}{\mathrm{d}t} = -\frac{\partial H}{\partial U_a}, \quad \frac{\mathrm{d}p_3}{\mathrm{d}t} = -\frac{\partial H}{\partial R_a}, \quad \frac{\mathrm{d}p_4}{\mathrm{d}t} = -\frac{\partial H}{\partial U_t},$$
$$\frac{\mathrm{d}p_5}{\mathrm{d}t} = -\frac{\partial H}{\partial R_t}, \quad \frac{\mathrm{d}p_6}{\mathrm{d}t} = -\frac{\partial H}{\partial U_{at}}, \quad \text{and} \quad \frac{\mathrm{d}p_7}{\mathrm{d}t} = -\frac{\partial H}{\partial R_{at}}.$$

These evaluation leads to the following adjoint system.

$$\frac{dp_1}{dt} = \mu p_1 + \{(\lambda_1+\lambda_2)(S-N)(p_2+p_4-p_1) + \eta_t U_t(p_6-p_4)\lambda_1 + \eta_a U_a(p_6-p_2)\lambda_2\}/N, \tag{4.2.6}$$

$$\begin{aligned}\frac{dp_2}{dt} =& -A_1 + d_1 p_2 - \sigma_1 p_3 + \{\beta_1(1-u_1)(S(p_1-p_2)+\eta_t U_t(p_4-p_6))\\ &+S(p_2+p_4-p_1)(\lambda_1+\lambda_2)+\eta_t U_t(p_6-p_4)\lambda_1+\eta_a(N-U_a)(p_2-p_6)\}/N,\end{aligned} \tag{4.2.7}$$

$$\begin{aligned}\frac{dp_3}{dt} =& d_2 p_3 + u_3\gamma_1(p_3-p_2) + \{S(p_2+p_4-p_1)(\lambda_1+\lambda_2) + [\beta_1 u_1[\eta_t\epsilon_1 U_t(p_4-p_6)\\ &-\zeta_1 S(p_1+p_2)+\eta_t U_t(p_6-p_4)\lambda_1+\eta_a U_a)(p_6-p_2)\lambda_2]\}/N,\end{aligned} \tag{4.2.8}$$

$$\begin{aligned}\frac{dp_4}{dt} =& -A_2 + d_3 p_4 - \sigma_3 p_5 + \{\beta_2 u_2(S(p_1-p_4)+\eta_a U_a(p_2-p_6))\\ &+S(p_2+p_4-p_1)(\lambda_1+\lambda_2)+\eta_t U_t(p_6-p_4)\lambda_1+\eta_a U_a(p_6-p_2)\lambda_2\}/N,\end{aligned} \tag{4.2.9}$$

$$\begin{aligned}\frac{dp_5}{dt} =& d_4 p_5 + u_3\gamma_3(p_5-p_4)\{\beta_2 u_2[\eta_t\epsilon_1 U_t(p_4-p_6)+\epsilon_1 S(p_1-p_4)+\eta_a U_a(p_2-\epsilon_1 p_6)]\\ &+[S(p_2+p_4-p_1)(\lambda_1+\lambda_2)+\eta_t U_t(p_6-p_4)\lambda_1+\eta_a U_a(p_6-p_2)\lambda_2\}/N,\end{aligned} \tag{4.2.10}$$

$$\begin{aligned}\frac{dp_6}{dt} =& -A_3 + d_5 p_6 - \rho_1(p_2+p_4) - \sigma_2 p_7 + \{\beta_1 u_1\zeta_2(S(p_1-p_2)+\eta_t U_t(p_4-p_6))\\ &+\beta_2 u_2\epsilon_2(S(p_1-p_4)+\eta_a U_a(p_2-p_4))S(p_2+p_4-p_1)(\lambda_1+\lambda_2)\\ &-\eta_t U_t(p_6+p_4)\lambda_1+\eta_a U_a(p_6-p_2)\lambda_2\}/N,\end{aligned} \tag{4.2.11}$$

$$\begin{aligned}\frac{dp_7}{dt} =& d_6 p_7 + u_3[(\gamma_2+\gamma_4+\gamma_5)p_7-\gamma_2 p_6-\gamma_4 p_2-\gamma_5 p_4] + \{\beta_1 u_1\zeta_3(S(p_1-p_2)\\ &+\eta_t U_t(p_4-p_6))+\beta_2 u_2\epsilon_3(S(p_1-p_4)-\eta_a U_a(p_2+p_6))\\ &+S(p_2+p_4-p_1)(\lambda_1+\lambda_2)+\eta_t U_t(p_6-p_4)\lambda_1+\eta_a U_a(p_6-p_2)\lambda_2\}/N.\end{aligned} \tag{4.2.12}$$

with transversality condition $p_i(T) = 0$ for $i = 1,\ldots,7$. We let $(\bar{S}, \bar{U}_a, \bar{R}_a, \bar{U}_t, \bar{R}_t, \bar{U}_{at}, \bar{R}_{at})$ be the optimum values of $(S(t), U_a(t), R_a(t), U_t(t), R_t(t), U_{at}(t), R_{at}(t))$ and p_i, for $i = 1,\ldots,7$, be the solutions of our adjoint system, where $d_1 = \mu+\sigma_1+\delta_1+\rho_3$, $d_2 = \mu+\rho_4$, $d_3 = \mu+\sigma_3+\delta_3+\rho_7$, $d_4 = \mu+\rho_6$, $d_5 = \mu+\rho_1+\rho_2+\delta_2+\sigma_2$ and $d_6 = \mu+\rho_5$.

Following methodology [22], we now state and prove the existence of optimal control in the subsequent sections.

Theorem 4.2.1. *There exists optimal controls, (u_1^*, u_2^*, u_3^*) which minimizes J over the region*

U given by the following expressions

$$u_1^* = \max\{0, \min(\bar{u}_1, 1)\}, \tag{4.2.13}$$
$$u_2^* = \max\{0, \min(\bar{u}_2, 1)\}, \tag{4.2.14}$$
$$u_3^* = \max\{0, \min(\bar{u}_3, 1)\}, \tag{4.2.15}$$

where

$$\bar{u}_1 = (S(p_2 - p_1) + \eta_t U_t(p_6 - p_4)) \left\{ \frac{\beta_1(U_a + \zeta_1 R_a + \zeta_2 U_{at} + \zeta_3 R_{at})}{2\alpha_1(S + U_a + R_a + U_t + R_t + U_{at} + R_{at})} \right\}, \tag{4.2.16}$$

$$\bar{u}_2 = (S(p_4 - p_1) + \eta_a U_a(p_6 - p_2)) \left\{ \frac{\beta_2(U_t + \epsilon_1 R_t + \epsilon_2 U_{at} + \epsilon_3 R_{at})}{2\alpha_2(S + U_a + R_a + U_t + R_t + U_{at} + R_{at})} \right\}, \tag{4.2.17}$$

$$\begin{aligned}\bar{u}_3 = &\{\gamma_1 R_a(p_2 - p_3) + \gamma_2 R_{at}(p_6 - p_7) + \gamma_3 R_t(p_4 - p_5) + \gamma_4 R_{at}(p_2 - p_7) \\ &+ \gamma_5 R_{at}(p_4 - p_7)\}/(2\alpha_3),\end{aligned} \tag{4.2.18}$$

and $p_i, i = 1, \ldots, 7$ *are the solutions of the adjoint system* (4.2.6)-(4.2.12).

Proof. We minimize the Hamiltonian H with respect to the controls (u_1, u_2, u_3) at the optimal control functions. This is done by differentiating the Hamiltonian function H with respect to each of the control variables on the set U; that is

$$\frac{\partial H}{\partial u_i} = 0.$$

Upon these computations, we obtain the following set of optimality conditions:

$$\begin{aligned}\frac{\partial H}{\partial u_1} =& 2\alpha_1 u_1 + \left\{ \frac{\beta_1(U_a + \zeta_1 R_a + \zeta_2 U_{at} + \zeta_3 R_{at})}{(S + U_a + R_a + U_t + R_t + U_{at} + R_{at})} \right\} (S(p_1 - p_2) + \eta_t U_t(p_4 - p_6)) = 0, \\ \frac{\partial H}{\partial u_2} =& 2\alpha_2 u_2 + \left\{ \frac{\beta_2(U_t + \epsilon_1 R_t + \epsilon_2 U_{at} + \epsilon_3 R_{at})}{(S + U_a + R_a + U_t + R_t + U_{at} + R_{at})} \right\} (S(p_4 - p_1) + \eta_a U_a(p_6 - p_2)) = 0, \\ \frac{\partial H}{\partial u_3} =& 2\alpha_3 u_3 + \{\gamma_1 R_a(p_3 - p_2) + \gamma_2 R_{at}(p_7 - p_6) + \gamma_3 R_t(p_5 - p_4) + \gamma_4 R_{at}(p_7 - p_2) \\ &+ \gamma_5 R_{at}(p_7 - p_4)\} = 0,\end{aligned}$$

at $u_1 = u_1^*$, $u_2 = u_2^*$ and $u_3 = u_3^*$ respectively. Upon solving for u_1^*, u_2^*, and u_3^*, we obtain

$$\begin{aligned}\bar{u}_1 =& (S(p_2 - p_1) + \eta_t U_t(p_6 - p_4)) \left\{ \frac{\beta_1(U_a + \zeta_1 R_a + \zeta_2 U_{at} + \zeta_3 R_{at})}{2\alpha_1(S + U_a + R_a + U_t + R_t + U_{at} + R_{at})} \right\}, \\ \bar{u}_2 =& (S(p_4 - p_1) + \eta_a U_a(p_6 - p_2)) \left\{ \frac{\beta_2(U_t + \epsilon_1 R_t + \epsilon_2 U_{at} + \epsilon_3 R_{at})}{2\alpha_2(S + U_a + R_a + U_t + R_t + U_{at} + R_{at})} \right\}, \\ \bar{u}_3 =& \{\gamma_1 R_a(p_2 - p_3) + \gamma_2 R_{at}(p_6 - p_7) + \gamma_3 R_t(p_4 - p_5) + \gamma_4 R_{at}(p_2 - p_7) \\ &+ \gamma_5 R_{at}(p_4 - p_7)\}/(2\alpha_3).\end{aligned}$$

Using the bounds for the controls set in **U**; that is

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

we obtain the expressions in Equation (4.2.16)-(4.2.16). □

4.3 Numerical simulation of the optimal system

In this section, we investigate numerically, the optimal solution to optimality system (4.2.3). We investigate the dynamics of the epidemic based on the proposed control strategies. We use the standard two-boundary point method as described by Lenhart and Workman in [41] to solve the optimality system. The co-abuse model system is integrated numerically using a fourth order Runge-Kutta scheme in Matlab (ODE integration scheme called ode45). Based on the given initial conditions, we solve the state variables $(S, U_a, R_a, U_t, R_t, U_{at}, R_{at})$ using the forward scheme method over the simulated time. On the other hand, based on the transversality conditions, we solve for the adjoint variables associated with the state variables using the backward scheme method. Owing to lack of data on multiple substance abuse, we estimate most of the parameters used in the simulations. This estimation is guided by available published literature. Other parameters are however obtained intuitively from information related to methamphetamine and alcohol transmission dynamics. The nominal values of the parameters used in numerically integrating the model system of equations are indicated in Table 4.2. Similarly, the estimated costs associated with the reduction of substance abusers (U_a, U_t and U_{at}) are given in Table 4.1.

In South Africa, the cost of treatment for substance abuse ranges between R10000 and R75000 per month. Although the costs are too high, most of the families that cannot afford these charges, often use the services of Alcohol Anonymous and Narcotics Anonymous as their support [2]. In this work, for purposes of simulations, we shall consider the minimal cost as the average cost of treatment. Since prevention is cheaper than treatment, we have assumed that the cost associated with prevention (α_1 and α_2) through educational campaigns is half the cost of ensuring improved efficacy in treatment α_3 for substance abuser.

Due to lack of data, it is important to recognize and acknowledge the challenges involved in estimating the weights associated with the integrand in the objective functional (4.2.2). We hereby recommend the need to carry out further investigation and evaluation of such weights. In this work, we have assumed that the process of altering the social dynamics within a population is much more difficult (more expensive in

this context) than reducing the likelihood of relapse into substance abuse for addicts in the same setting. Therefore, the relative costs tied to implementing the controls u_1 and u_2 are assumed to be higher than the relative costs tied to the controls u_3.

Similarly, we have considered the costs associated with alcohol abuse, U_a, methamphetamine abusers U_t and co-abuse of alcohol and methamphetamine U_{at} to mainly include the cost of dangerous behaviour and its consequences during substance abuse period. On the other hand, the cost associated with the controls u_1 and u_2 involves the cost of educating the public on the dangers of substance abuse and multiple substance abuse. After several numerical simulations, we give the weighting coefficients as $\alpha_1 = 5000$ per month, $\alpha_2 = 5000$ per month and $\alpha_3 = 10^4$ per month. We state that the proposed weights only serve the necessary theoretical interest; that is, to reveal the control strategies proposed in this project.

Coefficient	Cost Value
A_1	R10000 per percentage reduction in U_a
A_2	R10000 per percentage reduction in U_t
A_3	R10000 per percentage reduction in U_{at}

Table 4.1: Costs associated with controls

Symbol	**Value**	**Source**	**Symbol**	**Value**	**Source**
Λ	0.03	Estimated	σ_1	0.2	Estimated
μ	0.02	[55]	σ_2	0.3	Estimated
β_1	0.25	Estimated	σ_3	0.3	Estimated
β_2	0.2	Estimated	ρ_1	0.01	Estimated
γ_1	0.15	Estimated	ρ_2	0.01	Estimated
γ_2	0.1	Estimated	ρ_3	0.35	Estimated
γ_3	0.3	Estimated	ρ_4	0.25	Estimated
γ_4	0.3	Estimated	ρ_5	0.25	Estimated
γ_5	0.3	Estimated	ρ_6	0.78	Estimated
δ_1	0.03	Estimated	ρ_7	0.4	Estimated
δ_2	0.04	Estimated	η_a ,η_t,ζ_2 ϵ_2	1.05	Estimated
δ_3	0.033	Estimated	ζ_1, ζ_3, ϵ_1, ϵ_3	0.7	Estimated

Table 4.2: Nominal parameter values used in simulations

4.3.0.1 Simulation results

Figure 4.1 plots all the susceptibles S, abusers of alcohol U_a, methamphetamine abusers U_t and co-abusers of alcohol and methamphetamine U_{at}, without controls (solid lines) and with optimal controls (dotted lines). Considering a low-risk population, our results suggest that much less time is taken to clear the epidemic resulting

from alcohol abuse, methamphetamine abuse and co-abuse of alcohol and methamphetamine when optimal controls are applied than without the controls. See parts (b), (c) and (d) of Figure 4.1. Substance abuse is shown to be contained much earlier in time when appropriate and robust optimal controls are applied to the epidemic of alcohol and methamphetamine abuse. Optimal controls minimizes the incidence function accordingly. Part (a) of Figure 4.1 reveals that without controls, the susceptible population gets depleted at a higher rate due to unchecked or high transmission rates. However, with the applications of optimal controls such as public education, the population is shown to grow exponentially. More individuals get to stay in the susceptible class as compared to dynamics without controls.

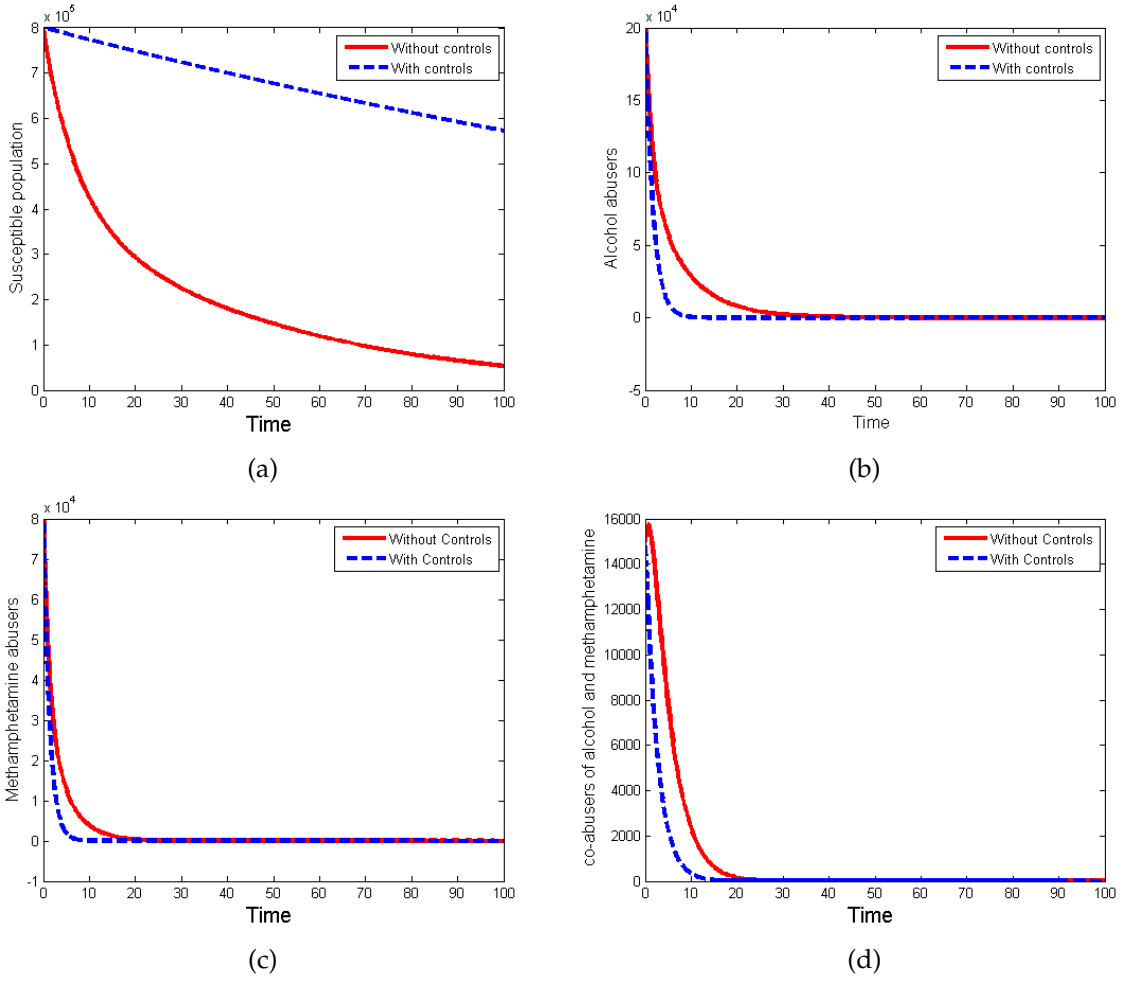


Figure 4.1: Graphs (a), (b), (c), (d) show the dynamics of susceptible population and substances abusers under different optimal control strategies, that is, without controls (solid curves) and with controls (dashed curves)

Figure 4.2 shows the typical plots of the rehabilitants (temporary recovered population) obtained from the implementation of the optimal controls. It reveals that the application of optimal controls to the co-abuse model ensures that a much less time is taken to clear the population of substance abusers under rehabilitation. See parts

(a) and (b) of Figure 4.2. On the other hand, we observe from part (c) that although improved treatment should result into a sustained decline in the population of rehabilitants under co-abuse of alcohol and methamphetamine, it is likely to create a second problem. The increased population of temporary recovered persons R_a, R_t and R_{at} may create a second pool of susceptibles hence worsening the alcohol-methamphetamine epidemic, hence the longer the time taken to clear the population under R_{at} as is shown in part (c) of Figure 4.2.

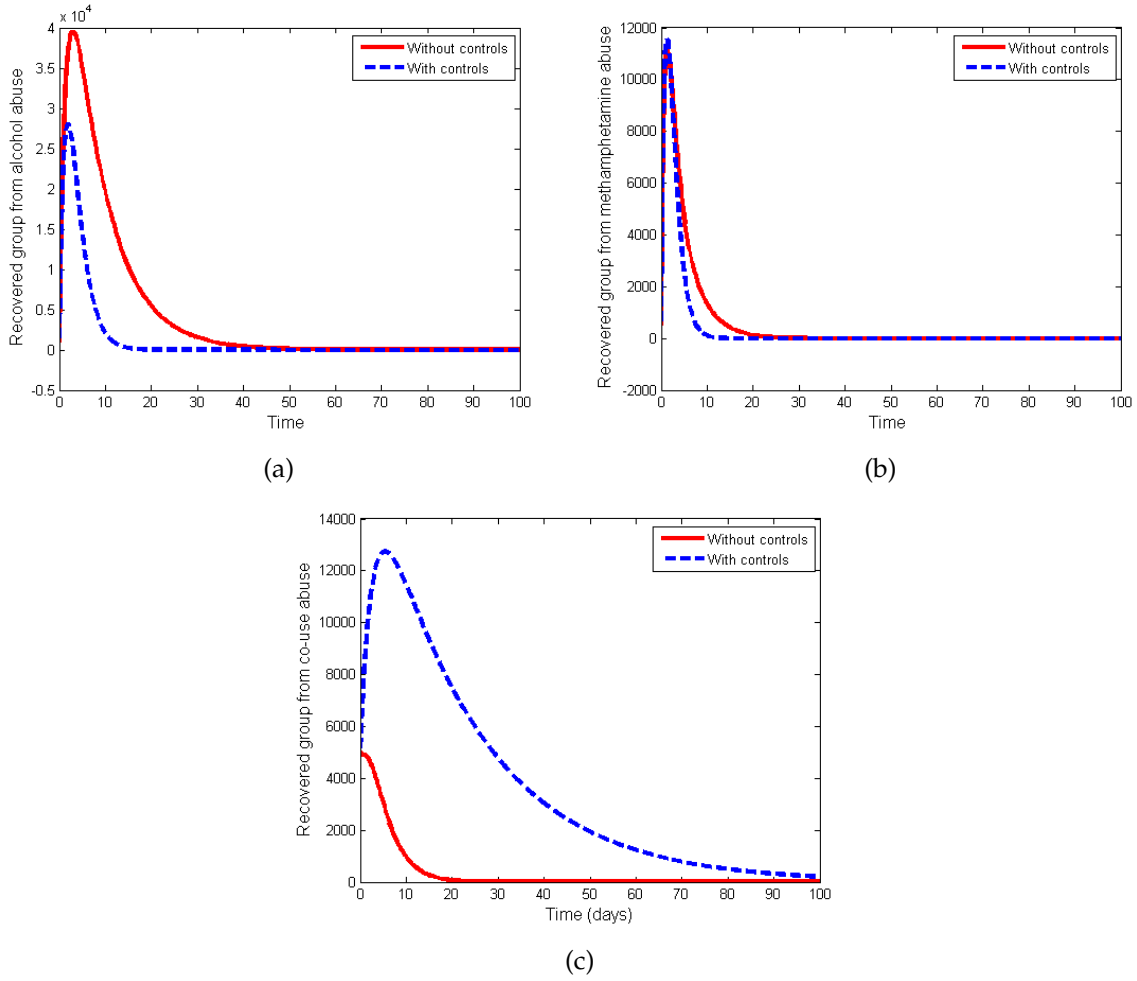


Figure 4.2: Graphs (a), (b) and (c) show the dynamics of rehabilitants under different optimal control strategies, that is, without controls (solid curves) and with controls (dashed curves)

The profiles of the optimal controls are shown in Figure 4.3. We observe that shapes of the plots of the optimal controls u_1 and u_1 are similar; that is, both require an initial strong start that should be maintained for a greater period of time if the epidemic is to be contained. In the beginning of the simulation, the control policies u_1 and u_2 should be increased exponentially until 30 days, then maintained for the next 60 days and finally rapidly decreased to 0 at the end of the simulation. Observe that the controls u_1 and u_2 help reduce the likelihood of the susceptible population getting initiated into alcohol abuse and methamphetamine abuse respectively. Educational campaigns on

the dangers of multiple substance abuse should be maximised to reduce transmission in the epidemic.

