A SYSTEMS APPROACH TO POINT SOURCE INDICATION OF METFORMIN FOUND IN LOCAL WATER SYSTEMS – THE CASE OF MILWAUKEE COUNTY

by

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ABSTRACT

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Under the Supervision of Professor Wilkistar Otieno

Pharmaceutical pollutants are present in traceable concentrations in Milwaukee County water system and Lake Michigan. The actual point sources and nature of entry into the water system is difficult to determine with certainty. Pharmaceuticals have been found to persist at the South Shore Wastewater Treatment Facility (SSWTF) in Milwaukee, Wisconsin. The highest concentration was found to be for the pharmaceutical drug metformin. Metformin is a first line drug for the treatment of type 2 diabetes mellitus.

The broad goal of this exploratory study; the first of its kind, is to correlate trace concentrations of drugs to the point sources. Particularly, we have analyzed the demographic and geographical location of the population in Milwaukee County as potential contributors of drugs in the waste water system. The study uses metformin as a pilot study. The objectives of the Thesis are as follows:

Objective 1: Analyze the current status of quantifiable pharmaceuticals in Milwaukee County water

Objective 2: Analyze Milwaukee County's geographic, demographic and socio-economic status to determine and quantify the main population agent attributes to be used in objective 3.

Objective 3: Build an Agent Based Simulation Model that incorporates county residents as API point source agents, whose attributes as listed in objective 2 to determine their degree of contribution towards APIs in the waterways.

We were able to develop a working model and verify and validate the results through publicly available empirical studies and records. No studies were found utilizing simulation modeling to determine specific sources of pharmaceutical drugs entering the water system. No studies were found measuring the effect of age, race, income and geographical location of potential drug contributors on pharmaceuticals found in the water system. In this study, the results for the total number of diabetics in Milwaukee County was determined to be within an acceptable margin of error specified in the model. The model results indicate approximately 91,353 type 2 diabetics in Milwaukee County which is corroborated by Wisconsin's department of health reports indicating 93,020 hence the results are within 2% margin of error. The adjusted contributors that account for the measured concentration of metformin at the SSWTF were determined to be within the range of concentrations measured in the influent stream – Minimum: 3,200ng/L, Median 55,000ng/L, Maximum 100,000ng/L. The model results indicate that 76,899.3 $\pm$ 3,844.97 ng/L concentration present from the contributors which is within range of the actual measured concentration of metformin at the SSWTF influent stream. The model

output includes geographical, income, race and age demographics of the contributors by count for each of the 34 zip codes in Milwaukee County. Results analysis indicate that a geographical, racial and socioeconomic difference exist in contributors overall for Milwaukee County. The results also confirm the prevalence of the drug metformin entering the water system while identifying a zip code level detail of individual contributors. This Thesis is an exploratory test bed example showing that agent based modeling can be a valuable tool for industrial engineers and operation research when dealing with geospatial problems that exhibit variability through agency.

To my beloved daughters

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LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredients
ABMS	Agent Based Modeling Simulation
DES	Discrete Event Simulation
PPCP	Pharmaceutical and Personal Care Products
T2DM	Type 2 Diabetes Mellitus

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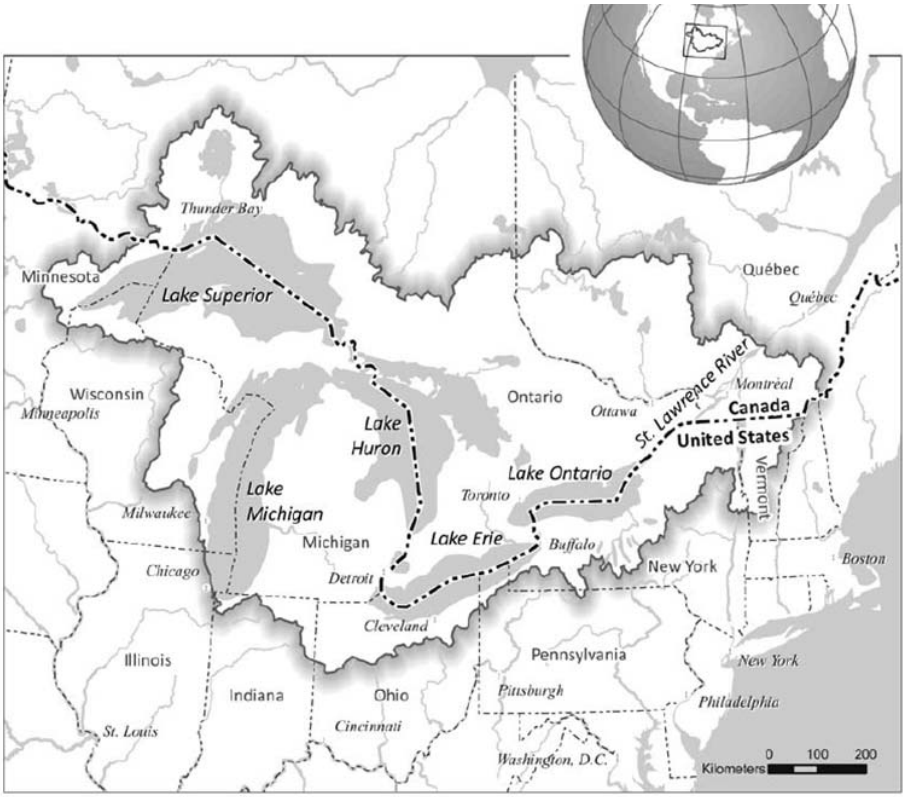
Chapter 1: Introduction

In recent years it has become more and more apparent that chemicals introduced by society are finding their way into our water systems. In a recent study in Milwaukee county, it has been determined that a wide variety of pharmaceutical ingredients are being found in Lake Michigan as well as the raw influent and effluent streams of the local water treatment facility (Muir 2006) and (Blair 2013). Although the impact of these results has not been fully determined, research has shown that these drugs have a more immediate impact on the aquatic environment, such as in lake fish (Ramirez 2009) and (Niemuth 2015). In particular, metformin has recently been found to cause gender bending effects in lake fish exposed to these drugs, such as males laying eggs. This same wildlife will find its way to being ingested at the dinner table of the local population.