On the other hand, plots for the controls on treatment efficacy u_3 show similar trends, see Figure 4.3. Treatment efficacy should be increased gradually over the given time period. Effective and efficient treatment services should be provided and maintained throughout the treatment period. It should be increased exponentially upto day 50, but with the substance abuse on going, the control effort of u_3 should gradually increase to the maximum and maintain this level until the 95th day; hereafter, it should be gradually decreased to the level of almost 0 in the end.

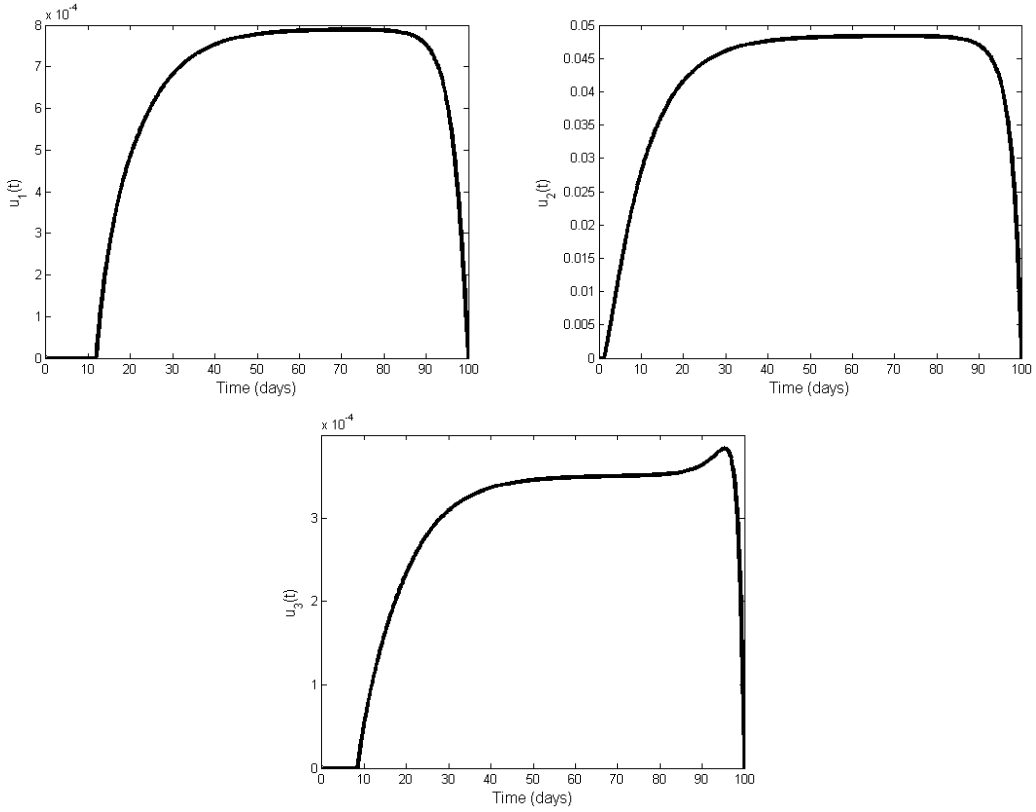


Figure 4.3: Profiles of educational campaign controls u_1, u_2 and the treatment efficiency control u_3.

The simulation shows that a lot more emphasis should be employed in reducing the social interactions that results into substance abuse. It also signifies the need to respond to substance abuse and hence multiple substance abuse throughout and not only when cases of relapse are experienced. More emphasis should be placed on public education on the dangers of multiple substance abuse and also, effective treatment services which ensures maximum quitting should be supported and encouraged. We suggest that treatment services should be patient specific, proper, efficient and timely.

Chapter 5

Conclusions

In this thesis, a deterministic model showing the dynamics of co-abuse of alcohol and methamphetamine epidemic is presented. In the first part, we analyse the co-abuse model and its sub-models without controls while in the second part, we introduce time-dependent control variables (policies) to the co-abuse model. For the model without controls, we establish the existence of equilibria points in terms of the basic reproduction numbers $\mathcal{R}_{a0}$ and $\mathcal{R}_{t0}$. By constructing a suitable lyapunov function, the analysis shows that the substance free equilibrium of the co-abuse model is globally asymptotically stable whenever $\mathcal{R}_{at0}$ is less than unity. The health implication of this observation is that keeping the reproduction numbers below one is necessary to curb the alcohol methamphetamine co-abuse epidemic in the Western Cape Province. This observation implies that the control efforts should target both substances of abuse and not just the more 'virulent' substance as is often the case.

To investigate the potential impact of treatment to the progression of drug/substance abuse epidemic, we carry out sensitivity analysis of the model parameters. The respective analysis shows that an increase in the rate at which addicts seek treatment results into a corresponding decline in new cases of drug/substance abuse. This therefore calls for the need to enhance even further the progression into treatment services by drug users. Families, religious organizations, communities and learning institutions should be encouraged and supported in sensitizing the public on the need for seek appropriate and prompt treatment services due to substance abuse. Similarly, the treatment services shouldn't only be focussed on the addicts, but on all drug users irrespective of the levels of their dependency on the preferred substance of abuse. Although the drug addicts may display clearly most of the consequences of substance abuse, treatment services, should be made available and affordable to majority drug/substance users. We further recommend that more and affordable drug/substance abuse treatment centres, should be constructed to reduce congestion on the already existing ones and also to increase access.

We also fitted the model to data on population under treatment for alcohol and methamphetamine abuse, with the objective of using the model parameters that give the best fit to obtain the incidence curve. Latin Hypercube Sampling and Partial Rank Correlation Coefficients reveals that the two parameters with the greatest impact on the outcome are the alcohol and methamphetamine transmission coefficients, β_1 and β_2 respectively. This implies that in order to minimize alcohol-methamphetamine co-abuse, the transmission parameters must be minimized. There is a need to minimize alcohol outlets, prohibit the location of bars and pubs close to learning institutions, increase taxation on licit substances such as alcohol and strictly prohibit production or manufacture of ingredients of methamphetamine.

Similarly, the alcohol relapse rate denoted by γ_3 was noted to be positively significant in enhancing the co-abuse epidemic. This suggests the need to employ social intervention programs aimed at new users, discourages new recruitment and encourages mass quitting by addicts. Preventive measures are however much cheaper than targeting the addicts either in quitting or rehabilitation. It follows therefore that the fight against multiple substance/drug abuse will be significantly dependent on social programmes. Multiple drug abuse has been shown to complicate treatment for those seeking help for drug problems. It also has implications for the efficacy of treatment. It is therefore critical to access the population level impact of multiple substance abuse and to devote resources to education, awareness and quitting programmes that are especially targeted at occasional users.

It is clear that a well coordinated approach to prevention in substance abuse epidemic is required. The new policies must however recognize the interrelated and multidimensional problems that multiple substance presents us with. We need for example, broad mass media campaigns to warn against multiple drug abuse in recreational settings, homes, places of worship and in institutions of learning. Other measures may include health warnings and advice that are passed through drug workers, peers and self-help groups.

The population of co-users of alcohol and methamphetamine are shown to increase with the increasing population of methamphetamine users. It is observed however that this proportion is much lower than the individual users of either alcohol and methamphetamine. This difference should not however be used to overlook the need to reduce multiple substance abuse which has been shown to have even greater negative effect than that which would be experienced by the abuse of the single substances. To eliminate or minimize co-abuse of alcohol and methamphetamine, relevant authorities tasked with drug/substance abuse management, should heavily focus on and fight the spread and abuse individual substances such as alcohol and methamphetamine.

The control policies must be implemented consistently and throughout the entire period of the epidemic. Although the presented model in this work is not without limitations, its analysis are instrumental in providing the useful insights on abuse of multiple substances. The study is equally useful in highlighting vital control strategies such as educational campaigns in learning institutions, health centres, religious gatherings among others. For apt management of epidemic due to multiple abuse of alcohol and methamohetamine in Cape Town and Western Cape Province of South Africa, we state the following recommendations:

1. There is an urgent need to collect and document data on multiple substance abuse in South Africa.
2. Educational campaigns against drug/substance abuse, should be carried out regularly.
3. More specialist treatment centres should be put in place to cater for multiple substance abuse victims.
4. The need to offer cost-effective and efficient treatment services to drug addicts should be emphasised.

The presented model recommends that data collection on substance abuse should not be restricted to the primary substances of abuse, but should consider as well cases of multiple abuse of substances. Owing to the numerous modelling assumptions made in this paper, the presented co-use substance abuse model may not provide an exact representation of the epidemic resulting from the co-use of alcohol and methamphetamine in the Western Cape Province of South Africa. The dynamics are much more complex than described here. However, the model provides the required insights to understanding co-use in substance abuse epidemic. The results are useful in designing intervention strategies aimed at combating multiple substance abuse. In future, the presented model could be improved by inclusion of other stages of substance abuse such as light and addiction stages, and the impact of the police and the drug lords in its dynamics.

Bibliography

[1] Alcohol abuse costs R9bn a year. http://www.news24.com/SouthAfrica/Politics/Alcohol-abuse-puts-R9bn-dent-in-economy-20110905. [Online; accessed on July 2, 2014].

[2] Rehab centres in south africa. http://www.ineedrehab.co.za/. [Online; accessed on January 22, 2014].

[3] Statistics South Africa. Mid-year population estimates. http://beta2.statssa.gov.za/publications/P0302/P03022014.pdf.[Online; accessed on January 4, 2014].

[4] T. E. Albertson, R. W. Derlet, B. E. Van, and B. E. Hoozen. Methamphetamine and the expanding complications of amphetamines. *Western Journal of Medicine*, 170:214–219, 1999.

[5] R. M. Anderson and R.M. May. *Infectious Diseases of Humans: Dynamics and Control*, volume 28. Wiley Online Library, 1992.

[6] American Psychiatric Association. *DSM-IV-TR: Diagnostic and statistical manual of mental disorders, text revision*. American Psychiatric Publication, 2000.

[7] S. L. Bailey. Adolescents' multisubstance use patterns: The role of heavy alcohol and cigarette use. *American Journal of Public Health.*, 82:1220–1224, 1992.

[8] B. Benedict. Modeling alcoholism as a contagious disease: How infected buddies spread problem drinking. *Society of Industrial and Applied Mathematics*, 40(3), 2007.

[9] C. P. Bhunu and S. Mushayabasa. A theoretical analysis of smoking and alcoholism. *Journal of Mathematical Modelling and Algorithms.*, 11.4:387–408, 2012.

[10] S. M. Blower and H. Dowlatabadi. Sensitivity and uncertainty analysis of complex-models of disease transmission an HIV model, as an example. *International Statistical Review.*, 62:229–243, 1994.

[11] B. Bower. Multiple Drug Use: A Dangerous Trend. *Science News*, 128:6(1), 1985.

[12] M. N. Burattini, E. Massad, and F. A. B. Coutinho. A mathematical model of the impact of crack-cocaine use on the prevalence of HIV/AIDS among drug users. *Mathematical and Computer Modelling*, 28:21, 1998.

[13] R. Caetano and C. Weisner. The association between DSM-III-R alcohol dependence, psychological distress and drug use. *Addiction*, 90:351–359, 1995.

[14] C. Castillo Chavez and F. Brauer. *Mathematical models in population biology and epidemiology. Texts in Applied Mathematics*, volume 40. 2001.

[15] C. Castillo Chavez and B. Song. Dynamical models of tuberculosis and their applications. *Mathematical Biosciences and Engineering.*, 1:361–404, 2004.

[16] D. A. Ciraulo, B. R. Sands, and R. I. Shader. Critical review of liability for benzodiazepine abuse among alcoholics. *Americal Journal of Psychiatry*, 145:1501–1506, 1988.

[17] C. Comiskey and G. Cox. Research outcome study in ireland (rosie): Evaluating drug treatment effectiveness, baseline findings. `http://www.drugsandalcohol.ie/11542/`. [Online; accessed on December 15, 2013]. *Substance Abuse Treatment*, 2005.

[18] Human Sciences Research Council. HIV/AIDS in South Africa: At last the glass is half full. `http://www.hsrc.ac.za/en/media-briefs/hiv-aids-stis-and-tb/`. [online; accessed on november 22, 2013], 2013.

[19] D. Czechowicz. Adolescent alcohol and drug abuse and its consequences: An overview. *American Journal of Drug and Alcohol Abuse*, 14:189–197, 1998.

[20] Republic of South Africa Department of Social Development. Central drug authority (cda). `http://www.dsd.gov.za/cda/`. [Online; accessed on October 13, 2013].

[21] EMCDDA. Poly drug use. Publications Office of the European Union, Luxembourg, 2002. `http://www.emcdda.europa.eu/html.cfm/index34913EN.html`. [Online; accessed on March 15, 2013].

[22] W. H. Fleming and R. W Rishel. *Deterministic and Stochastic Optimal Control*. Springer, 1975.

[23] Anchors for Change. Meth. `http://www.anchors4change.com/meth.htm`. [Online; accessed on September 4, 2014].

[24] Center for Substance Abuse Treatment. Medication-assisted treatment for opioid addiction in opioid treatment programs. treatment improvement protocol (tip) series 43, 2005. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration.

[25] K. E. Fritz, G. B Woelk, M. T. Bassett, W. C. McFarland, J.A. Routh, O. Tobaiwa, and D. R. Stall. The association between alcohol use, sexual risk behavior, and HIV infection among men attending beerhalls in Harare, Zimbabwe. *AIDS Behavour*, 6.3:221–228, 2002.

[26] D. Gibson, M. Leamon, and N. Flynn. Epidemiology and public health consequences of methamphetamine use in Califonia's central survey. *Psychoactive Drug*, 34:313–319, 2002.

[27] D. Gieringer. Medical cannabis potency testing project. *Bulletin of the Multidisciplinary Association for Psychedelic Studies.*, 9:20–22, 1999.

[28] M. N. Hesselbrock, R. E. Meyer, and J. Keener. Psychopathology in hospitalised alcoholics. *Archives of General Psychiatry*, 42.11:1050, 1985.

[29] Health System Trust (HST). Annual report 2012/2013. `http://www.hst.org.za/`. [Online; accessed February 15, 2013].

[30] R. Ives and P. Ghelenie. Pompidou group ministerial conference. *EMCDDA*. `http://www.emcdda.europa.eu/html.cfm/index27889EN.html`. [Online; accessed on July 12, 2014].

[31] D. T. Jamison, R. G. Feachmen, M. W. Makgoba, E. R. Bos, F. K. Baingana, K. J. Hofman, and K. O. Rogo. *Disease and Mortality in sub-Saharan Africa, Second edition.* World Bank, 2006 Washington D.C., 2008.

[32] S. Janet. Alcohol and south africa's youth. *South African Medical Journal.*, 102.7:587, 2012.

[33] H. R Joshi. Optimal control of an HIV immunology model. *Optimal Control Applications and Methods*, 23:199–213, 2002.

[34] D. B. Kandel and J. A. Logan. Patterns of drug use from adolescence to young adulthood: Periods of risk for initiation, continued use and discontinuation. *American Journal of Public Health*, 74.7:660–666, 1984.

[35] D. B. Kandel, K. Yamaguchi, and K. Chen. Stages of progression in drug involvement from adolescence to adulthood: Further evidence for the gateway theory. *Journal of Studies on Alcohol*, 53:447–457, 1992.

[36] T. K. Kar and Soovoojeet Jana. A theoretical study on mathematical modelling of an infectious disease with application of optimal control. *Biosystems*, 111(1):37–50, 2013.

[37] M. J. Keeling and P. Rohani. *Modeling infectious diseases in humans and animals.* Princeton University Press., 2008.

[38] E. Kelly, R. McKetin, and J. McLaren. The characteristics of treatment provided for amphetamine use in new south wales, australia. *Drug and Alcohol Review*, 24:433, 2005.

[39] G. O. Lawi, J. Y. T. Mugisha, and N. Omolo Ongati. Modeling co-infection of paediatric malaria and pneumonia. *International Journal of Mathematical Analysis*, 7:413–424, 2013.

[40] S. Lee, E. Jung, and C. Castillo Chavez. Optimal control intervention strategies in low-and high-risk problem drinking populations. *Socio-Economic Planning Sciences.*, 44(4):258–265, 2010.

[41] S. Lenhart and J. T. Workman. *Optimal Control Applied to Biological Problems.* Chapman & Hall/CRC. Boca Raton London Newyork., 2007.

[42] T. W. Lineberry and J. M. Bostwick. Methamphetamine abuse: a perfect storm of complications. *Mayo Clinic Proceedings*, No. 1. Elsevier:77–84, 2006.

[43] D. R. Mackintosh and G. T. Stewart. A mathematical model of a heroin epidemic: implications for control policies. *Journal of Epidemiology and Community Health*, 33:299–305, 1979.

[44] G. Mansergh, D. Purcell, R. Stall, M. McFarlane., S. Semaan., J. Valentine, and R. Valdiserri. CDC consultation on methamphetamine use and sexual risk behaviour for HIV/STD infection: Summary and suggestions. *Public Health Reports*, 121:127–132, 2006.

[45] J. Marsden, Boys, Annabel, and J. Strang. Understanding reasons for drug use amongst young people: a functional perspective. *Health Education Research*, 16.4:457–469, 2001.

[46] G. Matthew, Kirkpatrick, W. Erik, Gunderson, R. Frances, Levin, W. R. Foltin, and L. C. Hart. Acute and residual interactive effects of repeated administrations of oral methamphetamine and alcohol in humans. *Psychopharmacology.*, 219:191–204, 2012.

[47] M. D. McKay, R. J. Beckman, and W. J. Conover. A comparison of three methods for selecting values of input variables in the analysis of output from a computer code. *Technometrics*, 42(1):55, 2000.

[48] R. McKetin, J. McLaren, and E Kelly. *The Sydney methamphetamine market: patterns of supply, use, personal harms and social consequences.* National Drug Law Enforcement Research Fund Monograph no.13. Adelaide: Australasian Centre for Policing Studies, 2005.

[49] J. Mendelson, R. T. Jones, R. Upton, and P. Jacob. Methamphetamine and ethanol interactions in humans. *Clinical Pharmacology and Therapeutics.*, 57.5:559–568, 1995.

[50] K. S Mnyika, K. I. Klepp, G. Kvale, and N. Ole King'ori. Determinants of high risk sexual behaviour and condom use among adults in the Arusha region, Tanzan. *STD and AIDS*, 8:176–183, 1997.

[51] K. Morris and C. Parry. South African methamphetamine boom could fuel further HIV. *Lancet Infectious Diseases*, 6.8:471, 2006.

[52] G. Mulone and B. Straughan. A note on heroin epidemics. *Mathematical Biosciences*, 218:138–141, 2009.

[53] S. Mushayabasa and C. P. Bhunu. Modelling the effects of heavy alcohol consumption on the transmission dynamics of gonorrhea. *Nonlinear Dynamics.*, 66.4:695–706, 2011.

[54] National Institute on Drug abuse. National Household Survey on Drug Abuse: Main findings, 1887. `http://www.drugabuse.gov/national-survey-drug-use-health`. [Online; accessed on January 12, 2014].

[55] F. Nyabadza and S. D. Hove-Musekwa. From heroin epidemics to methamphetamine epidemics: Modelling substance abuse in a south african province. *Mathematical Biosciences*, 225:132–140, 2010.

[56] F. Nyabadza, J. B. Njagarah, and R. J. Smith. Modelling the dynamics of crystal meth ('tik') abuse in the presence of drug-supply chains in south africa. *Bulletin of Mathematical Biology*, 75(1):24–48, 2013.

[57] Minister of Economic Development and Western Cape Government Tourism. Tackling alcohol abuse together. `http://www.westerncape.gov.za/news/tackling-alcohol-abuse-together`. [Online; accessed on January 4, 2014].

[58] US Department of Justice. United States Drug Enforcement Administration. `www.justice.gov/dea/druginfo/ds.shtml`. [Online; accessed on August 26, 2013].

[59] Encyclopedia of Mental Disorders. Polysubstance dependence. `http://www.minddisorders.com/Ob-Ps/Polysubstance-dependence.html`. [Online; accessed on April 19, 2013].

[60] H. Parker and R. Eggington. Adolescence recreational alcohol and drug careers gone wrong: developing a strategy for reducing risks and harms. *International Journal of Drug Policy*, 13:419–432, 2002.

[61] C. Parry, P. Petersen, T. Carney, S. Dewing, and R. Needle. Rapid assessment of drug use and sexual HIV risk patterns among vulnerable drug using population in Cape Town, Durban and Pretoria, South Africa. *Social Aspects of HIV/AIDS*, 5:113–119, 2008.

[62] C. D. H Parry. Substance abuse in South Africa: Country report focusing on young persons, 1998. `http://www.samj.org.za/index.php/samj/article/view/6003/4278`. [Online; accessed on May 14, 2014].

[63] N. M. Petry. Alcohol use in HIV patients: What we don't know may hurt us. *International Journal of STDS and AIDS*, 10:561–570, 1999.

[64] A. Pluddemann, S. Dada, C. Parry, A. Bhana, V. Mohamed, T. Perreira, N. Erika, T. Mncwabe, P. Ina, and W. Roger. Monitoring alcohol and drug abuse trends in South Africa (July 1996 December 2011), 2012. SACENDU Research Brief, 6(2) phase 31, 2012a.

[65] A. Pluddemann, C. Parry, and B. Myers. Fact-sheet: Methamphetamine alcohol and drug abuse research unit, 2014. Medical Research Council. `http://www.sahealthinfo.org/admodule/sacendu.htm`. [Online; accessed on October 1, 2014].

[66] A. Pluddemann et al. Monitoring alcohol and drug abuse trends in South Africa (July 2012-December 2012), SACENDU Research Brief. *Mathematical Biosciences.*, 11, 2012.

[67] A. Pluddmann, A. Fisher, C. Mathew, T. Camey, and C. Lombamd. Adolescent methamphetamine use and sexual risk behaviour in secondary school students in Cape Town, South Africa. *Drug and Alcohol Review*, 27:687–692, 2008.

[68] L. S Pontryagin, V. G Boltyanskii, R. V Gamkrelidze, and E. F Mishchenco. *The Mathematical Theory of Optical Processes*. Wiley, New York, 1962.

[69] L Ramsoomar and NK Morojele. Trends in alcohol prevalence, age of initiation and association with alcohol-related harm among south african youth: Implications for policy. *South African Medical Journal.*, 102.7:609–612, 2012.

[70] R. Ross. *The prevention of Malaria.* London, 1911.

[71] C. Rossi. Operational models for epidemics of problematic drug use: the mover-stayer approach to heterogeneity. *Socio-Economic Planning Sciences*, 38:73–90, 2004.

[72] A. J. Ruttenber and J. L. Luke. Heroin-related deaths: new epidemiological insights. *Science*, 226:14–16, 1984.

[73] J. P. La Salle. The stability of dynamical systems. *Society for Industrial and Applied Mathematics.*, 1976.

[74] F. Sanchez, X. Wang, C. Castillo-Chavez, D.M. Gorman, and P.J Gruenwald. Drinking as an epidemic-a simple mathematical model with recovery and relapse. *Therapist's Guide to Evidence-Based Relapse Prevention*, page 353, 2007.

[75] M.A. Schuckit. The clinical implications of primary diagnostic groups among alcoholics. *Archives of General Psychiatry*, 42.11:1043, 1985.

[76] L. Simbayi, S. Kalichman, D. Cain, C. Cherry, N. Henda, and A. Cloete. Methamphetamine use and sexual risks for HIV infection in Cape Town, South Africa. *Substance Use*, 11:291–300, 2006.

[77] L.C. Simbayi, S. C. Kalichman, S. Jooste, V. Mathiti, D. Cain, and C. Chersey. Alcohol use and sexual risks for hiv infection among men and women receiving sexually transmit ted infection clinic services in cape town, south africa. *Journal of Studies on Alcohol and Drugs*, 65.4:434–442, 2004.

[78] Z. Sloboda. Drug abuse epidemiology: an overview. *The Science of Drug Abuse Epidemiology*, 1, 2002.

[79] F. Smit, K. Monshouwer, and J. Verdurmen. Polydrug use among secondary school students: Combinations, Prevalence and risk profiles. *Drugs: Education, Prevention and Policy*, 9(4):355–365, 2002.

[80] Department of Police presentation. The South African Police Service. Saps Crime statistics overview 2011/12. `http://www.saps.gov.za/resource_centre/publications/statistics/crimestats/2013/crime_stats.php`. [Online; accessed 0n August 23, 2014].

[81] TNT. The Naked Truth. `http://www.tnt.org.za`. [Online; accessed on February 20, 2014], 2010.

[82] J. W. Tsuang, E. Shapiro, T.L. Smith, and M.A. Schuckit. Drug use among primary alcoholic veterans. *American Journal of Drug and Alcohol Abuse*, 20:483–493, 1994.

[83] South Africa UNAIDS. Summary on hiv/aids 2012, 2013. `http://www.unaids.org/en/regionscountries/countries/southafrica/`. [Online; accessed on February 25, 2014].

[84] UNODC. World Drug Report. United Nations, New York. `http://www.unodc.org/wdr/`, 2013. [Online; accessed on September 23, 2013].

[85] UNODC. World drug report, 2011. United Nations, New York.

[86] P. Van den Driessche and J. Watmough. Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences.*, 180:29–48, 2007.

[87] E. White and C. Comiskey. Heroin epidemics, treatment and ODE modelling. *Mathematical Biosciences.*, 208(1):312–324, 2007.

[88] WHO. Alcohol and Injuries; emergency department studies in an international perspective. `http://www.who.int/substance_abuse/publications/alcohol/en/`, 2009. [Online; accessed on January 11, 2013].

[89] WHO. Global status report on alcohol and health 2014. `http://www.who.int/substance_abuse/publications/global_alcohol_report/en/`, 2014. [Online; accessed on November 2, 2013].

[90] WHO. Substance abuse. `http://www.who.int/substance_abuse/publications/alcohol/en/index.html`. [Online; accessed on October 22, 2013].

[91] Wikipedia. Linearization. `http://en.wikipedia.org/wiki/Linearization`, 2013. [Online; accessed on October 17, 2013].

Estimating the population of alcohol and methamphetamine co-users in the Western Cape province of South Africa

Titus Okello Orwa[†] and Farai Nyabadza[†*]
[†]*Department of Mathematical Science, University of Stellenbosch, Private Bag X1, Matieland, 7602, South Africa*

Abstract

The combined abuse of alcohol and the highly addictive methamphetamine has worsened the drug epidemic in South Africa, especially in the province of the Western Cape. In this paper, a mathematical model is formulated to model the dynamics of alcohol and methamphetamine co-abuse. We prove that the equilibria of the submodels are locally and globally asymptotically stable when the sub-model threshold parameters are less than unity. The model reproduction number due to co-use is shown to be the maximum of the two sub-model reproduction numbers. Sensitivity analysis reveals that the most sensitive parameters in the alcohol-methamphetamine co-use epidemic are the alcohol and methamphetamine recruitment rates β_1 and β_2 respectively. Using parameters values derived from the sub-model fittings to data, a population estimate of co-users of alcohol and methamphetamine under treatment is estimated with a prevalence of about 1%. Although the results show of a small proportion of co-users of alcohol and methamphetamine in the province, the prevalence curve is indicative of an endemic and continuous problem. The results are indicative of the need to promote social programs that raise awareness of the dangers posed by multiple substance abuse, through educational campaigns in learning institutions, social media and health institutions. Moreover, concerned authorities must focus on enhancing the quitting process in drug abuse while promoting support services to individuals after treatment to minimize relapse cases for those under rehabilitation.

Key words Alcohol · Methamphetamine · Co-use model · Latin Hypercube Sampling · Partial rank correlation coefficients · Multiple substance abuse.

1 Introduction

South Africa has experienced a continuous rise in multiple abuse of drugs, especially in the recent past [18]. According to a report by the South African Community Epidemiology Network on Drug and Use (SACENDU), alcohol still remains the primary and most preferred substance of abuse among patients seen at specialist treatment centres [20]. Furthermore, new and more dangerous drugs such as Methamphetamine, Cocaine, Marijuana (Dagga) and Heroin have increasingly become popular among alcohol and other drug users in South Africa [18]. Methamphetamine addiction and alcoholism remain the Western Cape Province's leading problems with substance abuse. Recent studies by the South Africa Medical Research Council in 2012, found that 28% of patients admitted to rehabilitation centres in the Western Cape were being treated for alcoholism, while 35% for methamphetamine [14]. These numbers do not only present a worrying trend but a serious public health quandary.

[*]Corresponding author: Email: *nyabadzaf@sun.ac.za*

Alcohol is known to have deleterious effects on the body's immune system. The short term effects of addiction may feature slowed down activity of the brain causing speech to slow and the irregular drift in body temperatures. The long term effects are however scary. Major body organs can be permanently damaged as they fight to cope with the constant flow of liquid poison around the circulatory system. The brain shrinks as exposure to alcohol deforms neurons and diminishes the cells. The heart is slowly weakened as it pumps contaminated blood around the body. The normal digestive process of the pancreas is sent to overdrive as it struggles to cope with both food and toxic alcohol. Eating causes extreme pain as the digestive organs become inflammable. The liver is repeatedly scourged, which can lead to total breakdown in its ability to function [1].

Methamphetamine on the other hand, is a highly addictive illicit drug. With over 26 million users worldwide [6], the demand, spread and abuse of this vicious stimulant has increased dramatically in the recent past. The bitter white crystalline powder, whose ingredients are readily available is popularly known as 'tik' in the streets of Cape town [18]. Internationally, methamphetamine abuse remains a major global health and social problem. The tremendous growth in the population of methamphetamine users in the Western Cape Province is documented to have reached epidemic levels [20].

It is a common knowledge that instead of latching onto a specific substance of abuse, substance users often abuse two or more substances during their substance using career. Young South Africans, tend to abuse drugs in combination [21]. Surprisingly, multiple drug users often admit to using a specific substance while seeking treatment services when infact they are on other substances. This act of denial or ignorance only complicates the treatment processes. Clinical research indicates that the habit of taking several substances at once in combination, degrades the process of detoxification during treatment programmes. Such individuals sometimes become addicted to more than one substance. Moreover, the resulting health consequences are often worsened. Despite the numerous negative consequences to the hosts, the trend of multiple substance abuse has continued to grow in recent years. Efforts to resolve the problem of multiple abuse of drugs is complicated by the fact that most, if not all, the treatment centres and medical facilities in South Africa only provide experienced services at treating single drug addiction cases [2]. Research work in [12], revealed that in comparison to single drug effects, alcohol-methamphetamine combination produces a greater elevation of heart beat and elation, which is arguably a motivation for the drug users who consider such effects as positive impacts of the drug combinations. Their data showed that methamphetamine combined with alcohol produced a profile of effects that was different from the effects of either drug alone. While there could be numerous reasons for using more than one substance, some of the attractions included the desire to increase, to balance and to maintain the effects of the primary substance of choice [2], to experience greater euphoria, and even longer hours of sleep. Clinical results as pointed out by Mendelson [13], indicated that the combined use of alcohol and methamphetamine results in increased heart rate coupled with heightened blood pressure beyond and above that seen which would be experienced by using methamphetamine alone. Other drug combinations with methamphetamine have equally produced intense effects to the users.

In treatment centres, individuals are treated for the primary substance they are addicted to. By treatment we mean the process of rehabilitating a drug addict. The data collected by SACENDU, reflects treatment for the primary substance of abuse for the different substances abused in all the provinces in South Africa. We present below Figure 1 which is Fig. 2, in the current summary of the SACENDU updates which shows the trends in the demand for heroin treatment as a primary substance of abuse for four regions; Western Cape (WC), Gauteng (GT),

Northern Region (NR) and KwaZulu natal (KZN).

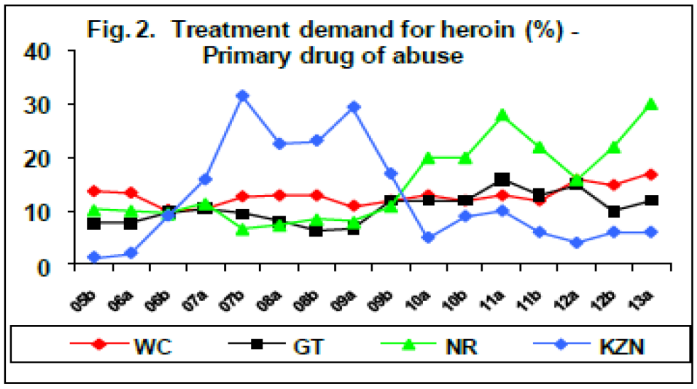


Figure 1: Source: *http://www.sahealthinfo.org/admodule/sacendu/2013-Dec-Update_Final.pdf*

Data on individuals who abuse more than one substance is not documented. Most substance abusers struggle with more than one intoxicant. It has been shown that recovering from drug abuse is much easier when only one drug is involved. The abuse of more than one substance will certainly increase the cost of treatment and relapses [5].

Very little has been done to estimate the number of individuals who abuse multiple substances in South Africa to the best of our knowledge. We argue that estimation can be done through the use of mathematical models. A sundry of research works on drug epidemic models have focussed on the abuse of a single substance, see for instance [4, 11, 15, 22]. Very little work has been done on the mathematical modelling of multiple abuse of substances. This can be attributed to lack of data on multiple abuse of substances. We ask: can we use the available data on primary substances of abuse to estimate the number of individuals who use more than one substance? We thus endeavour to model the dynamics of multiple abuse of substance. In this paper, we only consider a scenario in which an individual uses two different kinds of substances, in particular alcohol and methamphetamine for illustrative purposes. The model is an amalgamation of two submodels, one for alcohol abuse and the other for methamphetamine abuse. The submodels are then fitted to data for persons seeking treatment services on alcohol and methamphetamine addiction. The data is obtained from different treatment centers in the Western Cape province of South Africa by SACENDU [18]. Once each submodel has been fitted to the data, the corresponding model parameters are obtained. The model parameters are then used in the co-use model to estimate the number of individuals who get into treatment centres due to simultaneous use of alcohol and methamphetamine. The main objective of this paper is to use data on individuals seeking treatment for alcohol and methamphetamine addiction to estimate the number of individuals who get into treatment centres as a result of the two substances. We also present some mathematical analysis of the main model and submodels.

The rest of the paper is organized as follows. The co-use model of alcohol and methamphetamine, together with the sub-models are formulated and analysed in Sections 2, 3, 4 and 5. Numerical simulation of the model, parameter estimation, and sensitivity analysis are discussed and analysed in Section 6. In addition, a curve showing approximate population of combined users of both alcohol and methamphetamine is shown in Section 6. The paper is concluded in Section 7 with relevant discussions and recommendations.

2 Co-use Model Formulation

In this section we formulate a simple mathematical model that captures the co-use of alcohol and methamphetamine in the population. The total human population of size $N(t)$ at any time $t \geq 0$ is subdivided into seven compartments or classes of those individuals that have never taken alcohol or used methamphetamine, but are at risk of using either substance, denoted by S (they are also termed susceptibles); alcohol users not under treatment U_a; alcohol users under treatment R_a; methamphetamine users who are not under treatment U_t; methamphetamine users under treatment R_t; users of both alcohol and methamphetamine who are not under treatment U_{at} and users of both alcohol and methamphetamine under treatment R_{at}. Therefore, the total population at any time t is given by

$$N(t) = U_a(t) + R_a(t) + U_t(t) + R_t(t) + U_{at}(t) + R_{at}(t). \tag{1}$$

Individuals get recruited into the susceptible population through birth and immigration at a constant rate, Λ. The susceptibles become alcohol and/or methamphetamine abusers through interactive activities with friends, family members and colleagues in work places who use such substances. This is mainly driven by peer pressure. We thus assume that substance abuse spreads like a disease that spreads through contact or proximity to pathogen carriers. The class of substance abusers is often divided into light/moderate users and heavy users, see for instance [15, 16]. For simplicity, we combine these two classes because our primary interest is in those who abuse both alcohol and methamphetamine. Assuming homogeneous mixing of populations, non-alcohol drinkers acquire alcohol drinking habits at rate λ_1 with

$$\lambda_1 = \beta_1 \left(\frac{U_a + \zeta_1 R_a + \zeta_2 U_{at} + \zeta_3 R_{at}}{N} \right), \tag{2}$$

with the parameter β_1 denoting the effective contact rate (i.e. the contact with an alcohol drinker that will result in one taking alcohol). To account for the decreased chances of becoming an alcohol drinker after being in contact with alcoholics and co-users in rehabilitation, it is assumed here that those under treatment tend to have lower recruitment aptness relative to addicts. Those under the influence of alcohol are more likely to be co-users when the get in contact with those who abuse both substances and not under rehabilitation. Therefore, $\zeta_1,\ \zeta_3 < 1$, while $\zeta_2 > 1$. Similarly, individuals get initiated into using methamphetamine at the rate given by

$$\lambda_2 = \beta_2 \left(\frac{U_t + \epsilon_1 R_t + \epsilon_2 U_{at} + \epsilon_3 R_{at}}{N} \right), \tag{3}$$

where the parameter β_2 is the effective contact rate for initiation into methamphetamine abuse. The modification parameters ϵ_1 and ϵ_3 are both assumed to be less than unity. This would account for the reduced tendency to initiate new users into methamphetamine abuse by methamphetamine users under treatment. Like in the case of alcohol, we assume that $\epsilon_2 > 1$.

Individuals in the compartment U_a begin to use methamphetamine at a rate $\eta_a \lambda_2$ and move into the compartment U_{at} with $\eta_t \geq 1$ accounting for the increased chances of using methamphetamine by alcohol users when compared to non-alcohol users. Individuals not under treatment may die due to alcohol related causes at a rate δ_1 or die naturally at a rate μ, a rate that is also assumed for the rest of the population. Furthermore, those that abuse alcohol may seek treatment for alcohol dependence at a rate σ_1 or altogether, quit alcohol drinking at a rate ρ_3. Alcohol users, upon successful treatment in the compartment R_a, permanently quit alcohol at

the rate ρ_4. We assume that those that quit, do so permanently. Ideally, quitters should be allowed to relapse. In this model, we only assume relapse in the form of rehabilitation failure. This is a plausible assumption in the Western Cape scenario where drop-out rates of patients at facilities may be as high as 40% [19].

Similarly, susceptible individuals in S, get recruited into the class U_t at a rate $\lambda_2(t)$ through contact with those using methamphetamine. Some individuals in U_t acquire alcohol drinking habits at the rate $\eta_t\lambda_1$ and move into the class U_{at} with $\eta_t \geq 1$ accounting for the increased chances of drinking alcohol for methamphetamine users when compared to those not using methamphetamine. Others may enter into rehabilitation in compartment R_t at a rate σ_3 and may relapse back to U_t at a rate γ_3. Individuals in the class U_t may die due to methamphetamine-related causes at a rate δ_3 or permanently quit methamphetamine at a rate ρ_7.

Users of both alcohol and methamphetamine in the class, U_{at} may revert to alcohol abuse only at a rate ρ_1 or to methamphetamine abuse only at a rate ρ_2 upon quitting either substances of abuse. In addition, individuals in this class may die as a result of death related to abuse of both alcohol and methamphetamine such as liver cirrhosis and pancreatitis at a rate δ_2. They progress into the treatment class R_{at} at a rate σ_2. Individuals under treatment for alcohol and methamphetamine abuse in R_{at}, may relapse into alcohol-methamphetamine abuse compartment at a rate γ_2 or quit drinking of alcohol and relapse to U_t, at a rate γ_5. Similarly, they may quit methamphetamine and revert to the class of alcohol users not under treatment U_a at a rate γ_4. We also allow permanent quitting for individuals in the classes R_{at} and R_t at rates ρ_5 and ρ_6 respectively. We assume here that permanent quitting results from effective rehabilitation programs. Clearly, the presented model has additional assumptions. Individuals under treatment take alcohol and/or methamphetamine as the treatment process is taken to be outpatient and hence can initiate others. Although quitting both substances at the same time is unlikely, in this model, we allow permanent quitting of individuals in rehabilitation for both alcohol and methamphetamine.

The flow of individuals between classes is given in Figure 2.