Lake Michigan is one lake of the North American great lakes system. The Great Lakes form the largest surface water network on earth, containing close to 21% of the world's supply of fresh water, and 84% of fresh water in North America. Lake Michigan is bordered by 2 countries, Canada and the United States. On the U.S. side, Wisconsin, Illinois, Indiana, and Michigan States surround the lake, each having a shoreline, and are therefore constituents of Great Lakes–St. Lawrence River Basin Water Resources Compact (Great Lakes Compact-GLC). The GLC was established as a unique transboundary whole-basin approach to water management in the Lake Basin, to ensure collaborative management strategies. Other states that are part of this agreement include New York, Pennsylvania, Ohio, Vermont, Ontario and Quebec as shown in Figure 1. This shoreline is

therefore an integral part of the economical, recreational, ecological as well as socio-cultural well-being of the population around the great lakes region. In the past century (1909 to 2010), major focus of the discourse and discussions regarding the Great Lake Basin has been increased pollution especially from industrial effluents, increased withdrawals and diversions, which over time have caused adverse ecological and sociological impacts. It was not until very recent that focus was directed towards understanding the prevalence and effects of Active Pharmaceutical Ingredients - APIs) in the great lakes (NYDEC 2014). The challenge of APIs in lake Michigan for Milwaukee residents has been hightened by the current topic of discussion—Waukesha County's (west of Miwluakee) intent to draw fresh water from the lake and redirect their effluent back to the lake via Johnson Creek effluent treatment facility. The City of Milwaukee is concerned over the impact of the potential for additional APIs being introduced to the system from the City of Waukesha.



Source: Pacific Institute 2011.

Figure 1: The Great Lakes Basin: History of Shared Water Resource Management

Most research cover the challenge of identifying the prevalence of pharmaceuticals in the waterways from a top down approach, namely that concentrations of pharmaceuticals and personal care products in the water systems both nationally and internationally; (Kolpin 2002), (C. G. Daughton 2003), (Drewes 2003), (Boyd 2004), (Jones H. 2005), (Yu 2006), (Carlsson 2006), (Bartelt-Hunt 2009), (C. Daughton 2010), (Sui 2010), the great lakes (Muir 2006), and specific to Lake Michigan (Blair 2013), (Niemuth 2015). This study will mainly focus on a systemic bottom-up approach to API point source identification of potential contributors in Milwaukee County. Considering only the total final concentrations, or by utilizing pharmaceutical sales data if available (Oosterhuis

2013), the level of detail in the results would not be enough to identify the contributing sources to a manageable (localized) level. Simply knowing that the concentrations exist in the water system is analogous to only knowing that they come from the population feeding into the system. A greater level of variable data processing is needed to best simulate the real world complex system. This can be accomplished using the Agent Based Modeling Simulation (ABMS) approach, which offers flexibility to capture the social, cultural as well as economic dynamic attributes of a population that affect their contribution towards APIs in Milwaukee's watershed. ABMS is thus able to incorporate real world systems that require some level of human decision-making. The system is formulated from the perspective of the individual agents as discrete autonomous entities with particular goals and actions (Ng et al, 2010). As an illustrative example, in our case, the goal for a sick person (agent) to adhere (action) to medication is to get well. The agent then may make the autonomous decision that he/she is healed and hence stop taking medication. The next action may be to either dispose the remaining medication or take it to a collection point.

1.1 Active Pharmaceutical Ingredients (APIs) in the Water System

In the past, chemicals found in the environment that present ecological and social problems have been addressed by "end of the line" pollution control measures with treatment occurring at the wastewater stage However; the recognition of large trace-levels of "emerging" contaminants such as APIs has grown over the last several years,

especially in treated effluents. Ever evolving advancements and innovations have led to engineered treatment technologies capable of removing much lower traces of contaminants in treatment plants. However, despite these advanced potential solutions and available resources, limitations exist with regards to their economic sustainability (Jones H. 2005) From an engineering perspective the problem of waste water treatment is unique and complex. This is due to the wide range of chemical contaminants that can vary widely between municipalities. Some of the variables that dictates the prevalence of pharmaceutical compounds found is in direct relation to the prescribed treatments, prescription levels and varying health conditions of the contributing communities. Efforts to design innovative API removal are underway in both research and commercial fronts. Since the scope of this study is to consider population contribution of APIs and not their removal, we refer the reader to (Nakada 2007), (Radjenovic 2007), (Snyder 2008), (Verlicchi 2010), (Benitez 2011), (Jelić 2012), (Petrovic 2013) and (C. G. Daughton 2014), who provide reference of literature on API removal. Any efforts to address this challenge on a broad scale encompassing multiple targeted chemicals can pose a concern of waste especially when the treatment includes a target chemical not found in the local water system. The traditional reactionary means of addressing these environmental concerns is ill suited for long term sustainable contaminant reduction.

As the pressure on world resources increases with every passing day, Wisconsin finds itself among few fortunate states that have access to the regional fresh water lakes system. This privilege is tightly bound to the burden of responsibility associated with access and management of this valuable resource. Many of the world's concerns rely on

multidisciplinary approach to solutions. As industrial engineers, we may find that the tools we possess are of increasing importance to resolving issues of sustainability and the environment. The tools available to the industrial engineer include a systems perspective on identifying the problem and creating measurable solutions and improvements. There is no efficient strategy for the removal of all pharmaceuticals found in the water system. In order to propose a solution, it is imperative that the problem is correctly analyzed. As we now know, the amounts of active pharmaceuticals and personal care products entering the system are distinguishable and measurable (Kolpin 2002), (C. G. Daughton 2003), (Drewes 2003), (Boyd 2004), (Jones H. 2005), (Yu 2006), (Carlsson 2006), (Bartelt-Hunt 2009), (C. Daughton 2010), (Sui 2010). The immediate question that we seek to consider in this research is where do these chemicals come from? How do they enter the system? To answer these questions we will look at identifying the path of travel of these contaminants into the water system. By identifying the source of specific medications containing the prevalent APIs, we can begin to more effectively put into place measures that can eliminate or drastically reduce the prevalence of these chemicals entering the system from the point source.

Today, 68.1% of Americans are on at least one prescription medication, a statistic which is on the rise (Zhong 2013), (Law 2015). This means that there will be an associated rise in the numbers of contributors, a situation that will exacerbate the problem of pharmaceuticals entering the water system in the near future.

1.2 Hazardous Effects of APIs

Research on the hazards associated with the prevalence of these drugs in our greatest water resources in Wisconsin are still in their adolescent stages. More research continues to focus on identifying the side effects of these drugs to humans. So far however, the current trace level concentrations of APIs have already been shown to have detrimental gender bending effects on local wildlife, namely, fish (Ramirez 2009), (Niemuth 2015). These findings as well as the subsequent concern of long-term trace ingestion in humans, accelerates the need to prioritize holistic system-wide approaches to mitigate the dangers of letting APIs in our local effluent reach the main natural water system. The issue at hand is that the point source of these contaminants is not a chemical factory at the edge of the county or a multinational petroleum company, but rather a problem that we all participate in, oblivious to its consequences. Hence this problem is one that will require a concerted effort with the burden placed on us, the members of our community.