From the above assumptions, parameter definitions and variables, we have the following model system of differential equations, with non-negative initial conditions that describe the dynamics of the co-use alcohol and methamphetamine epidemic. The compartment Q is considered to be superfluous.

$$\left.\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \Lambda - (\mu + \lambda_1 + \lambda_2)S, \\
\frac{\mathrm{d}U_a}{\mathrm{d}t} &= \lambda_1 S + \rho_1 U_{at} + \gamma_1 R_a + \gamma_4 R_{at} - \eta_a\lambda_2 U_a - (\mu + \sigma_1 + \delta_1 + \rho_3)U_a, \\
\frac{\mathrm{d}R_a}{\mathrm{d}t} &= \sigma_1 U_a - (\mu + \gamma_1 + \rho_4)R_a, \\
\frac{\mathrm{d}U_t}{\mathrm{d}t} &= \lambda_2 S + \rho_2 U_{at} + \gamma_3 R_t + \gamma_5 R_{at} - \eta_t\lambda_1 U_t - (\mu + \sigma_3 + \delta_3 + \rho_7)U_t, \\
\frac{\mathrm{d}R_t}{\mathrm{d}t} &= \sigma_3 U_t - (\mu + \gamma_3 + \rho_6)R_t, \\
\frac{\mathrm{d}U_{at}}{\mathrm{d}t} &= \eta_a\lambda_2 U_a + \eta_t\lambda_1 U_t + \gamma_2 R_{at} - (\mu + \rho_1 + \rho_2 + \delta_2 + \sigma_2)U_{at}, \\
\frac{\mathrm{d}R_{at}}{\mathrm{d}t} &= \sigma_2 U_{at} - (\mu + \gamma_2 + \gamma_4 + \gamma_5 + \rho_5)R_{at},
\end{aligned}\right\} \tag{4}$$

$$S(0) = S_0,\ U_a(0) = U_{a0},\ R_a(0) = R_{a0},\ U_t(0) = U_{t0},\ R_t(0) = R_{t0},\ U_{at}(0) = U_{at0},\ R_{at}(0) = R_{at0}$$

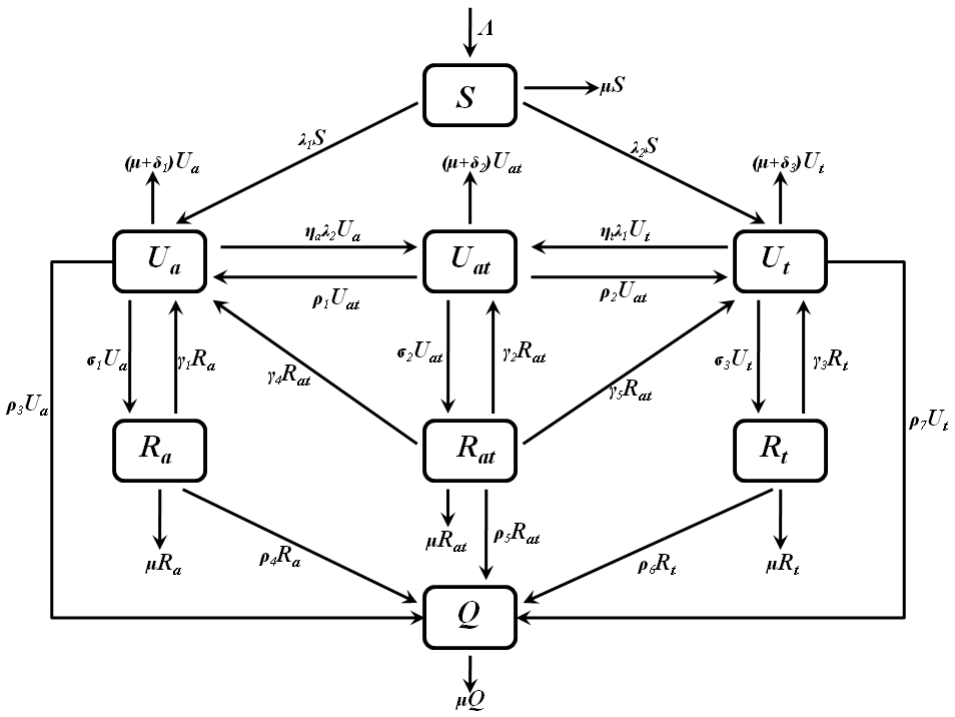


Figure 2: A compartmental representation of the epidemic of alcohol-methamphetamine co-use

where

$$\lambda_1 = \beta_1 \left(\frac{U_a + \zeta_1 R_a + \zeta_2 U_{at} + \zeta_3 R_{at}}{N} \right) \quad \text{and} \quad \lambda_2 = \beta_2 \left(\frac{U_t + \epsilon_1 R_t + \epsilon_2 U_{at} + \epsilon_3 R_{at}}{N} \right). \tag{5}$$

3 Model Analysis

3.1 Invariant Region

For every dynamical system, it is important to establish the long term behaviour of its solutions. The formulated model system model monitors changes in human population. We therefore assume that the variables and the parameters used are all non-negative for all time, $t \geq 0$.

Lemma 1. *The feasible region,* Ω *defined by*

$$\Omega = \left\{ (S(t), U_a(t), R_a(t), U_t(t), R_t(t), U_{at}(t), R_{at}(t)) \in \mathbb{R}_+^7 | 0 \leq N \leq \frac{\Lambda}{\mu} \right\}$$

with initial conditions $S_0 > 0, U_{a0} \geq 0, R_{a0} \geq 0, U_{t0} \geq 0, R_{t0} \geq 0, U_{at0} \geq 0,$ *and* $R_{at0} \geq 0,$ *is positively invariant and attracting with respect to system* (4) *for all* $t > 0$.

Proof. The total populations in this model is clearly not constant. Therefore, the evolution change in the population is given by

$$\begin{aligned} \frac{\mathrm{d}N}{\mathrm{d}t} =& \Lambda - \mu N - (\delta_1 U_a + \delta_2 U_{at} + \delta_3 U_t) - (\rho_3 U_a + \rho_4 R_a + \rho_5 R_{at} + \rho_6 R_t + \rho_7 U_t), \\ \leq& \Lambda - \mu N. \end{aligned}$$

It can easily be seen that

$$N(t) \leq \frac{\Lambda}{\mu} + \left(N_0 - \frac{\Lambda}{\mu}\right)\exp(-\mu t). \tag{6}$$

From equation (6), we observe that as $t \to \infty$, $N(t) \to \frac{\Lambda}{\mu}$. So that if $N_0 \leq \frac{\Lambda}{\mu}$ then $\lim_{t\to\infty} N(t) = \frac{\Lambda}{\mu}$. Clearly $\frac{\Lambda}{\mu}$ is the upper bound for of N. On the other hand, if $N_0 > \frac{\Lambda}{\mu}$, then $N(t)$ will decrease to $\frac{\Lambda}{\mu}$ as $t \to \infty$. This means that if $N_0 > \frac{\Lambda}{\mu}$, then the solution $(S(t), U_a(t), R_a(t), U_t(t), R_t(t), U_{at}(t), R_{at}(t))$ enters Ω or approaches it asymptotically. We thus conclude that the region Ω is positively invariant under the flow induced by system (4). Epidemiologically, the system model (4) is said to be well-posed in the region Ω. We can thus study the system (4) in the closed set Ω. □

3.2 Positivity

We prove that all solutions of the system (4) with positive initial data will remain positive for all times $t \geq 0$.

Lemma 2.
Let the initial conditions of the system (4) *be* $S_0 > 0, U_{a0} \geq 0, R_{a0} \geq 0, U_{t0} \geq 0, R_{t0} \geq 0, U_{at0} \geq 0, R_{at0} \geq 0$ *for all* $t > 0$. *Then the solutions* $(S(t), U_a(t), R_a(t), U_t(t), R_t(t), U_{at}(t), R_{at}(t))$ *of the model* (4) *remains positive for all time* $t > 0$.

Proof. Let us assume that T is the maximum time for the epidemic. That is, assume, $T = \sup\{t > 0, S > 0, U_a \geq 0, R_a \geq 0, U_t \geq 0, R_t \geq 0, U_{at} \geq 0 \quad and \quad R_{at} \geq 0\} \in [0, t]$. Therefore, $T > 0$ and from the first equation of model system (4), we obtain

$$\frac{\mathrm{d}}{\mathrm{d}t}\left[S(t)\exp\left\{\mu t + \int_0^t (\lambda_1(s) + \lambda_2(s))\mathrm{d}s\right\}\right] = \Lambda\exp\left[\mu t + \int_0^t (\lambda_1(s) + \lambda_2(2))\mathrm{d}s\right],$$

So that

$$S(T) \geq S(0)\exp\left[-\left\{\mu T + \int_0^T (\lambda_1(s) + \lambda_2(s))\mathrm{d}s\right\}\right] +$$
$$\exp\left[-\left\{\mu T + \int_0^T (\lambda_1(s) + \lambda_2(s))\mathrm{d}s\right\}\right]\left(\int_0^T \Lambda\exp\left[\mu T + \int_0^{\widehat{T}} ((\lambda_1(w) + \lambda_2(w))\mathrm{d}w\right]\mathrm{d}\widehat{T}\right) > 0.$$

Hence, $S(T) \geq 0$ for $\forall T > 0$.
Now, from equation (4), we have;

$$\begin{aligned}\frac{\mathrm{d}U_a}{\mathrm{d}t} &= \lambda_1 S + \rho_1 U_{at} + \gamma_1 R_a + \gamma_1 R_{at} - \eta_a\lambda_2 U_a - (\mu + \sigma_1 + \delta_1 + \rho_3)U_a,\\ &\geq -(\eta_a\lambda_2 - \mu + \sigma_1 + \delta_1 + \rho_3)U_a,\\ U_a(t) &\geq U_{a0}\exp\left[-\{(\mu + \sigma_1 + \delta_1 + \rho_3)t + \int_0^t \eta_a\lambda_2(s)\mathrm{d}s\}\right] > 0.\end{aligned} \tag{7}$$

It can similarly shown that $U_t \geq 0$, $R_t \geq 0$, $U_{at} \geq 0$ and $R_{at} \geq 0$. Thus the solutions of (4) remain positive for all $t \geq 0$. □

3.3 Equilibrium Points of the Co-use Model

Upon solving the derived system from the model system (4), we obtain in terms of the forces of infections λ_1 and λ_2, the model equilibrium states $(S^*, U_a^*, R_a^*, U_t^*, R_t^*, U_{at}^*, R_{at}^*)$, such that

$$\left.\begin{aligned} S^* =& \frac{\Lambda}{\mu+\lambda_1^*+\lambda_2^*},\\ R_{at}^* =& \frac{\sigma_2}{b_6}U_{at}^*,\\ R_t^* =& \frac{\sigma_3}{b_4}U_t^*,\\ R_a^* =& \frac{\sigma_1}{b_2}U_a^*,\\ U_a^* =& \Theta_1+\Theta_2 U_{at}^*,\\ U_t^* =& \Theta_3+\Theta_4 U_{at}^*,\\ U_{at}^* =& \frac{\eta_t\lambda_1\Theta_3+\eta_a\lambda_2\Theta_1}{b_5(1-\Phi_3)-(\eta_a\lambda_2\Theta_2+\eta_t\lambda_1\Theta_4)}. \end{aligned}\right\} \tag{8}$$

where
$\Theta_1 = \frac{\mathcal{J}_1}{\Psi_1}, \Theta_2 = \frac{\mathcal{K}_1}{\Psi_1}, \Theta_3 = \frac{\mathcal{J}_2}{\Psi_2}, \Theta_4 = \frac{\mathcal{K}_2}{\Psi_2}, \mathcal{J}_1 = \frac{\Lambda\lambda_1 b_6}{\mu+\lambda_1+\lambda_2}, \mathcal{J}_2 = \frac{\Lambda\lambda_2 b_6}{\mu+\lambda_1+\lambda_2},$
$\mathcal{K}_1 = b_6\rho_1+\sigma_2\gamma_4, \mathcal{K}_2 = b_6\rho_2+\sigma_2\gamma_5, \Psi_1 = b_1b_6(1-\Phi_1+\frac{\eta_a\lambda_2}{b_1}), \Psi_2 = b_3b_6(1-\Phi_2+\frac{\eta_t\lambda_1}{b_3}),$
$\Phi_1 = \frac{\sigma_1\gamma_1}{b_1b_2}, \Phi_2 = \frac{\sigma_3\gamma_3}{b_3b_4}, \ \Phi_3 = \frac{\sigma_2\gamma_2}{b_5b_6}, \ b_1 = \mu+\sigma_1+\delta_1+\rho_3, \ b_2 = \mu+\gamma_1+\rho_4,$
$b_3 = \mu+\sigma_3+\delta_3+\rho_7, \ b_4 = \mu+\gamma_3+\rho_6, b_5 = \mu+\rho_1+\rho_2+\delta_2+\sigma_2, \ b_6 = \mu+\gamma_2+\gamma_4+\gamma_5+\rho_5.$

Given that

$$\frac{\lambda_1}{\lambda_2} = \frac{\beta_1(U_a+\zeta_1R_a+\zeta_2U_{at}+\zeta_3R_{at})}{\beta_2(U_t+\epsilon_1R_t+\epsilon_2U_{at}+\epsilon_3R_{at})}, \tag{9}$$

the expressions in (8) when substituted into (9) yield the polynomial

$$p(\lambda_1,\lambda_2) = \lambda_1(\alpha_0+\alpha_1\lambda_1+\alpha_2\lambda_2+\alpha_3\lambda_1\lambda_2+\alpha_4\lambda_1^{*2}+\alpha_5\lambda_2^{*2}), \tag{10}$$

where

$$\begin{aligned} \alpha_0 =& b_1b_2b_3b_4b_5b_6(1-\Phi_1)(1-\Phi_2)(1-\Phi_3)(\mathcal{R}_{t0}-\mathcal{R}_{a0}),\\ \alpha_1 =& b_4\beta_1\eta_t(b_2+\zeta_1\sigma_1)(\mathcal{K}_1-b_5b_6(1-\Phi_3))+\mathcal{M}\beta_2(b_6\epsilon_2+\sigma_2\epsilon_3)+\mathcal{K}_2b_2\beta_2\eta_a(b_4+\epsilon_1\sigma_3),\\ \alpha_2 =& -\beta_1(b_6\zeta_2+\zeta_3\sigma_2)\mathcal{M}-\mathcal{K}_1b_4\beta_1\eta_t(b_2+\zeta_1\sigma_1)+b_2\beta_2\eta_a(b_4+\epsilon_1\sigma_3)(b_5b_6(1-\Phi_3)-\mathcal{K}_1),\\ \alpha_3 =& \alpha_4+\alpha_5,\\ \alpha_4 =& b_2b_4\beta_2\eta_a\eta_t(b_6\epsilon_2+\epsilon_3\sigma_2), \quad \text{and} \quad \alpha_5 = -b_2b_4\beta_1\eta_a\eta_t(b_6\zeta_2+\zeta_3\sigma_2) \end{aligned}$$

and $\mathcal{M} = b_2b_4(b_3\eta_a(1-\Phi_2)+b_1\eta_t(1-\Phi_1))$.

Note that if $\lambda_1 = 0$, then clearly $\lambda_2 = 0$. This gives the co-use-free equilibrium

$$\mathcal{E}_{at}^0 = \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0, 0\right).$$

The co-use-free equilibrium is a scenario in which a combined abuse of alcohol and methamphetamine does not exist in a community.

The solutions to the remaining part of the polynomial (10), described by equation (11) defines the possible endemic states of the model system (4). A scenario in which the combined abuse of alcohol and methamphetamine persists in the society. We thus have

$$p(\lambda_1, \lambda_2) = \alpha_0 + \alpha_1\lambda_1 + \alpha_2\lambda_2 + \alpha_3\lambda_1\lambda_2 + \alpha_4\lambda_1^2 + \alpha_5\lambda_2^2. \tag{11}$$

The existence of the endemic stable states for the co-use epidemic model, depend on the solutions of (11). The solutions must however be real and positive. Determining the explicit existence of the equilibria in mathematically intractable. We however have illustrate the possible equilibria by choosing specific parameter values and graphically present the plot of $p(\lambda_1, \lambda_2)$. The polynomial (11) is represented graphically as shown in Figure 3.

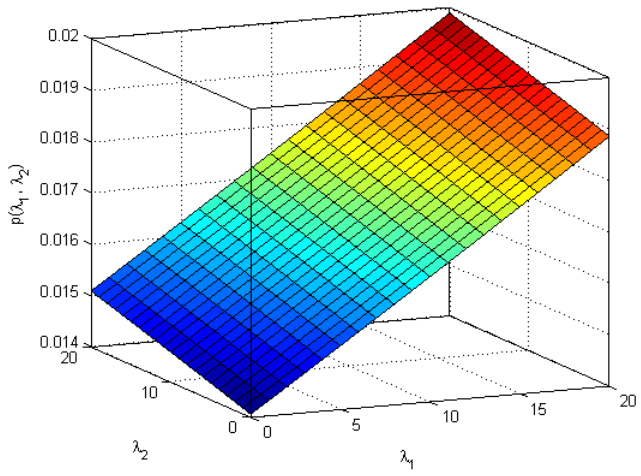


Figure 3: Endemic equilibrium points of the co-use model for the parameters values: $\mu = 0.02$, $\beta_1 = 0.25$, $\beta_2 = 0.45$, $\gamma_1 = 0.5$, $\gamma_2 = 0.4$, $\gamma_3 = 0.23$, $\gamma_4 = 0.1$, $\gamma_5 = 0.12$, $\delta_1 = 0.03$, $\delta_2 = 0.04$, $\delta_3 = 0.04$, $\sigma_1 = 0.53$, $\sigma_2 = 0.3$, $\sigma_3 = 0.421$, $\rho_1 = 0.2$, $\rho_2 = 0.03$, ρ_3= 0.35, $\rho_4 = 0.45$, $\rho_5 = 0.35$, $\rho_6 = 0.78$ $\rho_7 = 0.4$, $\eta_a = 1.005$, $\eta_t = 1.005$, $\zeta_1 = 0.85$, $\zeta_2 = 1.05$, $\zeta_3 = 0.805$, $\epsilon_1 = 0.05$, $\epsilon_2 = 1.003$, $\epsilon_3 = 0.04$, $\Lambda = 0.29$

From the surface plot in Figure 3, we notice that there exists multiple endemic steady states for the co-use epidemic model. Such steady states only exists for positive values of $p(\lambda_1, \lambda_2)$. We can not precisely state the conditions under wich the endemic steady states exist, but the fact that we have established the existance of the endemic steady states, it guarantees endemicity of multiple substance abuse.

3.4 Reproduction Number of the Co-use Model

The reproduction number of the co-use model system (4), denoted by R_{at}, is the spectral radius of the next generation matrix (FV^{-1}) as illustrated in [24]. Using the notations in [24] to model system (4), the matrices for new infections terms (F) and the transfer terms (V) at the drug-free equilibrium are respectively given by

$$\mathrm{F} = \begin{pmatrix} \beta_1 & \beta_1\zeta_1 & 0 & 0 & \beta_1\zeta_2 & \beta_1\zeta_3 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_2 & \epsilon_1\beta_2 & \epsilon_2\beta_2 & \epsilon_3\beta_2 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \text{ and } \mathrm{V} = \begin{pmatrix} b_1 & -\gamma & 0 & 0 & -\rho_1 & -\rho_4 \\ -\sigma_1 & b_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & b_3 & -\gamma_3 & -\rho_2 & -\gamma_5 \\ 0 & 0 & -\sigma_3 & b_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & b_5 & -\gamma_2 \\ 0 & 0 & 0 & 0 & -\gamma_2 & b_6 \end{pmatrix}. \tag{12}$$

R_{at} is thus given by

$$\mathcal{R}_{at} = \max\left\{ \frac{\beta_1[b_2 + \zeta_1\sigma_1]}{b_1 b_2[1-\Phi_1]}, \quad \frac{\beta_2[b_4 + \epsilon_1\sigma_3]}{b_3 b_4[1-\Phi_2]} \right\}, \tag{13}$$

where $\Phi_1 = \frac{\gamma_1\sigma_1}{b_1 b_2}$ and $\Phi_2 = \frac{\gamma_3\sigma_3}{b_3 b_4}$. The local stability of the co-use-free equilibrium state can be determined through the next generation matrix method in [24]. Following [24], we have the following results on the local stability of $\mathcal{E}^0_{at}$.

Theorem 1. *The alcohol-methamphetamine-free equilibrium denoted by $\mathcal{E}^0_{at}$ is locally asymptotically stable if $\mathcal{R}_{at} < 1$ and unstable if $\mathcal{R}_{at} > 1$.*

Because we could not explicitly determine the endemic equilibria, we comprehensively analyse the sub-models of the co-use model and resort to numerical simulations for further applications of the co-use model.

4 Alcohol Abuse Model

This model is given when $U_t = R_a = U_{at} = R_{at} = 0$. The co-use model (4) reduces to the following system of equations given by

$$\left.\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \Lambda - (\mu + \bar{\lambda_1})S, \\ \frac{\mathrm{d}U_a}{\mathrm{d}t} &= \bar{\lambda_1}S + \gamma_1 R_a - (\mu + \sigma_1 + \delta_1 + \rho_3)U_a, \\ \frac{\mathrm{d}R_a}{\mathrm{d}t} &= \sigma_1 U_a - (\mu + \gamma_1 + \rho_4)R_a, \end{aligned}\right\} \tag{14}$$

where

$$\bar{\lambda_1} = \frac{\beta_1(U_a + \zeta_1 R_a)}{N}.$$

The alcohol model (14) has an alcohol-free equilibrium given by $\mathcal{E}^a_0 = \left(\frac{\Lambda}{\mu}, 0, 0\right)$.

4.1 Reproduction Number for the Alcohol Epidemic Model ($\mathcal{R}_{a0}$)

We establish a threshold parameter resulting from the alcohol model. We are interested in establishing the possible number of new cases that would be produced by a single alcohol user, assuming the absence of the other drugs or substances of abuse, in a completely susceptible population.

Using the approach and notations described in [24], the matrices for the new infections terms and the transfer terms, denoted by F and V respectively at the alcohol-free equilibrium are given as follows,

$$\mathrm{F} = \begin{pmatrix} \beta_1 & \beta_1\zeta_1 \\ 0 & 0 \end{pmatrix} \quad \text{and} \quad \mathrm{V} = \begin{pmatrix} (\mu + \delta_1 + \rho_3 + \sigma_1) & -\gamma_1 \\ -\sigma_1 & (\mu + \gamma_1 + \rho_4) \end{pmatrix}. \tag{15}$$

It therefore follows that effective reproduction number due to alcohol abuse is given by

$$\mathcal{R}_{a0} = \frac{\beta_1[b_2 + \zeta_1\sigma_1]}{b_1 b_2[1 - \Phi_1]} \quad \text{where} \quad \Phi_1 = \frac{\gamma_1\sigma_1}{b_1 b_2}. \tag{16}$$

We now present the stability of the equilibrium points established from the alcohol abuse model (14).

4.2 Global Stability of the Alcohol-free Equilibrium

Theorem 2. *$\mathcal{E}_0^a$ is globally asymptotically stable in $\bar{\Omega} \subset \Omega$ if $\mathcal{R}_{a0} < 1$.*

Proof. Let

$$\mathrm{V} = b_2 U_a + (\beta_1\zeta_1 + \gamma_1) R_a, \tag{17}$$

be a candidate Lyapunov function.