1.3 API Removal

Many studies have focused on identifying the extend of pharmaceutical ingredients in the water systems that may subsequently find their way into the environment; (Kolpin 2002), (C. G. Daughton 2003), (Drewes 2003), (Boyd 2004), (Jones H. 2005), (Yu 2006), (Carlsson 2006), (Bartelt-Hunt 2009), (C. Daughton 2010), (Sui 2010), as well as removal; (Nakada 2007), (Radjenovic 2007), (Snyder 2008), (Verlicchi 2010),

(Benitez 2011), (Jelić 2012), (Petrovic 2013) and (C. G. Daughton 2014). Researchers at UWM's College of Fresh Water Sciences have carried out studies of APIs found at the raw influent and effluent streams of the Milwaukee County wastewater treatment facilities which is the basis for medication and concentration information utilized in this study (Blair 2013). Of the drugs identified as being at concentrations above the detection limits, several of these drugs stand out, namely, metformin (highest), codeine, carbamazepine, and Gemfibrozil. API trace records will be discussed in details in Chapter 3 of this Thesis. Concentrations of these drugs have been found to be relatively high into and throughout the stages of the treatment process. It is important to note that several of the drugs found in the highest concentrations are the same drugs with the worst removal efficiency and thus ultimately reach the lake. Several of these high concentration drugs are also attributed to chronic illnesses which means that the concentrations are unlikely to reduce on their own without intervention. This is because treatment for chronic illnesses is continuous and ongoing, thus a steady introduction of these medications into the water system. As more individuals are diagnosed, they will be prescribed medication in turn compounding the concentrations found in the system. We will briefly examine some of the reasons for this as well as the underlying conditions that the medication is intended to treat in Chapter 3.

1.4 Holistic Systems Approach to Understand Sources of APIs

Addressing the issue of APIs is a sensitive matter, given that medical and health information is protected by privacy laws. In addition, local and regional sales data of specific medications is proprietary information and thus difficult to obtain in the United States. In order to get an accurate assessment of the source of the drugs entering the system, we will need to look into publicly available local health information as a basis for isolating the sources of APIs and provide the data necessary to develop the agent based simulation model.

We know that the prevalence and amounts of APIs has been measured at the "end of the line" especially in Milwaukee River—the inlet into Jones' Island treatment plant as well as post treatment inlet into Lake Michigan. The model framework will use the recorded traces and back-track them through a traceable path to the sources. Since these medications are prescribed to individuals afflicted with a condition that is treated with certain medications, the concentrations of the drugs originate at the diagnosed and prescribed individual, who is a member of the local population. This means that the source of the medication can be seen to begin from the community members who fit the criteria of diagnosis and treatment. The model framework therefore relies on population census data as well as geographical or zoning location of the point source that feeds the medication concentrations recorded in the water system. This requires that a certain level of detail be included that can account for the varying individual behaviors of the population. The simulation model will be developed utilizing agent based modeling that

can best recreate the variations in individual contributors to the system as a whole. Once the model is developed, we will verify and validate the current model to public health information available as well as the final output of the mass load concentration of the drugs of interest, to ensure that the model structure is feasible and valid. The basis and structure of the model will be discussed in chapter two and three, with the analysis of the results as well as the impact of future research focus discussed in chapter four and five.

1.5 Research Statement, Goals and Objectives

We have briefly covered the basis and motivation for focusing research towards understanding the not only the effects of APIs in waterways but also the factors that contribute to their increased concentrations. Even though very low or no traces have been found at the points where Milwaukee County harvests its drinking water in Lake Michigan, the presence of these pharmaceuticals nonetheless present emerging concerns over their long term effects to both humans and aquatic life. The overall goal of this research is to present a holistic systematic bottom-up approach to explore and understand factors that contribute towards high levels of APIs in the Milwaukee County.

The proposed Agent Based Simulation tool will aid in identifying major geographical zones to implement specific mitigating approaches such as localized pre-treatment plants. Drug dosage, as it will be seen in Chapter 3, is the leading cause for the prevalence of APIs in the water system. Currently, especially in the U.S.A, there is an increase in public outcry, advocacy and civil education against drug misuse and over prescription by doctors. This problem is especially prevalent in pain management.

Generally, APIs get into the waste water system through two ways; disposal into landfills and eventual seepage into the waterways, or excretion after use. The later mode of entry accounts for the largest amounts of API traces. The amount of pharmaceuticals element excreted on the other hand, is dependent on drug metabolic residue (percentage of drug elements excreted). Unfortunately, unlike veterinary drugs which have enforced Maximum Residual Levels (MLRs), pharmaceuticals have no standardized maximum residual limits and may at times have above 60% metabolic residual effects. As such, the ideal strategy to combat APIs in our water would require collaborative efforts between government agencies, the medical industry, the pharmaceutical industry, academia and the community at large. This ideal strategy would incorporate a combination of the following elements: (1) better drug design that enables them to fully metabolize on the body, (2) standardization—where FDA would set standards for metabolic residue depending on drug toxicity, (3) use—increased education on drug usage and adequate prescription and (4) disposal—increased drug take back drop-off points in all communities.

The goal of our study is to present a novel bottom-up approach to addressing the challenge of understanding the contribution of the community in its geographical location, demographics, social-cultural and economic attributes to the prevalence of APIs. This goal was be attained through the following three objectives:

Objective 1: Analyze the current status of quantifiable pharmaceuticals in Milwaukee County.

Task: Gather and pre-process data from studies that quantify API trace levels in Milwaukee County.

Objective 2: Analyze Milwaukee County's geographic, demographic and socio-economic status to determine and quantify the main population agent attributes to be used in objective 3.

Task: Gather and pre-process data on demographics, socio-cultural as well as economic attributes of Milwaukee County residents.

Objective 3: Build an Agent Based Simulation Model, which incorporates county residents as API point source agents whose attributes are listed in objective 2, to determine their degree of contribution towards APIs in the waterways.

1.6 Research Contribution and Broader Impact

The simulation model can be used as a test bed to determine the efficacy of API reduction strategies from a temporal-spatial-and demographic perspective. A study measuring the prevalence of these drugs at various stages of the water treatment process and subsequent entry into Lake Michigan shows that there is in fact a wide range of drugs entering the water system at varying concentrations as well as how these concentrations

persist through the treatment process. Of the list of drugs found in the system, several drugs had a very poor removal efficiency meaning that the concentration remains relatively unchanged through the advanced water treatment process. These are the drugs that are most prevalent in the lake as well. Of these drugs, the one that is of the lowest removal efficiency, the highest concentration and subsequent environmental impact is Metformin (Blair 2013). I will aim to consider the metformin source finding its way into the water system in a simulation model. This will be covered in greater depth in chapter 2 and chapter 3 as well as the means of determining the source path of these environmental contaminants.

Chapter 2: Literature Review

In this section we will examine the literature on the general scope and scale of the pharmaceuticals and personal care products, how they finding their way into the water system as well as quantified concentrations. We will follow with a review related work that has incorporated agent based modeling approaches towards solving sociological research problems.

2.1 Pharmaceuticals in Water Systems

Among developed countries, the United States has the largest market for pharmaceuticals in excess of $200 billion in 2007. The figure below shows a comparison of the sales volume in USD by country, with the United States exceeding the totals from Japan, Germany, and France combined for the same time period.

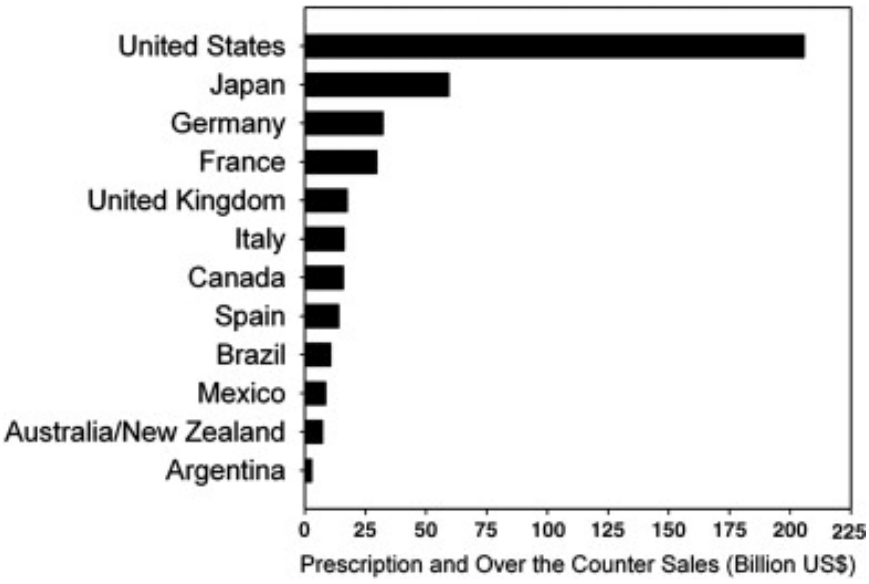


Figure 2: Pharmaceutical sales volume in USD by country

There are several methods for pharmaceuticals to enter the environment (C. Daughton 2013). However, as far as household sources of pharmaceuticals, there are 3 main ways that the drugs can be introduced into the environment, namely:

1- Excretion through the body system such as after ingestion, injection or infusion.

2- Topical medication being washed off such as during bathing

3- Disposal of leftover, unused or unwanted medication

Figure 3 below describes the lifecycle of pharmaceuticals and ways in which they enter the environment. The pathways and concentration levels vary by compound, structure, and use (Ruhoy 2007).

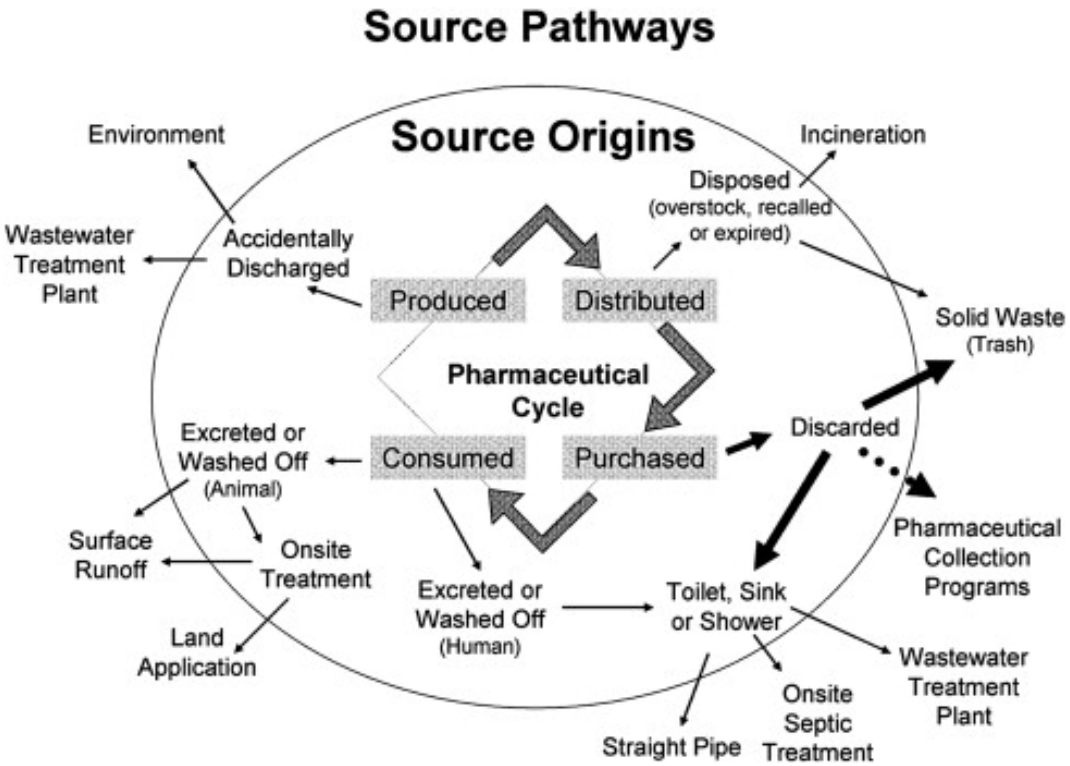


Figure 3: Source Pathways of PPCPs (Ruhoy 2007)

Addressing and remedying the prevalence of pharmaceuticals becomes difficult considering the biotransformation of pharmaceuticals in the human body or in the environment. In some cases even if a drug has been bio-transformed in the body, the parent compound may re-appear during wastewater treatment (Ruhoy 2007). Some proponents advocate that the reduction of pharmaceutical ingredients posing a threat to the environment and abusers would require efforts at the healthcare treatment level by prescribing, dispensing and medication consumptions in optimal quantities that would minimize the leftover quantities as well as the need for disposal.

The most common and recommended disposal practice of medication has been by flushing down the toilet, washing down the sink or disposal into household trash, which eventually ends up in municipal landfills. The first two disposal methods are the main means contributing to environmental concern. According to a study published in Environment International (Glassmeyer 2009), it is extremely difficult if not impossible to differentiate between drug consumption and disposal in wastewater effluents, through direct measurement. Many of the methods relied upon by studies to identify the medication disposal methods has been through questionnaire surveys of which the accuracy or sensitivity of this data is questionable.