The derivative of V with respect to time (t) is given by

$$\frac{\mathrm{dV}}{\mathrm{d}t} = [b_2(\beta_1 - b_1) + (\beta_1\zeta_1 + \gamma_1)\sigma_1]U_a, \tag{18}$$

$$= b_1 b_2 (1 - \Phi_1)[\mathcal{R}_{a0} - 1]U_a. \tag{19}$$

Noting that all the model parameters are positive, it follows that $\dot{\mathrm{V}} \leq 0$ for $R_{ao} < 1$ with $\dot{\mathrm{V}} = 0$ only if $U_a = 0$. Hence, V is a Lyapunov function on $\bar{\Omega} = (S, U_a, R_a)$. Since $\bar{\Omega}$ is invariant and attracting, it follows that the largest possible invariant set in $\{(S, U_a, R_a) \in \bar{\Omega} : \dot{\mathrm{V}} = 0\}$ is the singleton $\{\mathcal{E}_0^a\}$. Therefore, by the La-Salle's invariance principle [9], every solution to the equation in the alcohol-only model in system (14) with initial conditions in $\bar{\Omega}$ approaches $\mathcal{E}_0^a$ as time approaches infinity. That is, as $t \to \infty$, $(U_a(t), R_a(t)) \to (0, 0)$. Substituting for $U_a = R_a = 0$ into the model system (14), gives $S \to \frac{\Lambda}{\mu}$ as $t \to \infty$. Thus $(S(t), U_a(t), R_a(t)) \to \left(\frac{\Lambda}{\mu}, 0, 0\right)$ as $t \to \infty$ for $\mathcal{R}_{ao} < 1$ so that $\mathcal{E}_0^a$ is globally asymptotically stable in $\bar{\Omega}$ if $\mathcal{R}_{a0} < 1$. □

4.3 Endemic Equilibrium and its Stability

Upon equating model system (14) to zero and solving for S^*, U_a^* and R_a^* in terms of the force of infection λ_1^*, we obtain the following expressions.

$$S^* = \frac{\Lambda}{\mu + \bar{\lambda_1^*}}, \quad U_a^* = \frac{\Lambda\bar{\lambda_1^*} b_2}{b_1 b_2(\mu + \bar{\lambda_1^*})(1 - \Phi_1)}, \quad R_a^* = \frac{\Lambda\bar{\lambda_1^*}\sigma_1}{b_1 b_2(\mu + \bar{\lambda_1^*})(1 - \Phi_1)}. \tag{20}$$

Furthermore, on substituting equations in (20) into (15), we obtain the polynomial

$$\bar{\lambda_1^*}\left\{(1 - \mathcal{R}_{a0}) + \bar{\lambda_1^*}\left(\frac{b_2 + \sigma_1}{b_1 b_2[1 - \Phi_1]}\right)\right\} = 0. \tag{21}$$

From the polynomial (21), $\bar{\lambda_1^*} = 0$ corresponds to the alcohol free-equilibrium. A scenario in which there is no alcohol abuse in the community.
Similarly, $\bar{\lambda_1^*} = \left\{\frac{b_1 b_2(1-\phi_1)}{b_2+\gamma_1}(\mathcal{R}_{a0}-1)\right\}$ which exists for $\mathcal{R}_{a0} > 1$ corresponds to the endemic equilibrium, a state in which alcohol abuse persists in the community. Therefore, the alcohol endemic equilibrium point(s) is given by $\mathcal{E}_1^a = (S^*, U_a^*, R_a^*)$ where S^*, U_a^* and R_a^* are as described in equation (20) and exists only if $R_{a0} > 1$.

4.4 Global Stability of the Alcohol-endemic Equilibrium Point, $\mathcal{E}_1^a$

We show that if the population is constant, the endemic steady state $\mathcal{E}_1^a$, is globally asymptotically stable. We thus assume that

$$\Lambda = \mu N + (\delta_1 + \rho_3)U_a + \rho_4 R_a. \tag{22}$$

The differential equations in system (14), become

$$\left.\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= (\mu + \delta_1 + \rho_3)U_a + (\mu + \rho_4)R_a - \lambda_1 S, \\ \frac{\mathrm{d}U_a}{\mathrm{d}t} &= \lambda_1 S + \gamma_1 R_a - (\mu + \delta_1 + \rho_3 + \sigma_1)U_a, \\ \frac{\mathrm{d}R_a}{\mathrm{d}t} &= \sigma_1 U_a - (\mu + \gamma_1 + \rho_4)R. \end{aligned}\right\} \tag{23}$$

Since $N = S + U_a + R_a$, is a constant, we let S, U_a and R_a:

$$s = \frac{S}{N}, v = \frac{U_a}{N} \quad \text{and} \quad w = \frac{R_a}{N}.$$

We have a non-dimensionalized system given by

$$\left.\begin{aligned} \dot{s} &= (\mu + \delta_1 + \rho_3)v + (\mu + \rho_4)w - \beta_1(v + \zeta_1 w)s, \\ \dot{v} &= \beta_1(v + \zeta_1 w)s + \gamma_1 w - (\mu + \delta_1 + \rho_3 + \sigma_1)v, \\ \dot{w} &= \sigma_1 v - (\gamma_1 + \rho_4 + \mu)w. \end{aligned}\right\} \tag{24}$$

We argue here that system (24) has a unique endemic equilibrium following the analysis of the original model. We thus have the following theorem.

Theorem 3. *The alcohol-endemic equilibrium $\mathcal{E}_1^a$ is globally asymptotically stable whenever $\mathcal{R}_{a0}$ is greater than unity, and the if the population is constant within the modelling time.*

Proof. We propose a suitable Lyapunov function $\mathcal{V}$ such that

$$\mathcal{V} = \left(s - s^* - s^* \ln \frac{s}{s^*}\right) + A\left(v - v^* - v^* \ln \frac{v}{v^*}\right) + B\left(w - w^* - w^* \ln \frac{w}{w^*}\right). \tag{25}$$

The positive constants A and B are to be determined. We observe that from the proposed Lyapunov function in equation (25), the first partial derivatives with respect to any of the state variables is given by

$$\frac{\partial \mathcal{V}}{\partial s} = \left(1 - \frac{s^*}{s}\right), \quad \frac{\partial \mathcal{V}}{\partial v} = A\left(1 - \frac{v^*}{v}\right), \quad \frac{\partial \mathcal{V}}{\partial w} = B\left(1 - \frac{w^*}{w}\right), \tag{26}$$

are all zero at the corresponding alcohol-endemic steady state. That is, at the endemic steady states, $s = s^*$, $v = v^*$ and $w = w^*$.

In addition, the second partial derivatives of $\mathcal{V}$ with respect to any of the three state variables are given as follows;

$$\frac{\partial^2 \mathcal{V}}{\partial s^2} = \frac{s^*}{s^2}, \quad \frac{\partial^2 \mathcal{V}}{\partial v^2} = A\frac{v^*}{v^2} \quad \text{and} \quad \frac{\partial^2 \mathcal{V}}{\partial w^2} = B\frac{w^*}{w^2}. \tag{27}$$

We observe from equation (27) that all the second partial derivatives are positive. This indicates that the alcohol endemic equilibrium is the minimum of each of the state variables.

The time derivative of the Lyapunov function in (25) is given by

$$\dot{\mathcal{V}} = \left(1 - \frac{s^*}{s}\right)\dot{s} + A\left(1 - \frac{v^*}{v}\right)\dot{v} + B\left(1 - \frac{w^*}{w}\right)\dot{w}. \tag{28}$$

Substituting for $\dot{s}$, $\dot{v}$ and $\dot{w}$ from system (24), we have

$$\dot{\mathcal{V}} = \left(1 - \frac{s^*}{s}\right)[av + (\mu+\rho_4)w - \beta_1(v+\zeta_1 w)s] + \left(1 - \frac{v^*}{v}\right)A[\beta_1(v+\zeta_1 w)s + \gamma_1 w - b_1 v] + \left(1 - \frac{w^*}{w}B[\sigma_1 v - b_2 w\right). \tag{29}$$

where $a = \mu + \delta_1 + \rho_3$, $\quad b_1 = \mu + \gamma_1 + \rho_4$ and $b_2 = \mu + \delta_1 + \rho_3 + \sigma_1$.

We now use the system of equation (24) at $\mathcal{E}_1^a$ to obtain:

$$a = \frac{\beta_1(v^* + \zeta_1 w^*)s^* - (\mu+\rho_4)w^*}{v^*}, \quad b_1 = \frac{\beta_1(v^* + \zeta_1 w^*)s^* + \gamma_1 w^*}{v^*} \quad \text{and} \quad b_2 = \frac{\sigma_1 v^*}{w^*}. \tag{30}$$

We now substitute the terms in equation (30) into equation (29) so that

$$\begin{aligned}\dot{\mathcal{V}} = {} & \left(1 - \frac{s^*}{s}\right)\left[\beta_1 v^* s^*\left(\frac{v}{v^*} - \frac{vs}{v^* s^*}\right) + \beta_1\zeta_1 w^* s^*\left(\frac{v}{v^*} - \frac{ws}{w^* s^*}\right) + (\mu+\rho_4)w^*\left(\frac{v}{v^*} + \frac{w}{w^*}\right)\right] \\ & + A\left(1 - \frac{v^*}{v}\right)\left[\beta_1 v^* s^*\left(-\frac{v}{v^*} - \frac{vs}{v^* s^*}\right) + \beta_1\zeta_1 w^* s^*\left(-\frac{v}{v^*} + \frac{ws}{w^* s^*}\right) + \gamma_1 w^*\left(\frac{v}{v^*} + \frac{w}{w^*}\right)\right] \\ & + B\left(1 - \frac{w^*}{w}\right)\left[\sigma_1 v^*\left(\frac{v}{v^*} - \frac{w}{w^*}\right)\right].\end{aligned} \tag{31}$$

Let $\frac{s}{s^*} = J$, $\quad \frac{v}{v^*} = K$, $\quad$ and $\quad \frac{w}{w^*} = L$.

Therefore, $\dot{V}$ becomes

$$\begin{aligned}\dot{\mathcal{V}} = {} & \beta_1 v^* s^*\left[\left(2K - JK - \frac{K}{J}\right) + A(1 + JK - (K+J))\right] + (\mu+\rho_4)\left[(L+K) - \left(\frac{L}{J} + \frac{K}{J}\right)\right]w^* \\ & + \beta_1\zeta_1 w^* s^*\left[(K+L) - \left(JL + \frac{K}{J}\right) + A(1+JL) - \left(K + \frac{JL}{K}\right)\right] + A\gamma_1 w^*\left[(L+K) - \left(1 + \frac{L}{K}\right)\right] \\ & + B\sigma_1 v^*\left[(1+K) - \left(L + \frac{K}{L}\right)\right].\end{aligned} \tag{32}$$

Setting the coefficients of K, JK, JL, $\frac{K}{J}$ to zero, we obtain

$$A = 1 \quad \text{and} \quad B = \frac{\beta_1\zeta_1 w^* s^* + (\mu+\rho_4)w^*}{\sigma_1 v^*} > 0. \tag{33}$$

Upon substituting the expressions in equation (33) back into (29) we obtain

$$\dot{\mathcal{V}} = \left(1 - \frac{s^*}{s}\right)\dot{s} + \left(1 - \frac{v^*}{v}\right)\dot{v} + \left(1 - \frac{w^*}{w}\right)\left(\frac{\beta_1\zeta_1 w^* s^* + (\mu+\rho_4)w^*}{\sigma_1 v^*}\right)\dot{w}. \tag{34}$$

Also, on substituting the values of A and B in equation (33) into equation (32), and on further simplification, we obtain

$$\begin{aligned}\dot{V} = \beta_1 v^* s^* \left[(K-J)\left(1 - \frac{1}{J}\right)\right] + \beta_1\zeta_1 w^* s^* \left[(2 + K - \left(\frac{K}{J} + \frac{K}{L} + \frac{JL}{K}\right)\right] \\ +(\mu+\rho_4)w^* \left[1 + 2K - \left(\frac{L}{J} + \frac{K}{J} + \frac{K}{J}\right)\right] + \gamma_1 w^* \left(L - \frac{L}{K} + K - 1\right).\end{aligned} \tag{35}$$

From equation (35), we observe that the expression $(K-J)\left(1-\frac{1}{J}\right)$ is less than or equal to zero with the equality holding if and only if $J = 1$ or $K = J$.

Also, the expression $(L-K)\left(1-\frac{1}{K}\right) \leq 0$ with the equality holding if and only if $K = 1$ or $L = K$.

We can draw similar conclusions from the remaining expressions $\left(2 + K - \left(\frac{K}{J} + \frac{K}{L} + \frac{JL}{K}\right)\right)$ and $\left(1 + 2K - \left(\frac{L}{J} + \frac{K}{J} + \frac{K}{J}\right)\right)$. In the two cases, equality holds if and only if $K = J = L$.

Therefore, $\dot{\mathcal{V}} \leq 0$ with equality holding if and only if $K = J = L$. Since $\dot{\mathcal{V}} = 0$ only when $K = J = L$, which corresponds to $s = s^*$, $v = v^*$, and $w = w^*$ and Subsequently, to $S = S^*$, $U_a = U_a^*$ and $R_a = R_a^*$, the largest invariant set in $\{(S, U_a, R_a) \in \bar{\Omega} : \dot{\mathcal{V}} = 0$ is the singleton $\{\mathcal{E}_1^a\}$. By LaSalle's invariance principle [9], we therefore conclude that the endemic equilibrium $\mathcal{E}_1^a$ is globally asymptotically stable in the interior of $\bar{\Omega}$. This shows that every solution in $\bar{\Omega}$ or that intersects $\bar{\Omega}$, would approach the endemic equilibrium $\mathcal{E}_1^a$. □

5 Methamphetamine Abuse Model

The co-use model reduces to the following model when only methamphetamine is being abused.

$$\left.\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= \Lambda - (\mu + \bar{\lambda}_2)S, \\ \frac{\mathrm{d}U_t}{\mathrm{d}t} &= \bar{\lambda}_2 S + \gamma_3 R_t - (\mu + \sigma_3 + \delta_3 + \rho_7)U_t, \\ \frac{\mathrm{d}R_t}{\mathrm{d}t} &= \sigma_3 U_t - (\mu + \gamma_3 + \rho_6)R_t,\end{aligned}\right\} \tag{36}$$

where

$$\bar{\lambda}_2 = \frac{\beta_2(U_t + \epsilon_1 R_t)}{N}.$$

5.1 Model Equilibria

Setting the right hand side of equations in model system (36) to zero, and solving for S, U_t and R_t, we obtain the polynomial

$$\bar{\lambda}_2^{**}\left[b_3 b_4(1-\Phi_2)(1-\mathcal{R}_{t0}) + \bar{\lambda}_2^{**}(\sigma_3 + b_4)\right] = 0 \tag{37}$$

$$\text{where } \mathcal{R}_{t0} = \frac{\beta_2[b_4 + \zeta_2\sigma_3]}{b_3 b_4[1-\Phi_2]} \quad \text{and} \quad \Phi_2 = \frac{\gamma_3\sigma_3}{b_3 b_4}. \tag{38}$$

Note that $\mathcal{R}_{t0}$ is the methamphetamine abuse reproduction number.

5.2 Stability Analysis

From polynomial equation given in (37),

$$\bar{\lambda}_2^{**} = \left\{ \left(\frac{b_3 b_4 (1-\Phi_2)}{\sigma_3 + b_4} \right) (R_{t0} - 1) \right\}$$

which exists only if $\mathcal{R}_{t0} > 1$, and corresponds to the methamphetamine-endemic equilibrium, denoted by $\mathcal{E}_1^t$ such that $\mathcal{E}_1^t = (S^{**}, U_t^{**}, R_t^{**})$ where,

$$S^{**} = \frac{\Lambda}{\mu + \bar{\lambda}_2^{**}}, \quad U_t^{**} = \frac{\Lambda \bar{\lambda}_2^{**} b_4}{b_3 b_4 (\mu + \bar{\lambda}_2^{**})(1-\Phi_2)}, \quad R_t^{**} = \frac{\Lambda \bar{\lambda}_2^{**} \sigma_3}{b_3 b_4 (\mu + \bar{\lambda}_2^{**})(1-\Phi_2)}. \tag{39}$$

Due to similarity between the structures of the two sub-models, we state the following theorems on the stability of the steady states.

Theorem 4. *The unique methamphetamine-free equilibrium point, $\mathcal{E}_0^t$ is locally asymptotically stable for $\mathcal{R}_{t0} < 1$ and unstable for $\mathcal{R}_{t0} > 1$.*

Theorem 5. *The unique endemic equilibrium, $\mathcal{E}_1^t$ is globally stable for $\mathcal{R}_{t0} > 1$ if the population is constant over the modelling time.*

Remark:

We notice from equation (13) that the reproduction number due to the combined abuse of alcohol and methamphetamine is basically the maximum of either of the sub-model reproduction numbers. Therefore $\mathcal{R}_{at} = \max\{\mathcal{R}_{a0}, \mathcal{R}_{t0}\}$, where $\mathcal{R}_{a0}$ is the average number of new alcohol drinkers produced as a result of associating with an individual who drinks alcohol during his or her entire drinking life and $\mathcal{R}_{t0}$ is the average number of new methamphetamine users produced as a result of associating with an individual who uses methamphetamine, during his or her entire methamphetamine-using career.

6 Numerical Simulation

6.1 Parameter Estimation

In this section, we estimate the co-use model parameters to be used in the simulations. While most parameters are obtained from the fitting of the sub-models to alcohol and methamphetamine data, some parameters are simply estimated based on available literature, see [3, 4, 15, 16, 23]. On average, the life expectancy in Sub-Sahara Africa and that of South Africa at the beginning of the modelling time, i.e 1997 was about 50 years [8]. This therefore corresponds to a mortality rate of 0.02 per annum. We thus have the natural mortality rate, $\mu = 0.02$. According to Gray in [7], the average birth rate in South Africa is approximated 0.028 per annum. To account for impact immigration into the Western Cape Province of South Africa, we shall set our recruitment rate Λ to be greater than 0.028 per annum. The actual mortality rate due to substance abuse is complex to estimate. This could be due to variations in risky behaviours by individuals while under the influence of substances of abuse [4]. This variation also extends within and among a population. The mortality rate for example among injecting crank-cocaine users in [4] was 0.018 per year. According to a report in [17], a smokers life expectancy is increased by about 14% if he/she quits smoking at about age 35. Since treatment impacts positively on the quality of life, we assume that it reduces mortality rate related to substance abuse. Thus, we choose $\zeta_1 = 0.005$, $\zeta_3 = 0.05$, $\epsilon_1 = 0.05$ and $\epsilon_3 = 0.00001$ per year.

The observed treatment demand for methamphetamine users was 17% in [15]. In this paper, we choose the average treatment demand of 30% as the corresponding treatment rate of 0.3. The summary of parameter values used in the numerical simulations is given in Table 1.

Table 1: Description of Parameters used in the model, their values and their ranges. The baseline values were obtained from [3, 4, 15, 16, 23]. Meth is Methamphetamine

Symbol	**Description**	**Value**	**Range**
Λ	Recruitment rate for susceptible persons	0.03	0.03-0.8
μ	Natural mortality rate	0.02	0.01-0.02
β_1	Alcohol transmission rate	0.25	0-1.0
β_2	Meth transmission rate	0.2	0-1.0
γ_1	Alcohol drinking relapse rate	0.15	0-1.0
γ_2	Alcohol-meth co-use relapse rate	0.1	0-1.0
γ_3	Rate of relapse into meth use upon treatment	0.3	0 1.0
γ_4	Alcohol reversion rate upon treatment for co-users	0.3	0-1.0
γ_5	Rate of reversion into meth abuse upon treatment	0.3	0-1.0
δ_1	Alcohol related death rate	0.03	0-1.0
δ_2	Alcohol-meth related death rate	0.04	0-1.0
δ_3	Meth related death rate	0.033	0-1.0
σ_1	Treatment rate for alcohol abuse	0.2	0-1.0
σ_2	Treatment rate for co-users of alcohol and meth	0.3	0-1.0
σ_3	Treatment rate for meth abuse only	0.3	0-1.0
ρ_1	Rate of reversion to meth use by co-users	0.01	0-0.5
ρ_2	Rate of reversion to alcohol use by co-users	0.01	0-0.5
ρ_3	Rate of quitting alcohol abuse without treatment	0.35	0-1.0
ρ_4	Rate of quitting alcohol abuse upon treatment	0.25	0-1.0
ρ_5	Rate of quitting alcohol-meth abuse upon treatment	0.25	0-1.0
ρ_6	Rate of quitting meth abuse upon treatment	0.78	0-1.0
ρ_7	Rate of quitting meth abuse without treatment	0.4	0-1.0
η_a ,η_t,ζ_2 ϵ_2	Enhancement factors	> 1	
ζ_1, ζ_3, ϵ_1, ϵ_3	Enhancement factors	< 1	

6.2 Sensitivity Analysis

We use Latin Hypercube Sampling (LHS) to determine the Partial Rank Correlation Coefficients (PRCCs) with 1000 simulations per run to establish the sensitivity of the model parameters to the population of alcohol-methamphetamine abusers in the compartment U_{at}. We observe from Figure 4, that the parameters with the greatest potential to worsen the co-use epidemic of alcohol and methamphetamine abuse are the effective person to person contact rates, β_1 and β_2. Similarly, the relapse rate from the treatment to the class of methamphetamine users is observed to be highly significant, and may easily worsen the epidemic. Moreover, the quitting parameter, ρ_6 is the parameter with the greatest potential to make the epidemic better when increased.