One of the main ways to control or eliminate the impact of unused drugs on the wastewater systems is by altering the recommendations and methods of disposal to eliminate the direct to sewer methods, such as flushing. Many local and state governments have put in place medication drug take back programs which are set to reduce the quantity of unused and unwanted medication entering the environment as

well as a reduction in the drugs available for theft, abuse and accidental poisoning. The Milwaukee Metropolitan Sewer District (MMSD) has set up 2 day biannual events aimed at raising environmental concerns about pharmaceutical ingredients in the water systems. The efficacy of these efforts is questionable with only 600-700 people participating in 2008. There are several laws and regulations that pose limitations on these efforts that are beyond the scope of this paper such as those enforced by the DEA for transportation of drugs (considered trafficking) that are not prescribed to the individual transporting them. A collection program has the potential to provide valuable data such as unused drug inventory, reasons for non-use, and the types of drugs that are most in excess at this level. Although there is an insufficient understanding of the impact and significance of drug disposal and environmental impact, the disposal of unwanted medications is an easy target for early source control. "A more optimal and sustainable solution would be various alterations to the healthcare system to minimize the incident of leftover drugs to begin with, by optimizing the amounts prescribed and dispensed (Glassmeyer 2009) and (Ruhoy 2007)."

According to an article published in 2013 Home Health Care Management & Practice (Vaughn 2013), the majority of the approximately 3.9 billion prescriptions issued in the U.S. each year will remain unused. The variation in use is related to the underlying condition being treated (acute, chronic, illness or seasonal). The unused drugs pose concern because of the potential impact they would have on the environment as well as the contribution to unintentional poisonings and substance abuse. There are currently no federal regulations with regards to the disposal of unwanted medications and only

recommendations made by some government agencies. Unintentional poisoning deaths are rather widespread and are second only to motor vehicle accidents nationwide.

The FDA acknowledges the environmental concern for the disposal method, however, the FDA claim that the risk of accidental poisoning and abuse currently outweigh the potential risk to the environment due to flushing. The increasing concern about trace concentrations of medications in water supplies has raised concern for alternative and more effective disposal practices. Drug take back programs are an increasing means of control however the availability of these programs is limited and not available in every community. In addition the utility of these drug take back programs has limitations related to the dictates of the Controlled Substance Act. Specifically the individuals participating in the program are at risk of being accused of transportation of unused medicines especially if they are not the intended user. This violation is considered trafficking. It is also acknowledged that abusers of these medications acquire the drugs from friends or relatives, often contributing to abuse and accidental poisoning (Vaughn 2013).

Prescription medicine	Active ingredient
Abstral, tablets (sublingual)	Fentanyl
Actiq, oral transmucosal lozenge	Fentanyl Citrate
Avinza, capsules (extended release)	Morphine Sulfate
Daytrana, transdermal patch system	Methylphenidate
Demerol, tablets	Meperidine Hydrochloride
Demerol, oral solution	Meperidine Hydrochloride
Diastat/Diastat AcuDial, rectal gel	Diazepam
Dilaudid, tablets	Hydromorphone Hydrochloride
Dilaudid, oral liquid	Hydromorphone Hydrochloride
Dolophine Hydrochloride, tablets	Methadone Hydrochloride
Duragesic, patch (extended release)	Fentanyl
Embeda, capsules (extended release)	Morphine Sulfate; Naltrexone Hydrochloride
Exalgo, tablets (extended release)	Hydromorphone Hydrochloride
Fentora, tablets (buccal)	Fentanyl Citrate
Kadian, capsules (extended release)	Morphine Sulfate
Methadone Hydrochloride, oral solution	Methadone Hydrochloride
Methadose, tablets	Methadone Hydrochloride
Morphine Sulfate, tablets (immediate release)	Morphine Sulfate
Morphine Sulfate, oral solution	Morphine Sulfate
MS Contin, tablets (extended release)	Morphine Sulfate
Nucynta ER, tablets (extended release)	Tapentadol
Onsolis, soluble film (buccal)	Fentanyl Citrate
Opana, tablets (immediate release)	Oxymorphone Hydrochloride
Opana ER, tablets (extended release)	Oxymorphone Hydrochloride
Oramorph SR, tablets (sustained release)	Morphine Sulfate
Oxecta, tablets (immediate release)	Oxycodone Hydrochloride
Oxycodone Hydrochloride, capsules	Oxycodone Hydrochloride
Oxycodone Hydrochloride, oral solution	Oxycodone Hydrochloride
Oxycontin, tablets (extended release)	Oxycodone Hydrochloride
Percocet, tablets	Acetaminophen; Oxycodone Hydrochloride
Percodan, tablets	Aspirin; Oxycodone Hydrochloride
Xyrem, oral solution	Sodium Oxybate

Figure 4: FDA Prescription medications Recommended for disposal by Flushing

The EPA has in place a list identifying priority pollutants as well as accompanying water quality criteria. This list of 129 Priority Pollutants developed by the EPA was compiled with limited technical input, and does not fully encompass the wide variety of chemicals present in wastewater and storm water runoff that can pose a threat to our water systems (C. G. Daughton 2003). One important and largely impactful source of contaminants that has a worldwide implication is the chemicals introduced by urban activities and consumption by society. These Pharmaceuticals and Personal Care Products (PPCP) are derived from individual usage as well as disposal of unwanted expired medications. These have been present in the water system, caused by continued contribution by individuals in society, more so being true in areas of high population density. These contaminants do not necessarily need to have environmental persistence to produce negative effects because of the continuous nature of their introduction to the environment. To exacerbate the situation, the use of pharmaceuticals is increasing annually also leading to an increase of the contribution to the system (Law 2015) and (Zhong 2013).

The dominant source method of these prescribed pharmaceuticals and personal care products entering the urban water environment (i.e. sewer system, local rivers and lakes, landfills, storm water runoff) is through individual household usage. The disposal of unwanted cosmetics and medications into the sewer system as well as through excretion after consumption will lead to native active compounds as well as metabolites after use. The persistence of these drugs have also been shown through groundwater studies indicating some of these PPCP's remain intact after 8+ years of travel through the

subsurface waters (Drewes 2003). In order to evaluate the long term toxicity levels; the chemical persistence, continued low dose exposure and bioaccumulation potential should be considered. Studies have also indicated that the highest concentrations are more likely to be associated with intense wet weather events where PPCP loadings goes up by an order of magnitude with the increased storm water flow (Boyd 2004). The cause of this increase is related to the release and re-suspension of these chemicals from contaminated sediment in the pipes due to the increase in flow. PPCPs are intimately related to consumption patterns, societal lifestyles as well as aging populations that require greater number and doses of medications. "The issue (PPCP prevalence) necessitates much closer communication between science and medical healthcare if it is to be addressed in an effective manner." (Ellis 2006).

Acknowledging that water is a basic element of life, the increase in the global population and the subsequent increase in demand for water resources will begin to put a strain on resource quality and availability worldwide. Resource consumption begins to necessitate the consideration of purifying water of lower initial quality for reuse after treatment. In order to address this issue more attention has been placed on supporting water supplies with reclaimed water. In order to address the issues of water and resource management, efforts have been placed on identifying the chemicals finding their way into our water systems, such as pharmaceuticals and personal care products (PPCP). Determining whether PPCP pose a threat to public health is an issue that has not yet been fully resolved. Focus on these emerging contaminants will increase as water shortages

will drive municipalities to find alternative methods of addressing contaminants in water reclamation efforts.

Limited data is available associated with the prevalence and removal of these emerging contaminants (PPCPs) in municipal wastewater treatment plants. In addition, the studies on the factors related to their PPCP removal are in their infantile stages. A study by Yu, 2006 examined the occurrence and biodegradability of select pharmaceuticals in sewage effluent. The study, which involved empirical evaluation of 18 PPCP's, including their occurrence and removal evaluation, found that "the extent of removals were highly variable and could not be correlated to drug classification or structure." (Yu 2006). The study further found that several of the target drugs were effectively biodegraded during the multiphase water treatment processes. Continual improvements in analytical equipment and methodologies allows for the measurement of pharmaceuticals at lower and lower concentration levels in different environmental matrices.

According to a more recent study looking at pharmaceuticals in near shore habitats of Lake Michigan; the predictive ability of the fate of PPCPs in the environment is still lacking "particularly in lentic ecosystems" (Ferguson 2013). The authors looked in to the spatial and temporal variation of pharmaceuticals and personal care products in near-shore habitats of Lake Michigan. This study found that both time and temperature (and associated time of year) had significant influence on the concentration of the pharmaceuticals considered. However the variations in concentrations were found to differ at certain sites of the study likely attributable to amplified spring precipitation as

well as seasonal snowmelt. PPCP concentration found in Lake Michigan may be a function of temporal variation related to the associated collection systems and wastewater facilities. The relationship between combined sewer overflow and PPCP concentrations is murky at best. The study also found that the total temporal variation of PPCP concentrations differed from the variation in concentrations of individual pharmaceuticals considered. Temporal variation of PPCPs is not well documented or studied, and the association with environmental prevalence is not currently clear.

In order to assess the removal of PPCPs through waste water treatment plants, the chemical characteristics of the pharmaceuticals, the treatment process employed by the wastewater treatment facility as well as the concentrations entering the treatment facility in the influent stream should be considered (Le-Minh 2010), (Verlicchi 2010) and (USEPA, 2010). This has been considered in several studies examining the removal of these contaminants in the wastewater treatment process (Nakada 2007), (Radjenovic 2007), (Snyder 2008), (Verlicchi 2010), (Benitez 2011), (Jelić 2012), and (Petrovic 2013). For the purposes of analysis of the model inputs for this thesis, we will take a closer look an empirical study of the prevalence of PPCPs in local water systems. In a study examining the prevalence of pharmaceuticals and personal care products in Milwaukee County, PPCPs were measured at the Milwaukee County South Shore Water Reclamation Facility in Oak Creek, WI over a 2 year period (6 dates from spring to fall) (Blair 2013). Samples were taken at the inlet of the facility, as well as at the various stages of treatment and at the exit stream from the facility. This study allowed the authors to assess the amounts of 54 select PPCPs across the subsequent steps of water treatment, allowing for the

identification of the prevalence and removal efficiency of these chemicals at the south shore water reclamation facility. Even with direct measurement, the large number of variables potentially influencing the removal of these differing compounds limits the ability to determine a general biological degradation rate constant. This study however does help in identifying the variation of removal efficiency amongst the considered PPCPs. These findings support the notion that a broad stroke implementation at treatment facilities does not have the ability to remove the large number of differing chemicals that are introduced to the water system from the local community. This would necessitate additional efforts at mitigating the introduction to the water treatment facility to include efforts such as drug take back programs, health awareness, dose adjustments, and prevention. In order to effectively undertake such efforts would require additional information on whom and where these efforts would be most beneficial.

Maximum removal of the PPCPs would require an individual or partially grouped approach to achieve effective treatment. Many of the PPCPs measured did in fact see a significant reduction if not complete removal from the waste water system. This however was not the fate of a few of the drugs evaluated where the concentrations persisted above measureable levels through to the effluent stages of treatment. One limitation of the study is the failures to account for the time of year that the measurements were taken. The measurements were taken during the spring/summer period only. In the summer period for instance, the temporal variation and seasonal nature of some of the PPCPs considered would indicate a low measurement, yet the PPCPs may be present in high concentrations at other times of the year. An example of this would be drugs such

as antibiotics used to treat Influenza complications where more cases of associated hospital visits are reported in the winter months that at any other time (SurvNet DHS 2014). Another example would be for antihistamines used to treat seasonal allergies. It is of note that the drugs found that persisted with the highest concentrations at both the influent and effluent streams were prescribed pharmaceutical medications for chronic or acute health conditions (Blair, 2013). The single drug with the highest persistent concentration in Milwaukee County was found to be metformin – a drug primarily used to treat type 2 diabetes mellitus.

2.2 Measuring and Estimating Pharmaceutical Concentrations in Wastewater

In a 2010 study aimed at estimating wastewater pharmaceutical influent concentrations, a mass balance model was introduced to estimate the prescription pharmaceutical loadings to municipal wastewater facilities (Ottmar 2010). Prescription pharmaceutical ingredients are different from other pollutants and should be recognized as such, due to the predominant source of consumption and excretion by humans. This is an important factor in determining their environmental behavior and fate "because the principal points of loading for these anthropogenic contaminants are municipal wastewater treatment plants (Ottmar 2010)." The majority of for human consumption pharmaceutical ingredients will find their way to the wastewater treatment facilities, yet many of these treatment facilities have not been designed or engineered to remove pharmaceuticals. Efforts have been made to determine specific methods of drug removal

although generally specific to particular chemicals (Miller 2010). Additionally, the long-term impacts of these compounds, which are designed to induce a physiological effect even at low concentrations, are just starting to be examined in aquatic ecosystems. Part of the reason that this issue is an emerging phenomenon is due to the fact that the PPCPs are being reported at trace level concentrations in municipal water systems. These low concentration detections may have been limited by the technology and sensitivity to measurement at trace concentrations. This presents both technological and economical analytical challenges in the ability to quantify the concentrations present in natural and wastewater samples. These challenges are exaggerated by the limited number of studies published to measure the effluent and influent pharmaceutical prevalence in wastewater treatment plants despite the increasing scale of prescription drug use in the developed world (Ottmar 2010).