Using the parameter values defined in Table 1, we illustrated the Monte Carlo simulations for the four parameters whose PRCC magnitudes are as shown in Figure 5. We observe from Figure 5, that the parameters β_1, β_2, γ_3 and Λ are positively correlated with the population of co-users of alcohol and methamphetamine (U_{at}). The parameters β_1 and β_2 are highly significant whereas the parameters Λ and γ_3 are less significant in the correlation. This means that in increase in

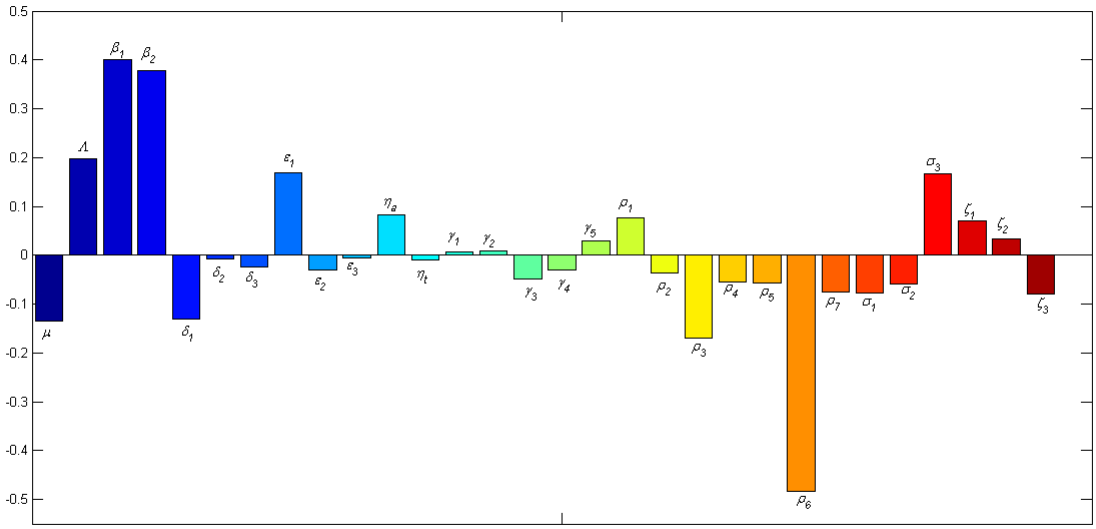


Figure 4: PRCCs for the full range of parameters from Table 1.

these parameters will worsen the substance abuse epidemic. Those that show some negative correlation decrease the epidemic when they are increased. Typically this is observed in the permanent quitting rates.

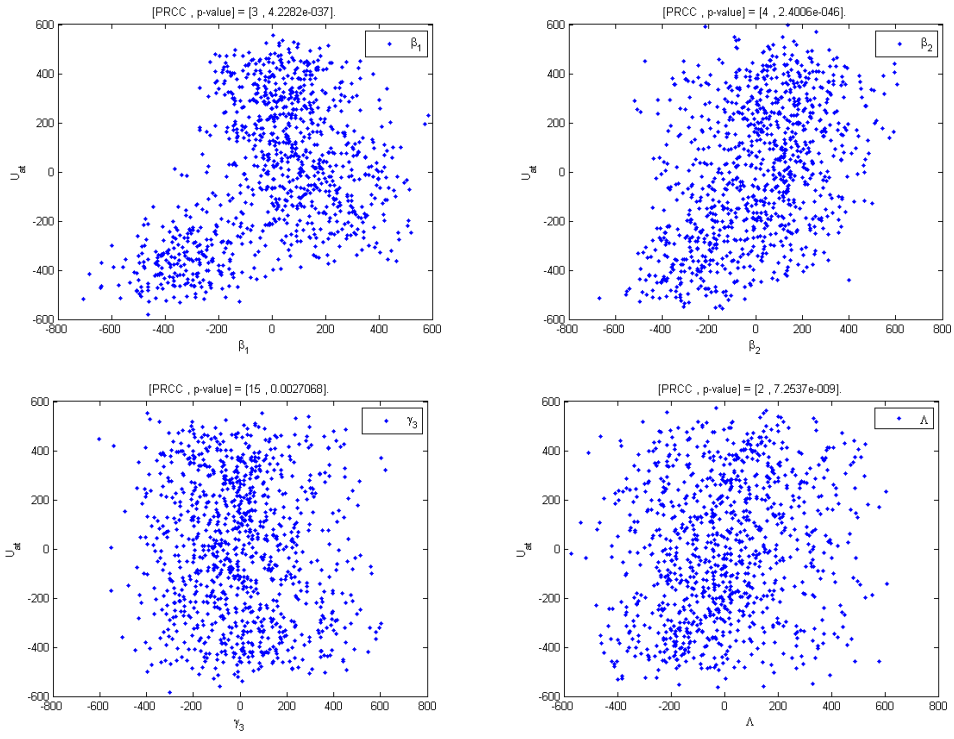


Figure 5: Graphs (a), (b), (c) and (d) show the Monte Carlo simulations for four parameters, using the values in Table 1 and 1,000 simulations per run.

6.3 Numerical Results

In this subsection, we fit the model systems (14) and (36) to the data of individuals seeking treatment for alcohol and methamphetamine as their primary substance of abuse at specialised treatment centres in Cape Town and Western Cape Province respectively. The data was collected from 1996 to 2011 on a six month interval by SACENDU [20] and is given in Tables 2 and 3.

Table 2: Primary Methamphetamine-abuse for the period 1997a to 2011a in % (Source: [20]). The letters a and b represents the first six months (January-June) and the second six months (July-December)of the year respectively.

Year	1997a	1997b	1998a	1998b	1999a	1999b	2000a	2000b	2001a
% Meth users use	0	0.1	0	0.1	0.1	0.1	0.2	0.1	0.1
Year	2001b	2002a	2002b	2003a	2003b	2004a	2004b	2005a	2005b
% Meth users	0.3	0.3	0.8	2.3	2.3	10.7	19.3	26.1	34.7
Year	2006a	2006b	2007a	2007b	2008a	2008b	2009a	2009b	2010a
% Meth users	37.2	42.3	40.7	36.1	35.8	35.1	40.6	35.5	33.6
Year	2010b	2011a	2011b						
% Meth users	35.1	35.3	38.8						

The least squares curve fit is used to fit the models to data. A Matlab code is used in which, the unknown parameter values are given a lower bound and an upper bound from which the set of parameter values that produce the best fit are obtained. The data on the demand for treatment is used to model growth in the R_t class in the methamphetamine sub-model.

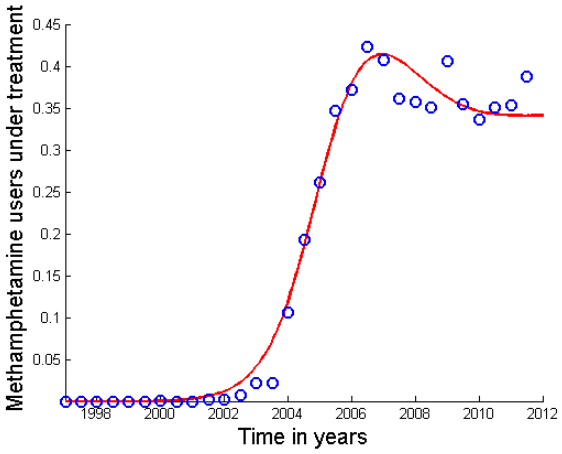


Figure 6: Shows methamphetamine model (36) fitted to data for addicts seeking treatment for methamphetamine as a primary substance of abuse in the Western Cape Province of South Africa.

Figure 6 shows the graphical representation of model (14) fitted to data for persons seeking treatment for methamphetamine abuse. The circles and the solid line each represent the actual data points and the model fit to the data respectively. We observe that the model fits well with the data. Furthermore, we notice that there was no population of methamphetamine users before 1996. The unavailability of such data could be attributed to lack of data collection before the year 1996 [15]. Individuals may have been using the drugs but never really sort treatment services. It is equally important to notice that the population methamphetamine users under treatment peaked in the year 2006. The results showed a short-term and fast growing methamphetamine

epidemic in which there was a significant increase in the number of users between 2002 and 2005, followed by a significant slow down in the generation of new cases. The data shows an epidemic that is stabilizing at about 35% of the rehabilitants. The model also show a steady state solution close to this value.

The data showing the demand for treatment for alcohol addiction is shown in Table 3. As with methamphetamine, the alcohol data was similarly collected by SACENDU [20] from 1996 to 2012 in time intervals of six months.

Table 3: Primary Alcohol abuse: by six month period (from 1997a to 2011a in % (Source: [20])

Year	1997a	1997b	1998a	1998b	1999a	1999b	2000a	2000b	2001a
% Alcohol users	82.0	78.0	74.0	64.0	56.0	50.0	48.0	51.0	46.0
Year	2001b	2002a	2002b	2003a	2003b	2004a	2004b	2005a	2005b
% Alcohol users	46.0	48.0	47.0	43.6	39.4	38.3	33.7	34.4	25.1
Year	2006a	2006b	2007a	2007b	2008a	2008b	2009a	2009b	2010a
% Alcohol users	30.2	26.4	29.5	29.7	30.0	27.6	26.8	29.4	29.8
Year	2010b	2011a	2011b						
% Alcohol users	27.5	27.5	23.7						

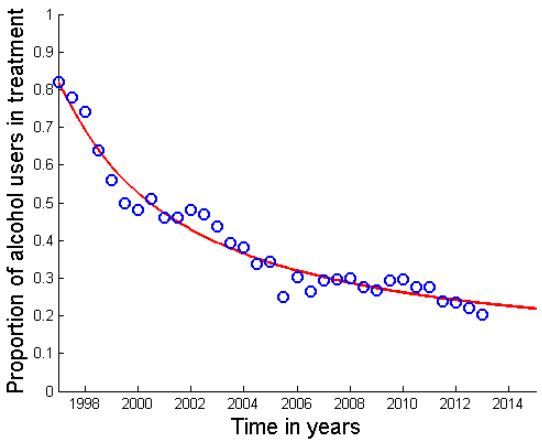


Figure 7: Shows alcohol-model (14) fitted to data for individuals seeking treatment for alcohol abuse in Cape town and Western Cape province of South Africa.

From Figure 7, we observe that the proportion of individuals seeking treatment for alcohol abuse has been on a steady decline. The decline could be attributed to the fact that some alcohol users may have found refuge in other substances of abuse, thereby quitting alcohol or reducing their alcohol intake.

It is important to predict the future trends of the abuse of substances. We give the projected populations of individuals under treatment. The projected populations of alcohol and methamphetamine patients under treatment in the Western Cape Province till the year 2018, are given in Figures 8 and 9 respectively. We observe that the population of methamphetamine users would remain constant for the five year period. This is supported by the data that seems to fluctuate around this steady state. The population of alcohol users under treatment is however shown to be on the decline. The decline once again could be attributed to preference for other drugs/substances of abuse. This results into decreased prevalence of alcoholism and increased prevalence for other drugs of abuse such as heroin, cocaine and even methamphetamine.

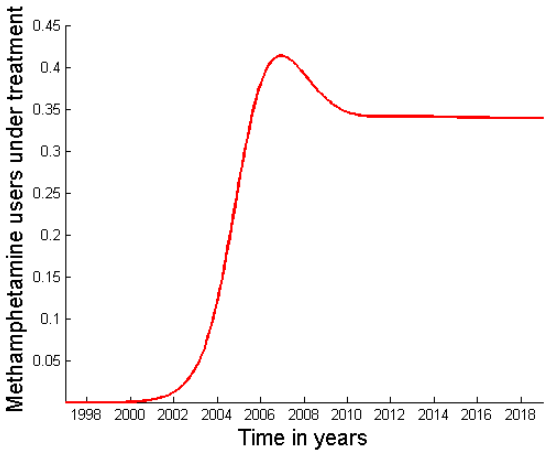


Figure 8: Shows the projected population of methamphetamine abuse patients seeking treatment.

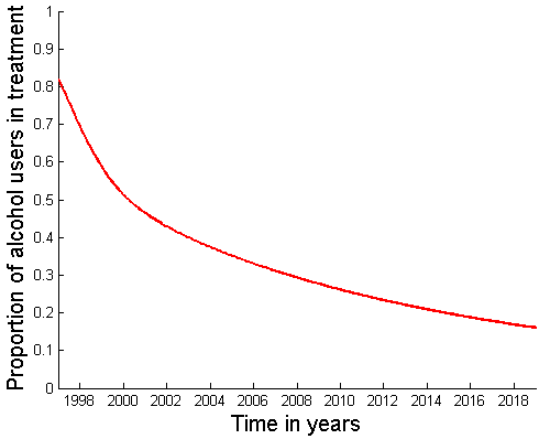


Figure 9: Shows the projected population of alcohol abuse patients seeking treatment.

6.4 Alcohol-methamphetamine Co-use Results

We now use the co-use model to predict the proportion of individuals using both alcohol and methamphetamine in the Western Cape Province. Due to lack of data, it is only prudent that such estimation be done by considering the parameters values derived from the sub-models of alcohol and methamphetamine only. Using the listed parameter values in Figure 10, we obtained the estimated population curve of co-users of alcohol and methamphetamine in the Western Cape Province as shown in Figure 10.

From Figure 10, it is estimated that the population of co-users of alcohol and methamphetamine in the Western Cape Province is about 1% of the total population of patients reporting for treatment of alcohol and\or methamphetamine abuse. The constant trend exhibited is consistent with the growing popularity of methamphetamine in the province [10]. Our results are consistent with the clinical results which have shown a strong link between the abuse of alcohol and methamphetamine. The increased abuse of methamphetamine enhances the use and abuse of alcohol and vice versa as described in [12].

For example, using the values in Table 2 and Table 3, we observe that in the year 2011, the population of individuals under treatment for methamphetamine abuse (2093 individuals) was

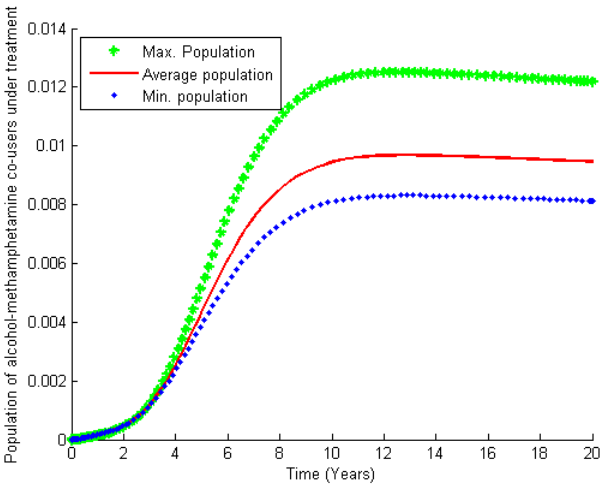


Figure 10: Graph showing the population of alcohol-methamphetamine users under treatment in the Western Cape Province of South Africa. Parameters:$\mu = 0.02$, $\beta_1 = 0.25$, $\beta_2 = 0.2$, $\gamma_1 = 0.15$, $\gamma_2 = 0.1$, $\gamma_3 = 0.3$, $\gamma_4 = 0.3$, $\gamma_5 = 0.02$, $\delta_1 = 0.6626$, $\delta_2 = 0.22$, $\delta_3 = 0.02$, $\sigma_1 = 0.3372$, $\sigma_2 = 0.4$, $\sigma_3 = 1.9693$, $\rho_1 = 0.2$, $\rho_2 = 0.3$, ρ_3= 0.7292, $\rho_4 = 0.0118$, $\rho_5 = 0.01$, $\rho_6 = 0.9998$, $\rho_7 = 0.9$, $\eta_a = 0.01$, $\eta_t = 0.02$, $\zeta_1 = 0.0780$, $\zeta_2 = 0.01$, $\zeta_3 = 0.01$, $\epsilon_1 = 0.00054933$, $\epsilon_2 = 0.1$, $\epsilon_3 = 0.02$, $\Lambda = 1.934$ (for the Min. Population), $\Lambda = 4.3525$ (for the Max. Population).

higher than that for persons under treatment for alcohol addiction (1553 people). In reference to the approximation curve in Figure 10, we observe that there were approximately 40 individuals under treatment for abuse of both alcohol and methamphetamine. Whereas most substance abuse treatment centres in South Africa do not cater for individuals under addiction for multiple substances abuse, it is vital to observe that co-users of alcohol and methamphetamine exist, and that they should not be ignored if the fight against drug abuse is to be successful. Without minimizing the need for proper treatment, we recognize that treatment for multiple substance abuse is an expensive activity and will obviously require more resources as compared to those used in the case of treatment for single substance.

7 Discussion and Conclusion

In this paper, we have demonstrated through a deterministic model of co-use of alcohol and methamphetamine that compartmental models can be used to estimate the number of individuals co-abusing alcohol and methamphetamine. The model generated interesting estimates of the population of individuals co using alcohol and methamphetamine. The mathematical analysis of the model is also presented, through the analysis of the submodels. We establish that the co-use model reproduction number is the maximum of the sub-model reproduction numbers, $\mathcal{R}_{a0}$ and $\mathcal{R}_{t0}$. The model is decomposed into sub-models; the alcohol submodel and methamphetamine submodel. By constructing a suitable lyapunov function, the analysis shows that the alcohol free equilibrium of the model is globally asymptotically stable whenever $\mathcal{R}_{a0}$ is less than unity. The health implications of this observation is that keeping the reproduction numbers below unity may be necessary in the control of the growth of the alcohol epidemic and subsequently the co-use epidemic of alcohol and methamphetamine. The model presented also emphasised that data collection on substance abuse should not be restricted to the primary substances of abuse but should also take into account multiple abuse of substances.

The population of co-users of alcohol and methamphetamine are shown to increase with the increasing population of methamphetamine users. It is observed however that this proportion is much lower than the individual users of either alcohol and methamphetamine. This difference should not however be used to overlook the need to reduce multiple substance abuse which has been shown to have even greater negative effect than that which would be experienced by the abuse of the single substances.

The results from the sensitivity analysis suggests that the control of the combined abuse of methamphetamine and alcohol pivots around social intervention programs aimed at new users. Limiting new cases through preventive measures such as educational campaigns and other activities that encourages new users to quit. Secondly, cases of relapse should be minimised. Furthermore, there is the need to adopt to in-patient treatment methods as opposed to the usual out-patient method, as this would limit contact with other drug users and hence lowering new relapse cases.

The model is not without limitations. First, it was fitted to imperfect data that is subject to customary censures. Criticisms such as the bias of self-reports, the difficulty of taking a truly representative random sample of drug users and so on, are common. The models greatest value is not as a predictive tool but rather a tool for organizing the thinking around multiple substance abuse and the generation of useful insights into the dynamics of multiple abuse of substances. The dynamics are much more complex than described here. We argue that the presented model provides the required insights to understanding co-use of alcohol and methamphetamine. The results are relevant in designing intervention strategies aimed at combating multiple substance abuse.

Acknowledgements

We are grateful to the University of Stellenbosch and the African Institute for Mathematical Sciences (AIMS) for their support during the production of this manuscript. The second author acknowledges the support of the National Research Foundation (NRF) for their financial support.

References

[1] G.A. Barclay, J. Barbour, S. Stewart, C.P. Day, E. Gilvarry, Adverse physical effects of alcohol misuse, Adv. Psychiatr. Treat., Vol 14 (2008) 139151.

[2] B. Bower, Multiple Drug Use: A Dangerous Trend, Science News, Vol. 128 (1985) 6(1).

[3] C.P. Bhunu, S. Mushayabasa, A theoretical analysis of smoking and alcoholism. Math Model Algor. Vol.11 (2012) 387-408.

[4] MN. Burattini, E. Massad, F.A.B. Coutinho, A Mathemaitical model of the impact of crack-cocain use on the prevalence of HIV/AIDS among drug users, Math. Comput. Model. Vol.28 (1998) 21-29.

[5] Center for Substance Abuse Treatment. Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs. Treatment Improvement Protocol (TIP) Series 43. HHS Publication No. (SMA) 12-4214. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2005.

[6] Foundation for a Drug-free World. Available from *http://www.drugfreeworld.org/drugfacts/crystalmeth/a-worldwide-epidemic-of-addiction.html*

[7] C. Day, A. Gray, Health and related indicators. Available from: *http:// www.hst.org.za/uploads/files/chap16_08.pdf¿.*

[8] DT Jamison, RG Feachmen, MW Makgoba, ER Bos, FK Baingana, KJ Hofman, KO Rogo (editors), Disease and mortality in Sub-Saharan Africa. Second edition, World Bank, 2006 Washington D.C, 2006.

[9] J. P. La Salle, The stability of dynamical systems. SIAM, (1976).

[10] K. Marris, C. Parry, South African Methamphetamine boom could fuel further HIV, Lacent. Vol.6 (2006) 471.

[11] G. Mulone, B. Straughan, A note on heroin epidemics. Math. Biosci. Vol.218 (2009) 138-141.

[12] G. Matthew, Kirkpatrick, W. Erik, Gunderson, R Frances, Levin, W. R. Foltin, L. C. Hart, Acute and residual interactive effects of repeated administrations of oral methamphetamine and alcohol in humans. Psychopharmacol. Vol.219 (2012) 191-204.

[13] J. Mendelson, Jones, R. Upton R., Jacob P, Methamphetamine and ethanol interactions in humans. Clin Pharmacol Ther. Vol.57 (1995) 559-568.

[14] N. Mposo, Tik and alcohol leading problems in WCape, http://www.iol.co.za/news/crime-courts/tik-and-alcohol-leading-problems-in-wcape-1.1334219♯.U2xC7_mSxtY. Accessed on 8 May 2014.

[15] F. Nyabadza, S.D Hove-Musekwa, From Heroin epidemics to Methamphetamine epidemics. Modelling substance abuse in a South African Province. Math. Biosci. Vol.225 (2010) 132-140.

[16] F. Nyabadza, J.B.H. Njagarah, R.J. Smith, Modelling the dynamics of Crystal Meth ('Tik') abuse in the presence of drug-supply chains in South Africa, Bul. Math. Biol., 75(1) (2013) 24-48.

[17] National Institute on Drug Abuse, Cigarettes and other tobacco products. Available from *http://www.drugabuse.gov/infofact/tobacco.html*. Last accessed, 2012.

[18] A. Pluddemann, S. Dada, C.Parry, A. Bhana, V. Mohamed, T. Perreira, N. Erika, T. Mncwabe, P. Ina , W. Roger, Monitoring alcohol and drug abuse trends in South Africa (July 1996-December 2011), SACENDU Research Brief, 6(2) phase 31, 2012a. Available from: *http://www.sahealthinfo.org/admodule/sacendu.htm*

[19] S. Ramlagan, K. Peltzer, G. Matseke, Epidemiology of drug abuse treatment in South Africa, SAJP 16(2) (2010) 40-49.