Given the way the current healthcare system operates in the United States, industrialized healthcare is reliant on prescription medication to treat illness. . Some studies have tried to assess the prevalence and persistence of PPCPs in the environment (Ottmar 2010), (Carlsson 2006), (H. Jones 2005) (Ferguson 2013) (Radjenovic 2007), (Nikolaou 2007), (Snyder 2008), (Yu 2006), (Verlicchi 2010), and many of the early efforts did not consider drug metabolism in the body. Some studies have considered pharmaceutical sales data as the source of evaluation for instance in Europe (Oosterhuis 2013), however, this information is not readily available in the United States. In addition, the study focused on correlating sales data to an estimate of the concentration being introduced into the water system; and the objective is one of estimating the mass

population (as a whole) contribution estimate. The concentrations are empirically available and the empirical data will always more accurate than simulation of the system. Simulation modeling is most effective in situations where it is not physically or economically feasible to make system changes or predictions (Kelton 2003).

Many of the drugs entering the water system with high measured concentrations are neither top prescribed pharmaceuticals nor the most extensively researched, such as metformin, oxycodone and gabapentin (Ottmar 2010). Their influent estimation model presents useful estimates of influent concentrations utilizing a handful of publicly available input parameters. The study of the transportation, source occurrence, and environmental impact of drugs that exhibit a high concentration in the effluent such as metformin and gabapentin are of special interest; as they possess significant risk of inducing environmental toxicity.

A 2013 study in Australia, published in "Environmental Science and Technology" (O'Brien 2013) identifies that population density is an important input parameter to normalize chemical loads measured through wastewater analysis to obtain an estimation of per capita consumption or exposure. A major factor identified in validating population estimates is that the number of people contributing to the PPCPs waste water system should be as accurate as possible. In their study the measurements of certain drugs were recorded on census day in Australia where the assumption is made that the most accurate time specific population representations are made. An alternative method of population estimates are also discussed where population count can also be based on the number of tax payers contributing to the wastewater streams. These are 2 of the 4 options listed for

calibrating the Bayesian inference model for estimating population size and subsequent contribution to the wastewater stream. The study does make the case that results from wastewater analysis can be directly related to population by determining the mean dose, thus defining the number of the population that are contributors.

There have been several proposals of estimating illicit (and prescription) drug consumption in populations by quantifying the drug concentrations in wastewater samples (C. G. Daughton 2001), (Zuccato 2005) and (F. Y. Lai 2011). The development of this concept also considers that temporal variations exist that may affect the concentrations measured due to several reasons. This serves as a refinement in getting accurate insight to data and estimations made for use in health and law enforcement efforts to understand the ubiquity of this phenomenon in populations in question. These studies have introduced sophisticated analytical methods to estimating the drug consumption per capita through back calculations and average dose concentrations. They have supported the application and methods of these studies, yet uncertainty still exists with relation to sample collection and insufficient reporting on the numbers of people contributing to the analysis along with measured concentrations.

Many variables that are still in development contribute to this complexity including sampling location, characteristics of the sewer system which requires additional considerations such as increased sampling frequency, flow proportion considerations and temporal variations in flow. This serves to reduce the effects of random artifacts in sampling ranging from over 100% to small enough where the change is not significant (Ort 2010). In addition to the measurement concerns, reliable information on the population

contributing is important for the back calculation accuracy. Methods in consideration of this have aimed to use census data, such as on census days (F. Y. Lai 2013) as well as specific design capacities of sewage and water treatment plants. In addition some researchers have introduced practical correction methods utilizing indicators in analysis to improve the estimation and accuracy of study efforts (F. Y. Lai 2011). An introduction of 5% error in sewer loads is used to account for unknown uncertainties, as well as up to 20% for the treatment plant flow capacities. The variations in consideration are generally attributed to temporal variation such as high rain loads which would effectively dilute measured drug concentrations or even increase due to the dislodging of residue in pipes from higher flow rates (Ruhoy 2007). As far as excretion rates are concerned, these values are not commonly reported and presented only as ranges. In this case a normal distribution is used rather than uniform distribution to avoid excluding values outside of the minimum and maximum range values (F. Y. Lai 2011). It is recommended that in the absence of regional or local drug consumption data, an assumption of homogenous distribution of national annual consumption suffices, with care taken to demonstrate the local demographics do not differ significantly from the national average. In order to make the most of the contributor estimations, the drugs under review would need to be assumed to have not significantly biodegraded in the sewer system as well as being measurable without additional extraction. Some of the most prevalent drugs are those that are relatively persistent and not effectively removed from water in the treatment process (Blair 2013). The uncertainty assessment introduced by developing studies aim to account for the inherent variation in sampling, chemical analysis, flow readings,

excretion rates and contributor estimates feeding the wastewater system. The benefit of this uncertainty consideration is that it provides a measure by which any difference or alterations related to drug loads in the system (smaller than the introduced uncertainty factor) can be considered insignificant (F. Y. Lai 2011).

2.3 Agent Based Modeling

In this section we will define Agent Based Models Simulation (AMBS), its inherent basic structure as well as attributes of a problem that would make ABMS a viable tool of choice. An article presented at the Proceedings of the National Academy of Sciences (Bonabeau 2002) describes some of the basic elements of agent based modeling (ABMS). These include the aspect that each agent is responsible for its own situational assessment and makes decisions based on a defined set of rules. The initial developers of ABMS identified ABMS as a mindset that is adopted at the onset of model development used to describe the system in question from the point of view of the model constituents. The behavior of the constituents or agents, along with their interactions with each other and/or the environment, serve to capture emergent phenomenon from the bottom up in simulations. Where there is potential for emergent phenomenon, ABMS is recognized as most applicable when agent behavior is nonlinear and can be characterized by defining logic such as, using if and then rules or setting thresholds. Agent based modeling is a first line choice when examining a system composed of entities with some level of behavioral logic. Agent based modeling is also recognized as being a flexible solution due to the relative ease of adding agents and modifying the agent complexity made through the

behavioral and environmental factors. This is also useful where the appropriate level of complexity is not clearly defined and is achieved through fine tuning the defined parameters.

As the scope and definition of agent based modeling continues to be explored, ABM's that are empirically based (Janssen 2006) are examined. "There is more confidence that ABMS is a valid technical methodology that can provide novel insight to scientific inquiry." Since ABMS are derived from human and social interactions and decisions. Usually, empirical information (be it quantitative or qualitative) can be used in a variety of ways to supplement the model information (parameters and variables). This empirical information can be used as input data for the model and to examine a particular situation from which the data is derived. "With ABM, the researcher explicitly describes the decision processes of simulated actors (agents) at the micro level. Structures emerge at the macro level as a result of the actions of the agents (Janssen 2006)".