[20] A. Pluddemann et al, Monitoring alcohol and drug abuse trends in South Africa (July 2012-December 2012), SACENDU Research Brief. Math. Biosci. Vol.11 (2012).

[21] Rehabilation programs offered. http://www.sancawc.co.za/master/article.php?id=19, Accessed on 8 May 2014.

[22] E. White, C. Comiskey, Heroin epidemics treatment and ODE modelling. Math. Biosci. Vol.208 (2007) 312-324.

[23] UNODC, World Drug Report, United Nation Publication Sales No. E Vol.12 (2013). Available from: *http://www.unodc.org/unodc/en/data-and-analysis/WDR-2013.html*.

[24] P. van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibrium for the compartmental model of disease transmission, Biosci. Vol.180 (2002) 29-48.

Application of optimal control to a dynamic model of alcohol-methamphetamine co-abuse

Titus Okello Orwa[‡] and Farai Nyabadza[‡*]

[‡]*Department of Mathematical Science, University of Stellenbosch, Private Bag X1, Matieland, 7602, South Africa*

Abstract

In this paper, a deterministic model is formulated to model the dynamics of alcohol and methamphetamine co-abuse epidemic in the presence of time dependent control measures. Optimal control theory is applied to investigate optimal strategies for controlling the co-abuse of alcohol and methamphetamine using educational campaigns and rehabilitation as the system control variables. The characterization of the optimal control is performed analytically by applying Pontryagin Maximum Principle. Numerically, the optimality system is solved using Runge-Kutta based forward-backward sweep solver. The possible impacts of the controls are examined. Simulation results reveal that proper use of controls lead to a considerable decrease in the time taken to achieve a substance free-state and hence minimize the population co-abusing alcohol and methamphetamine.

Key words Alcohol · Methamphetamine · Optimal control · Co-abuse.

1 Introduction

It is known that substance users often use two or more substances during their substance using career. Surprisingly, most of these multiple substance users, often admit to using only a specific drug/substance of abuse during treatment. Clinical research indicates that abuse of multiple drugs/substances degrades the process of detoxification during treatment programmes and further worsens health consequences. Efforts to resolve this problem is complicated by the fact that most drug treatment facilities only provide experienced services at treating single drug addiction cases [8]. Data on individuals who abuse more than one substance is equally not well documented in most countries.

Research work in [9], revealed that in comparison to single drug effects, alcohol-methamphetamine combination produces a greater elevation of heart beat and elation, which is arguably a motivation for the drug users who consider such effects as positive impacts of the drug combinations. Some of the motivation to co-abuse of substances include but not limited to; the desire to increase, to balance and to maintain the effects of the primary substance of choice [8], to experience greater euphoria, and even longer hours of sleep. Clinical results as pointed out by Mendelson [10], indicated that the combined use of alcohol and methamphetamine results in increased heart rate coupled with heightened blood pressure beyond and above that seen which would be experienced by using methamphetamine alone.

*Corresponding author: Email: *nyabadzaf@sun.ac.za*

The management of substance abuse is never an easy quest. Both preventive or curative measures have been put in place to manage the drug menace. Preventive measures include educational campaigns against substance abuse. Further, education also includes many elements such as: providing relevant knowledge and information, addressing issues such as peer influence; normative beliefs; protective factors and risk factors, considering influences such as the media, building the personal and social confidence and competence of young people to weigh up and make appropriate and healthy choices and decisions. On the other hand, curative measures occur through treatment administered in rehabilitation centres. The importance of these control strategies are tested in this paper.

The basis of epidemiological study of any kind is the need to improve existing control strategies and ultimately eradicate the epidemic from the affected population. The application of optical control is vital to decision making in terms of viable control strategies to be employed to eradicate an epidemic [15]. Optimal control theory has been applied to several infectious disease models including HIV/AIDS [2, 4, 5], malaria [3, 6, 7] and Cholera [1]. A part from single substance abuse models in [11], the applications of optimal control in multiple substance is yet to be done to the best of our knowledge.

Our goal is to develop a mathematical model for co-abuse of alcohol and methamphetamine with control strategies. We seek to investigate the impact of educational campaigns and effective treatment in multiple drug/substance abuse epidemics. We characterize the optimal control problem analytically by applying Pontryagin Mmaximum Principle. The optimality system is then solved using a Runge-Kutta based forward-backward sweep solver. The rest of the paper is organized as follows. The co-abuse model is formulated and described in Section 2, stating model assumptions and parameter definitions. In Section 3 we state the control problem, objective functional to be minimized and then apply the Pontryagin's Maximum Principle to find the necessary conditions for the optimal control. The numerical results showing population dynamics with and without preventive measures (educational campaigns) and effective treatment are presented and discussed in Section 4.

2 Model Formulation

The model sub-divides the total human population, denoted by $N(t)$ at any time $t \geq 0$ into seven sub-populations of; susceptibles ($S(t)$), individuals that have never taken alcohol or used methamphetamine before but are at risk of using either of the substances, alcohol users not under treatment $U_a(t)$, alcohol users under treatment $R_a(t)$, methamphetamine users who are not under treatment $U_t(t)$, methamphetamine users under treatment $R_t(t)$; users of both alcohol and methamphetamine who are not under treatment $U_{at}(t)$ and users of both alcohol and methamphetamine under treatment $R_{at}(t)$. So that

$$N(t) = U_a(t) + R_a(t) + U_t(t) + R_t(t) + U_{at}(t) + R_{at}(t). \tag{1}$$

We give a schematic diagram showing the movements of individuals between compartments as their drug using habits worsen or improve.

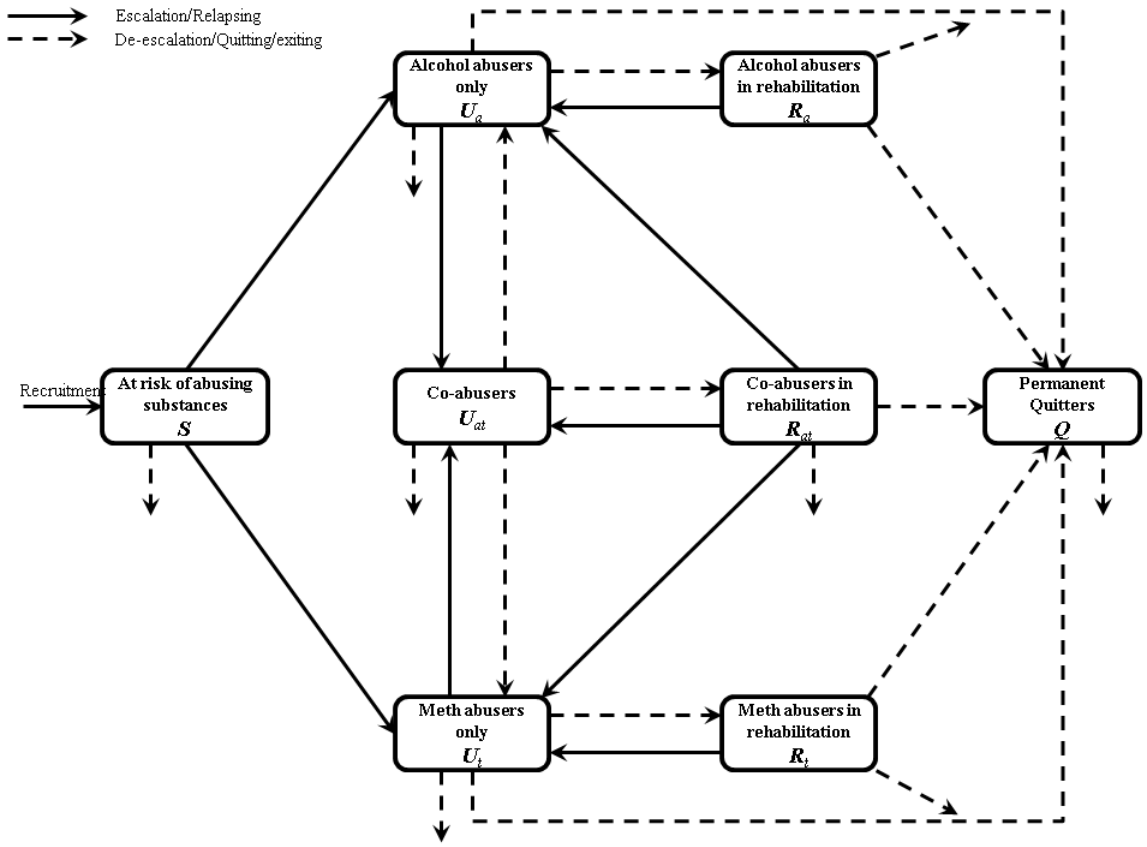


Figure 1: The schematic model diagram and the associated flows

We now give a detailed mathematical exposition of the transitions between compartments. It is assumed that individuals get recruited into the susceptible sub-population through birth and immigration at a constant rate, Λ. The susceptibles become alcohol and/or methamphetamine abusers following contact with other drug/substance abusers. The transmission is mainly driven by peer pressure. Assuming homogeneous mixing of populations, susceptible individuals acquire alcohol drinking habits at rate λ_1, where

$$\lambda_1 = \beta_1 \left(\frac{U_a + \zeta_1 R_a + \zeta_2 U_{at} + \zeta_3 R_{at}}{N} \right), \tag{2}$$

with the parameter β_1 denoting the effective contact rate (i.e. the contact with an alcohol drinker that will result in one taking alcohol). To account for the decreased chances of becoming an alcohol drinker after being in contact with alcoholics and co-abusers in rehabilitation, it is assumed here that those under treatment tend to have lower recruitment aptness relative to addicts. Those under the influence of alcohol are more likely to be co-abusers when they get into contact with those who abuse both substances and not under rehabilitation. Therefore, $\zeta_1,\ \zeta_3 < 1$, while $\zeta_2 > 1$. Similarly, individuals get recruited into methamphetamine abuse at the rate given by

$$\lambda_2 = \beta_2 \left(\frac{U_t + \epsilon_1 R_t + \epsilon_2 U_{at} + \epsilon_3 R_{at}}{N} \right), \tag{3}$$

The modification parameters ϵ_1 and ϵ_3 are both assumed to be less than unity. This accounts for the reduced tendency to initiate new users into methamphetamine abuse by methamphetamine users under treatment. Like in the case of alcohol, we assume that $\epsilon_2 > 1$.

Alcoholics in U_a begin to use methamphetamine at a rate $\eta_a\lambda_2$ and progress into the compartment U_{at} with $\eta_t \geq 1$ accounting for the increased chances of using methamphetamine by alcohol users when compared to non-alcohol users. Individuals not under treatment may die due to alcohol related causes at a rate δ_1 or die naturally at a rate μ, (a rate that is also assumed constant for the rest of the population in the model). Furthermore, Alcohol abusers in U_a may seek treatment at a rate σ_1 or quit alcohol drinking at a constant rate of ρ_3. Following successful treatment, individuals in the compartment R_a, quit alcohol at the rate ρ_4. We assume that those that quit, do so permanently. Ideally, quitters should be allowed to relapse. In this model, we only assume relapse in the form of rehabilitation failure.

Similarly, susceptible individuals get recruited into the methamphetamine abuse, U_t at a rate $\lambda_2(t)$ following effective contact with other methamphetamine users. Some individuals in U_t acquire alcohol drinking habits at the rate $\eta_t\lambda_1$ and move into the class U_{at} with $\eta_t \geq 1$ accounting for the increased chances of drinking alcohol for methamphetamine users when compared to those not using methamphetamine. Others may enter rehabilitation compartment R_t at a rate σ_3 and relapse to U_t at a rate γ_3. Individuals in the class U_t may die due to methamphetamine-related causes at a rate δ_3 or permanently quit methamphetamine at a rate ρ_7.

Users of both alcohol and methamphetamine, U_{at} may revert to alcohol abuse only at a rate ρ_1 or to methamphetamine abuse only at a rate ρ_2 upon quitting either substances of abuse. In addition, individuals in this class may die due to diseases and challenges related to drug/substance abuse, such as liver cirrhosis and pancreatitis at a rate δ_2. They may progress into the treatment class R_{at} at a rate σ_2. Individuals under treatment for alcohol and methamphetamine abuse in R_{at}, may relapse into alcohol-methamphetamine abuse compartment at a rate γ_2 or quit drinking of alcohol and relapse to U_t, at a rate γ_5. Similarly, they may quit methamphetamine and revert to the class of alcohol users not under treatment U_a at a rate γ_4. We also allow permanent quitting for individuals in the classes R_{at} and R_t at the rates ρ_5 and ρ_6 respectively. We assume here that permanent quitting results from effective and efficient rehabilitation programs. Some additional modelling assumptions include the following. The treatment process is assumed to be outpatient. Rehabilitants can therefore initiate others into the drug epidemic. Although quitting both substances at the same time is unlikely, in this model, we allow permanent quitting of individuals in rehabilitation for both alcohol and methamphetamine.

From the above assumptions, parameter definitions and variables, we have the following model system of differential equations, with non-negative initial conditions that describe the dynamics of the co-abuse of alcohol and methamphetamine. The compartment Q is considered to be superfluous.

$$\left.\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} =& \Lambda - (\mu + \lambda_1 + \lambda_2)S, \\
\frac{\mathrm{d}U_a}{\mathrm{d}t} =& \lambda_1 S + \rho_1 U_{at} + \gamma_1 R_a + \gamma_4 R_{at} - \eta_a \lambda_2 U_a - (\mu + \sigma_1 + \delta_1 + \rho_3)U_a, \\
\frac{\mathrm{d}R_a}{\mathrm{d}t} =& \sigma_1 U_a - (\mu + \gamma_1 + \rho_4)R_a, \\
\frac{\mathrm{d}U_t}{\mathrm{d}t} =& \lambda_2 S + \rho_2 U_{at} + \gamma_3 R_t + \gamma_5 R_{at} - \eta_t \lambda_1 U_t - (\mu + \sigma_3 + \delta_3 + \rho_7)U_t, \\
\frac{\mathrm{d}R_t}{\mathrm{d}t} =& \sigma_3 U_t - (\mu + \gamma_3 + \rho_6)R_t, \\
\frac{\mathrm{d}U_{at}}{\mathrm{d}t} =& \eta_a \lambda_2 U_a + \eta_t \lambda_1 U_t + \gamma_2 R_{at} - (\mu + \rho_1 + \rho_2 + \delta_2 + \sigma_2)U_{at}, \\
\frac{\mathrm{d}R_{at}}{\mathrm{d}t} =& \sigma_2 U_{at} - (\mu + \gamma_2 + \gamma_4 + \gamma_5 + \rho_5)R_{at},
\end{aligned}\right\} \tag{4}$$

$$S(0) = S_0,\ U_a(0) = U_{a0},\ R_a(0) = R_{a0},\ U_t(0) = U_{t0},\ R_t(0) = R_{t0},\ U_{at}(0) = U_{at0},\ R_{at}(0) = R_{at0}$$

where

$$\lambda_1 = \beta_1 \left(\frac{U_a + \zeta_1 R_a + \zeta_2 U_{at} + \zeta_3 R_{at}}{N} \right) \quad \text{and} \quad \lambda_2 = \beta_2 \left(\frac{U_t + \epsilon_1 R_t + \epsilon_2 U_{at} + \epsilon_3 R_{at}}{N} \right). \tag{5}$$

The mathematical analysis of the above co-abuse model is available in the thesis titled 'Alcohol methamphetamine co-abuse epidemic in the Western Cape Province of South Africa'. We therefore refer the reader to the stated thesis project.

3 Formulation of controls

We modify the original model (4) by adding two types of controls: educational campaigns and treatment efficacy. We formulate a framework that minimizes the population of substance abusers (U_a, U_t, U_{at}). Educational campaign policies, minimize the rate of recruitment into substance abuse; that is, alcohol abuse, methamphetamine abuse and co-abuse of alcohol and methamphetamine, whereas treatment as a control ensures that rampant cases of relapse among rehabilitants (individuals under rehabilitation) is minimised. We define a linear function $\hat{u}_i(t)$ such that $\hat{u}_i = 1 - u_i, i = 1, 2, 3$. The time dependent controls $u_1(t)$ and $u_2(t)$ (with $0 \leq u_1 \leq 1$ and $0 \leq u_2 \leq 1$) are tied to prevalence reduction through educational campaigns; that is, campaigns aimed at reducing social interactions between users and non-users and also providing relevant information on the dangers of drug/substance abuse. On the other hand, the control $u_3(t)$ (with $0 \leq u_3 \leq 1$) is tied to efficacy of rehabilitation centres. As the efficacy improves (as u_3 increases), the function $\hat{u}_3$ decreases, resulting into decreased cases of relapse. The forces of initiation λ_1 and λ_2 corresponding to alcohol abuse and methamphetamine abuse are reduced by factors $\hat{u}_1$ and $\hat{u}_2$ respectively. We therefore have

$$\lambda_1 = \frac{\hat{u}_1 \beta_1 (U_a + \zeta_1 R_a + \zeta_2 U_{at} + \zeta_3 R_{at})}{N} \quad \text{and} \quad \lambda_2 = \frac{\hat{u}_2 \beta_2 (U_t + \epsilon_1 R_t + \epsilon_2 U_{at} + \epsilon_3 R_{at})}{N}, \tag{6}$$

The impact of relapse is minimised by improved treatment services while reducing the intensity of interactions between individuals in $U_a - R_a$, $U_t - R_t$, $U_{at} - R_{at}$, $U_{at} - R_a$, and $U_{at} - R_t$ classes. Here, we have assumed that effective treatment minimizes the rates of relapse (given by γ_1, γ_2, γ_3, γ_4 and γ_5)by a common factor of $\hat{u}_3 = 1 - u_3$, where u_3 represents the control on treatment efficacy .

Due to lack of data, we focus on achieving an optimal solution that minimizes the defined relative effort or costs. To identify the required level of effort to control multiple substance abuse, we propose an objective functional denoted by J which aims to minimize the population under substance abuse (U_a, U_t and U_{at}), and the cost of employing the the suggested controls u_1, u_2, and u_3. We therefore endeavour to find the most-effective strategy that reduces the prevalence of co-abuse of alcohol and methamphetamine at a minimal cost, subject to the state equations in (8) and the initial conditions therein. In view of this, our objective functional to be minimised is given by:

$$J(u_1, u_2, u_3) = \int_0^T (A_1 U_a + A_2 U_t + A_3 U_{at} + \alpha_1 u_1^2 + \alpha_2 u_2^2 + \alpha_3 u_3^2)\mathrm{d}t, \tag{7}$$

where T is the terminal time and the parameters A_1, A_2 and A_3 are positive balancing cost factors. So, the optimal control problem is to minimize the objective functional $J(u_1, u_2, u_3)$ subject to the differential equation system

$$\left.\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \Lambda - (\mu + \lambda_1 + \lambda_2)S, \\
\frac{\mathrm{d}U_a}{\mathrm{d}t} &= \lambda_1 S + \rho_1 U_{at} + u_3\gamma_1 R_a + u_3\gamma_4 R_{at} - \eta_a\lambda_2 U_a - (\mu + \sigma_1 + \delta_1 + \rho_3)U_a, \\
\frac{\mathrm{d}R_a}{\mathrm{d}t} &= \sigma_1 U_a - (\mu + u_3\gamma_1 + \rho_4)R_a, \\
\frac{\mathrm{d}U_t}{\mathrm{d}t} &= \lambda_2 S + \rho_2 U_{at} + u_3\gamma_3 R_t + u_3\gamma_5 R_{at} - \eta_t\lambda_1 U_t - (\mu + \sigma_3 + \delta_3 + \rho_7)U_t, \\
\frac{\mathrm{d}R_t}{\mathrm{d}t} &= \sigma_3 U_t - (\mu + u_3\gamma_3 + \rho_6)R_t, \\
\frac{\mathrm{d}U_{at}}{\mathrm{d}t} &= \eta_a\lambda_2 U_a + \eta_t\lambda_1 U_t + u_3\gamma_2 R_{at} - (\mu + \rho_1 + \rho_2 + \delta_2 + \sigma_2)U_{at}, \\
\frac{\mathrm{d}R_{at}}{\mathrm{d}t} &= \sigma_2 U_{at} - (\mu + u_3\gamma_2 + u_3\gamma_4 + u_3\gamma_5 + \rho_5)R_{at},
\end{aligned}\right\} \tag{8}$$

with initial conditions given by, $S(0) = S_0$, $U_a(0) = U_{a0}$, $R_a(0) = R_{a0}$, $U_t(0) = U_{t0}$, $R_t(0) = R_{t0}$, $U_{at}(0) = U_{at0}$, $R_{at}(0) = R_{at0}$.

The coefficients A_1, A_2 and A_3 are the costs associated with minimizing 'infectives', i.e. the number of alcohol abusers, methamphetamine abusers and the co-abusers of alcohol and methamphetamine respectively. Similarly, the parameters α_1, α_2 and α_3 are the weights constants associated with the controls u_1, u_2, and u_3 respectively. The weight constants accounts for the relative importance pre-assigned by the modeller to the contributing terms in the objective functional [11]. T is the time period of intervention. Following the work by Joshi in [4] and Kar in [15], we assume that the costs of 'infection', A_1U_a, A_2U_t and A_3U_{at} are linear functions whereas the cost on the controls $\alpha_1 u_1^2$, $\alpha_2 u_2^2$ and $\alpha_3 u_3^2$ are non-linear and takes the quadratic forms.

We seek to minimize the population of substance abusers through proper implementation of the policies u_1, u_2, and u_3 over a time interval given by $[0, T]$. Mathematically, this is equivalent to minimizing the objective functional over the given time as described below. We thus seek an optimal control set (u_1^*, u_2^*, u_3^*) such that

$$J(u_1^*, u_2^*, u_3^*) = \min_{\mathbf{U}} J(u_1, u_2, u_3). \tag{9}$$

where $\mathbf{U} = \{(u_1, u_2, u_3) | 0 \leq u_i(t) \leq 1, i = 1, 2, 3\}$ is the control set. These control functions u_1, u_2 and u_3 are bounded and Lebesgue integrable.

Using Pontryagin's Maximum Principle [14], the optimality system [(7),(8), (9)] is converted into an equivalent problem; that is, a problem of minimizing a pointwise Hamiltonian H, with respect to u_1, u_2 and u_3 and is given by

$$H = A_1U_a + A_2U_t + A_3U_{at} + \alpha_1u_1^2 + \alpha_2u_2^2 + \alpha_3u_3^2 + \sum_1^7 p_if_i, \tag{10}$$

where f_i is the right hand side of the differential system (8). Furthermore, $p_i, i = 1, \dots 7$ are the adjoint (or co-state) variables solutions of the following differential system.

$$\begin{aligned}
\frac{\mathrm{d}p_1}{\mathrm{d}t} =& \mu p_1 + \{(\lambda_1+\lambda_2)(S-N)(p_2+p_4-p_1) + \eta_tU_t(p_6-p_4)\lambda_1 + \eta_aU_a(p_6-p_2)\lambda_2\}/N, && (11)\\
\frac{\mathrm{d}p_2}{\mathrm{d}t} =& -A_1 + d_1p_2 - \sigma_1p_3 + \{\beta_1(1-u_1)(S(p_1-p_2) + \eta_tU_t(p_4-p_6))\\
&+S(p_2+p_4-p_1)(\lambda_1+\lambda_2) + \eta_tU_t(p_6-p_4)\lambda_1 + \eta_a(N-U_a)(p_2-p_6)\}/N, && (12)\\
\frac{\mathrm{d}p_3}{\mathrm{d}t} =& d_2p_3 + u_3\gamma_1(p_3-p_2) + \{S(p_2+p_4-p_1)(\lambda_1+\lambda_2) + [\beta_1u_1[\eta_t\epsilon_1U_t(p_4-p_6)\\
&-\zeta_1S(p_1+p_2) + \eta_tU_t(p_6-p_4)\lambda_1 + \eta_aU_a)(p_6-p_2)\lambda_2]\}/N, && (13)\\
\frac{\mathrm{d}p_4}{\mathrm{d}t} =& -A_2 + d_3p_4 - \sigma_3p_5 + \{\beta_2u_2(S(p_1-p_4) + \eta_aU_a(p_2-p_6))\\
&+S(p_2+p_4-p_1)(\lambda_1+\lambda_2) + \eta_tU_t(p_6-p_4)\lambda_1 + \eta_aU_a(p_6-p_2)\lambda_2\}/N, && (14)\\
\frac{\mathrm{d}p_5}{\mathrm{d}t} =& d_4p_5 + u_3\gamma_3(p_5-p_4)\{\beta_2u_2[\eta_t\epsilon_1U_t(p_4-p_6) + \epsilon_1S(p_1-p_4) + \eta_aU_a(p_2-\epsilon_1p_6)]\\
&+[S(p_2+p_4-p_1)(\lambda_1+\lambda_2) + \eta_tU_t(p_6-p_4)\lambda_1 + \eta_aU_a(p_6-p_2)\lambda_2\}/N, && (15)\\
\frac{\mathrm{d}p_6}{\mathrm{d}t} =& -A_3 + d_5p_6 - \rho_1(p_2+p_4) - \sigma_2p_7 + \{\beta_1u_1\zeta_2(S(p_1-p_2) + \eta_tU_t(p_4-p_6))\\
&+\beta_2u_2\epsilon_2(S(p_1-p_4) + \eta_aU_a(p_2-p_4))S(p_2+p_4-p_1)(\lambda_1+\lambda_2)\\
&-\eta_tU_t(p_6+p_4)\lambda_1 + \eta_aU_a(p_6-p_2)\lambda_2\}/N, && (16)\\
\frac{\mathrm{d}p_7}{\mathrm{d}t} =& d_6p_7 + u_3[(\gamma_2+\gamma_4+\gamma_5)p_7 - \gamma_2p_6 - \gamma_4p_2 - \gamma_5p_4] + \{\beta_1u_1\zeta_3(S(p_1-p_2)\\
&+\eta_tU_t(p_4-p_6)) + \beta_2u_2\epsilon_3(S(p_1-p_4) - \eta_aU_a(p_2+p_6))\\
&+S(p_2+p_4-p_1)(\lambda_1+\lambda_2) + \eta_tU_t(p_6-p_4)\lambda_1 + \eta_aU_a(p_6-p_2)\lambda_2\}/N. && (17)
\end{aligned}$$

with transversality condition $p_i(T) = 0, i = 1, \dots, 7$. We let $(\bar{S}, \bar{U}_a, \bar{R}_a, \bar{U}_t, \bar{R}_t, \bar{U}_{at}, \bar{R}_{at})$ be the optimum values of $(S(t), U_a(t), R_a(t), U_t(t), R_t(t), U_{at}(t), R_{at}(t))$.

The adjoint system in (11)-(17) is obtained directly from the application of Pontryagin's Maximum principle in [14]; that is

$$\frac{\mathrm{d}p_i}{\mathrm{d}t} = -\frac{\partial H}{\partial X_i}, i = 1, \dots 7 \quad \text{and} \quad X = [S, U_a, R_a, U_t, R_a, U_{at}, R_{at}]$$

.

Using the existence results in [12], we state the following theorem.

Theorem 1. *The optimal controls, (u_1^*, u_2^*, u_3^*) which minimizes J over the region $\boldsymbol{U}$ is given by the following expressions.*

$$u_1^* = \max\{0, \min(\bar{u}_1, 1)\}, \tag{18}$$
$$u_2^* = \max\{0, \min(\bar{u}_2, 1)\}, \tag{19}$$
$$u_3^* = \max\{0, \min(\bar{u}_3, 1)\}, \tag{20}$$

where

$$\bar{u}_1 = (S(p_2 - p_1) + \eta_t U_t(p_6 - p_4)) \left\{ \frac{\beta_1(U_a + \zeta_1 R_a + \zeta_2 U_{at} + \zeta_3 R_{at})}{2\alpha_1(S + U_a + R_a + U_t + R_t + U_{at} + R_{at})} \right\}, \tag{21}$$

$$\bar{u}_2 = (S(p_4 - p_1) + \eta_a U_a(p_6 - p_2)) \left\{ \frac{\beta_2(U_t + \epsilon_1 R_t + \epsilon_2 U_{at} + \epsilon_3 R_{at})}{2\alpha_2(S + U_a + R_a + U_t + R_t + U_{at} + R_{at})} \right\}, \tag{22}$$

$$\bar{u}_3 = \frac{[\gamma_1 R_a(p_2 - p_3) + \gamma_2 R_{at}(p_6 - p_7) + \gamma_3 R_t(p_4 - p_5) + \gamma_4 R_{at}(p_2 - p_7) + \gamma_5 R_{at}(p_4 - p_7)]}{2\alpha_3}, \tag{23}$$

and $p_i, i = 1, \ldots, 7$ *are the solutions of the adjoint system* (11)-(17).

Proof. We simply different the Hamiltonian H with respect to the controls (u_1, u_2, u_3) at the optimal control functions and then equate the resulting expressions to zero; that is

$$\frac{\partial H}{\partial u_1} = \frac{\partial H}{\partial u_2} = \frac{\partial H}{\partial u_3} = 0.$$

Upon solving for $u_1^* = u_1$, $u_2^* = u_2$ and $u_3^* = u_3$, we derive the optimal controls u_1^*, u_2^* and u_3^* as given by Theorem (1).

Using the bounds for the controls set in $\mathbf{U}$; that is

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

we obtain the expressions in Equation (23). □

4 Numerical simulation of the optimal system

We use the standard two-boundary point method as described in [13] to solve the optimality system (7), (8) and (11)-(17). Based on the given set of initial conditions, the state variables $(S, U_a, R_a, U_t, R_t, U_{at}, R_{at})$ are solved using the forward fourth order Runge-Kutta scheme over the simulated time. On the other hand, based on the transversality conditions, we solve for the adjoint variables associated with the state variables using the backward fourth order Runge-Kutta scheme. Then the controls are updated and the process is repeated until favourable values are obtained. Owing to lack of data on multiple substance abuse, we shall estimate most of the parameters used in the numerical simulation based on available literature. Other parameters are however be obtained intuitively from information related to methamphetamine and alcohol transmission dynamics. The nominal values of the parameters used in numerically integrating the model system of equations are indicated in Table 2. Similarly, the estimated costs associated with the reduction of substance abusers (U_a, U_t and U_{at}) are given in Table 1.

In South Africa, the cost of treatment for substance abuse ranges between R10000 and R75000 per month [16]. Although the costs are too high, most of the families that cannot afford these charges, often use the services of Alcohol Anonymous and Narcotics Anonymous as their support. In this work, for purposes of simulations, we shall consider the minimal cost as the average cost of treatment. Since prevention is cheaper than treatment, we have assumed that the cost associated with prevention (α_1 and α_2) through educational campaigns is half the cost of ensuring improved efficacy in treatment α_3 for substance abuser.

In this paper, we have assumed that the process of altering the social dynamics within a population is much more difficult (more expensive in this context) than reducing the likelihood of relapse into substance abuse for addicts in the same setting. Therefore, the relative costs tied to implementing the controls u_1 and u_2 are assumed to be higher than the relative costs tied to the controls u_3. Furthermore, we have considered the costs associated with alcohol abuse, U_a, methamphetamine abusers U_t and co-abuse of alcohol and methamphetamine U_{at} to mainly include the cost of dangerous behaviour and its consequences during substance abuse period. On the other hand, the cost associated with the controls u_1 and u_2 involves the cost of educating the public on the dangers of substance abuse and multiple substance abuse. After several numerical simulations, we give the weighting coefficients as $\alpha_1 = 5000$ per month, $\alpha_2 = 5000$ per month and $\alpha_3 = 10^4$ per month. We state that the proposed weights only serve the necessary theoretical interest.

Table 1: Costs associated with controls

Coefficient	Cost Value
A_1	R10000 per percentage reduction in U_a
A_2	R10000 per percentage reduction in U_t
A_3	R10000 per percentage reduction in U_{at}

Table 2: Nominal parameter values used in simulation

Symbol	**Value**	**Source**	**Symbol**	**Value**	**Source**
Λ	0.03	Estimated	σ_1	0.2	Estimated
μ	0.02	[17]	σ_2	0.3	Estimated
β_1	0.25	Estimated	σ_3	0.3	Estimated
β_2	0.2	Estimated	ρ_1	0.01	Estimated
γ_1	0.15	Estimated	ρ_2	0.01	Estimated
γ_2	0.1	Estimated	ρ_3	0.35	Estimated
γ_3	0.3	Estimated	ρ_4	0.25	Estimated
γ_4	0.3	Estimated	ρ_5	0.25	Estimated
γ_5	0.3	Estimated	ρ_6	0.78	Estimated
δ_1	0.03	Estimated	ρ_7	0.4	Estimated
δ_2	0.04	Estimated	η_a ,η_t,ζ_2 ϵ_2	1.05	Estimated
δ_3	0.033	Estimated	ζ_1, ζ_3, ϵ_1, ϵ_3	0.7	Estimated

4.0.1 Simulation results and Discussions

From Figure 2 we see that much less time is taken to clear the epidemic resulting from alcohol abuse, methamphetamine abuse and co-abuse of alcohol and methamphetamine when optimal controls are applied than without the controls. That is, the application of the two control strategies would result into a quicker decline in the population of substance abusers U_a, U_t, U_{at}.

Figure 2(a) reveals that without controls, the susceptible population gets depleted at a higher rate due to unchecked or high transmission rates. However, with the applications of optimal controls such as public education, the population is shown to grow exponentially. More individuals get to stay in the susceptible class as compared to dynamics without controls.

The profiles of the optimal controls are shown in Figure 3. We observe that shapes of the plots of the optimal controls u_1 and u_2 are similar; that is, both require an initial strong start

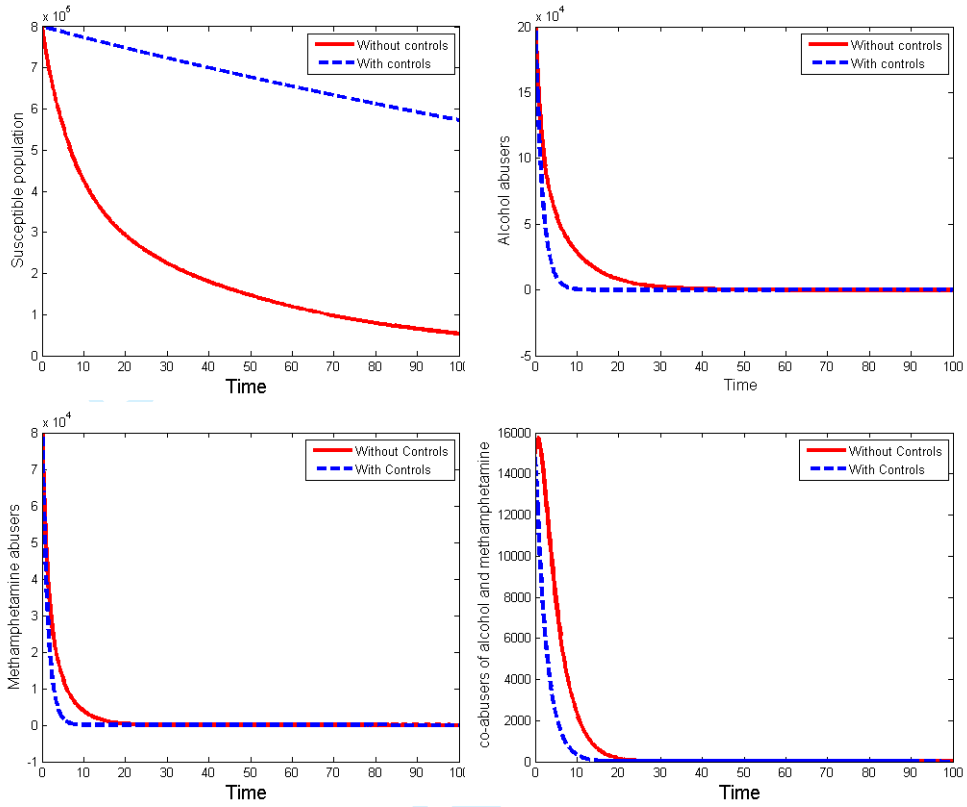


Figure 2: Graphs (a), (b), (c), (d) show the dynamics of susceptible population and substances abusers under different optimal control strategies, that is, without controls (solid curves) and with controls (dashed curves)

that should be maintained for a greater period of time if the epidemic is to be contained. In the beginning of the simulation, the control effort of u_1 and u_2 should be increased exponentially until 30 days, then maintained for the next 60 days and finally rapidly decreased to 0 at the end of the simulation. Observe that the controls u_1 and u_2 help reduce the likelihood of the susceptible population getting initiated into alcohol abuse and methamphetamine abuse respectively. Educational campaigns on dangers of multiple substance abuse should be maximised to reduce transmission.

On the other hand, plots for the controls on treatment efficacy u_3 show similar trends. See Figure 3(c). Treatment efficacy should be increased gradually over the given time period. Effective and efficient treatment services should be provided and maintained throughout the treatment period. It should be increased exponentially upto day 50, but with the substance abuse on going, the control effort of u_3 should gradually increase to the maximum. It then levels off until the day 95; hereafter, it should be gradually decreased to the level of almost 0 in the end.

The simulations show that a lot more emphasis should be employed in reducing the social interactions that result into substance abuse. This is tantamount to improved family support structures, social integration and cohesion and reduction of risk factors related to exposure to drugs. More resources should be channelled to public educational campaigns that raises awareness on the dangers of multiple substance abuse. Also, effective treatment services which ensures maximum quitting should be supported and encouraged. We suggest that the treatment services should be patient specific, proper, efficient and timely.

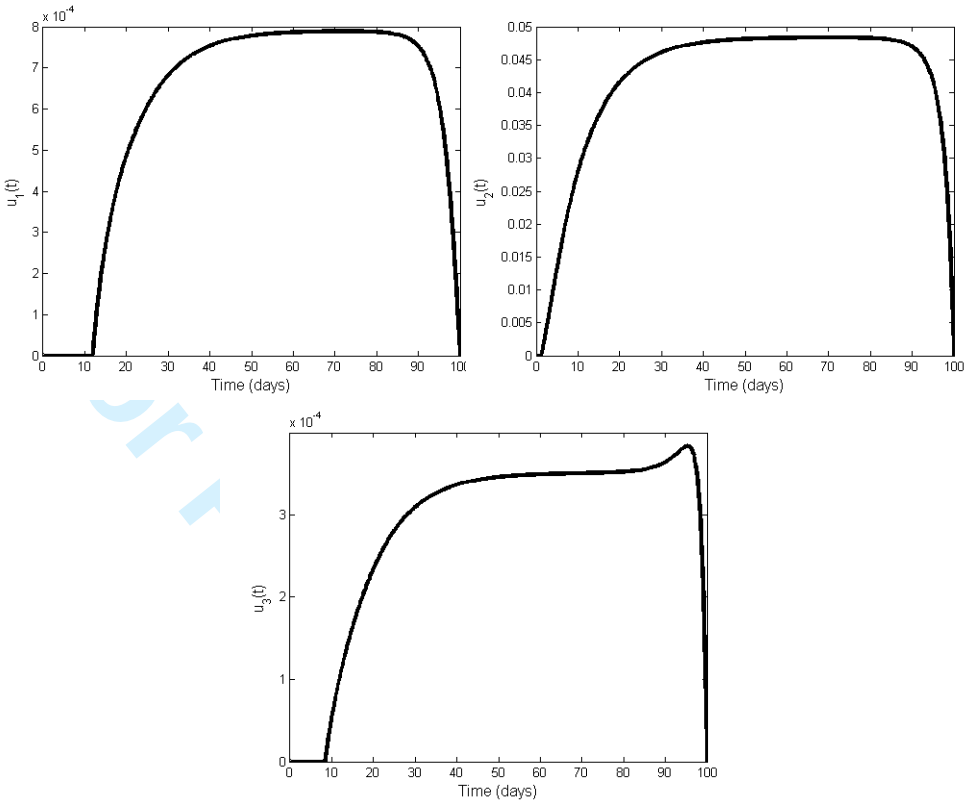


Figure 3: Profiles of the optimal controls u_1, u_2 and u_3

In conclusion, a deterministic model of co-abuse of alcohol and methamphetamine that includes educational campaigns and treatment efficacy as controls is presented and analysed. Using optimal control strategy, we establish the optimal controls. From the simulation results, we conclude that the combination of educational campaigns and effective treatment is very effective in minimizing the population under influence of alcohol and methamphetamine co-abuse and hence the attainment of substance free equilibrium in a much shorter time unlike the case without controls. Further, the presented model provides the required insights to understanding co-abuse in substance abuse epidemic and the impact of applied control policies. The results from our study are relevant in designing intervention strategies aimed at combating multiple substance abuse. This model

Acknowledgements

We are grateful to the University of Stellenbosch and the African Institute for Mathematical Sciences (AIMS) for their support during the production of this manuscript.

References

[1] J. P. Tian, S. Liao, and J. Wang. Dynamical analysis and control strategies in modelling cholera. Vol. 14 (2010).

[2] B. M. Adams, H. T. Banks, H. Kwon, T. Tran Hien. Dynamic multi-drug therapies for HIV: Optimal and STI control approaches, Math. Bio. and Eng., 1 (2) (2004), 223-241.

[3] K. Blayneh, Y. Cao, H. Kwon. Optimal control of vector-borne diseases: Treatment and Prevention. Discrete and continuous dynamical systems series B, 11 (3) (2009)., 587-611.

[4] H. R. Joshi. Optimal Control of an HIV Immunology Model, Optim. Control Appl. Math, 23 (2002), 199-213.

[5] D. Kirschner, S. Lenhart, S. Serbin. Optimal Control of the Chemotherapy of HIV. J. Math. Biol. 35 (1997), 775-792.

[6] M. Rafikov, L. Bevilacqua, A. P. P. Wyse, Optimal control strategy of malaria vector using genetically modified mosquitoes. J. Theoretical Biology, 258 (2009), 418-425.

[7] R. C. A. Thom, H. M. Yang, L. Esteva. Optimal control of Aedes aegypti mosquitoes by the sterile insect technique and insecticide. Mathematical Biosciences, 223 (2010), 12-23.

[8] B. Bower, Multiple Drug Use: A Dangerous Trend, Science News, Vol. 128 (1985) 6(1).

[9] G. Matthew, Kirkpatrick, W. Erik, Gunderson, R Frances, Levin, W. R. Foltin, L. C. Hart, Acute and residual interactive effects of repeated administrations of oral methamphetamine and alcohol in humans. Psychopharmacol. Vol.219 (2012) 191-204.

[10] J. Mendelson, Jones, R. Upton R., Jacob P, Methamphetamine and ethanol interactions in humans. Clin Pharmacol Ther. Vol.57 (1995) 559-568.

[11] S. Lee and E. Jung and C. Castillo-Chavez. Optimal control intervention strategies in low- and high-risk problem drinking populations. Socio-Economic Planning Sciences. Vol. 44(4) (2010) 258-265.

[12] W. H. Fleming and R. W Rishel. Deterministic and Stochastic Optimal Control. Springer (1975).

[13] S. Lenhart and J. T. Workman. Chapman & Hall/CRC. Boca Raton London Newyork. Optimal Control applied to biological problems (2007).

[14] L. S Pontryagin and V. G Boltyanskii and R. V Gamkrelidze and E. F Mishchenco. The Mathematical Theory of Optical processes. Wiley, New York (1962).

[15] T. K. Kar and Soovoojeet Jana. A theoretical study on mathematical modelling of an infectious disease with application of optimal control. Biosystems. Vol. 111(1) (2013) 37-50.

[16] Rehab centres in South Africa. Available from http://www.ineedrehab.co.za/.

[17] F. Nyabadza, S.D Hove-Musekwa, From Heroin epidemics to Methamphetamine epidemics. Modelling substance abuse in a South African Province. Math. Biosci. Vol.225 (2010) 132-140.