However the methods of evaluating a model through statistical analysis or goodness of fit are not sufficient in the application of Agent Based Models where in some cases there may not even be data to perform a statistical evaluation. There are other criteria by which the model can be evaluated which include the inquiry of whether the empirical observations are provided with a benefit of gaining a better understanding through the ABMS approach. There are several approaches to incorporating data sources into the model, as well as the wide range of data types involved. Sources include case studies, lab experiments, stylized facts and role games. In many ABM's, multiple sources may be available but may not provide complete information. In these instances a

compilation of field observations, case studies, surveys and the like are used to develop the various components of the system in evaluation.

When reviewing what an agent is in the ABMs, there is still no universal agreement on the definition of an agent. However, it is generally accepted that agents represent independent entities in the model (Macal 2005). This can range from reactive decision or behavior rules to a more complex adaptive artificial intelligence. It is common to see that agents should contain both foundational rules as well as a higher level set of rules that can be called upon to alter the base level rules providing adaptation. It is also ubiquitous that an agent possesses the capability to make independent decisions. An agent is also considered situated, being in a specified environment. The behavior of agents are driven by an objective or goal which provides a "motivation" for agent behavior and decision making while being autonomous and self-directed. An entity or agent is also varied by it attributes and resources accumulated.

Agent based Modeling has a history derived from multi-agent systems as well as robotics and artificial intelligence while modeling more complex human social behavior and individual decision logic (Macal 2005) and (Bonabeau 2002). In order to develop an agent based model, the approach is similar to the way one would approach any type of simulation or model. One differentiating element is that ABMs takes the perspective of the agent primarily. According to the Tutorial on Agent-Based Modeling and Simulation (Macal 2005), some of the requirements of AMBs beyond the standard model building procedures are as follows:

- Identify the agents and define a theory of associated behaviors
- Identify the agent relationships if any, and the associated agent interactions
- Define ABMS development strategy and platform
- Acquire the agent related data
- Validate the model as well as the agent behavior models
- "Run the model and analyze the output from the standpoint of linking the micro-scale behaviors of the agent to the macro-scale behaviors of the system."

It is important to note that entities or agent are the decision makers in the system. ABMS can provide either an overarching framework for the components of the model based on the approach or it can incorporate agent sub models that are embedded into larger model systems. Using ABMS in combination with other modeling techniques are known by different names including hybrid modeling or model blending (Macal 2005). Many agent based models can find benefit by starting with system identification as well as the cause – effect relationships in the model. In modeling ABMS it is important to know the specific target and not increase the complexity of the behavior rules beyond the necessity of the model objectives. Agent based modeling defines a new frontier in expanding the traditional modeling approaches in ways that are not otherwise possible. The scope of agent based modeling continues to expand and has developed into a broad disciplines beyond its biological or ecological roots. One of the more developing areas of agent based modeling its application in analyzing patterns and structures that emerge from a system level, which are not apparent from the behaviors of individual entities. To

determine whether or not an agent approach is warranted, the following considerations should be addressed.

- Agents are present naturally in a system
- Discretely defined decisions and behaviors present in the system being modeled
- Agents adapt and change their behaviors
- Agents could learn and engage in dynamic strategy behaviors
- Entities (agents) have spatial components to behaviors (environment contributes to behavior decisions)

According to the book "Design of Agent based Models" (Šalamon 2011) an agent can be structured in different ways. Reactive agents (behavior-based) are "one of two most important paradigms of agency." Reactive agents are simple yet important type of agent especially where a large number of relatively simple agents are required. They react to precepts and information from the environment rather than define or model the environment for future action planning. Much of the logic, intelligence and considerations that determine actions taken by reactive agents stem from the "if then" logic selections. This is the type of agent that will be utilized in this model. There are no widespread rules indicating candidacy for agent based models. However, Salomon presents some guidelines or questions used to determine the efficacy of agent based modeling as the simulation tool as follow:

Are there entities that can make decisions?

Does the system appear to possess dynamic characteristics (i.e. former states influence future states)?

Is the behavior of the system at the micro level?

Are spatial factors of the environment important for the simulation?

In an article published in the 22nd International Conference of the System Dynamics Society in 2004, an overview and link between the more mature systems dynamics and discrete event simulation modeling to agent based modeling techniques is discussed (Borshchev 2004). In the modeling level chart below, the problems at the top of the chart represent aggregate values, system trends and other such global behaviors and the problems at the bottom of the chart are representative of micro scale, operational problems, and often contain more details that are important to the singular objective rather than the overall system's goal. As can be seen, agent based modeling has the flexibility and ability to be used in a wide range of levels of abstraction.

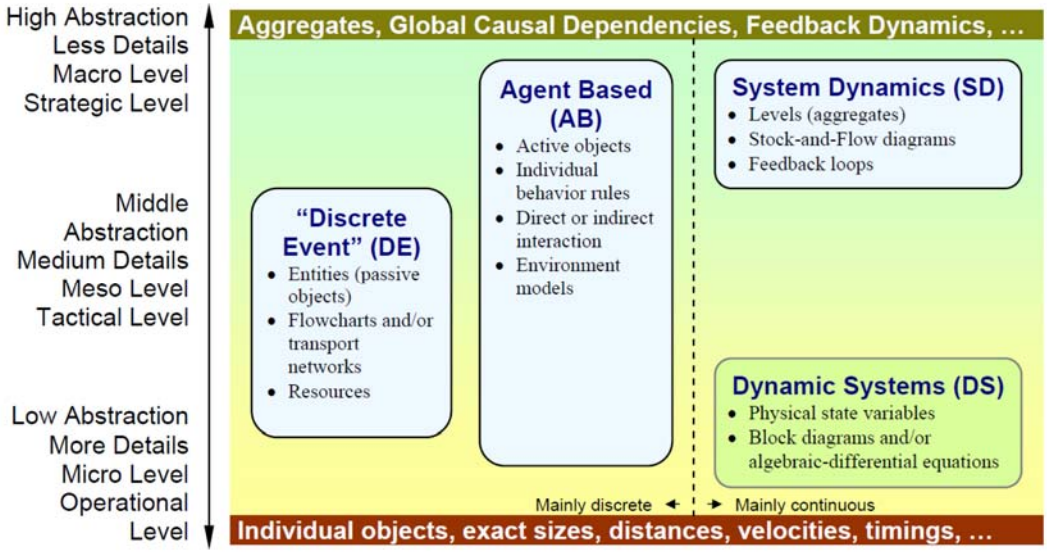


Figure 5: Paradigms in Simulation Modeling on Abstraction Level Scale (Borshchev 2004)

The similarity between Discreet Event (DE) Simulations and ABMS are many. Just like in ABMS, DE modeling has entities which can easily become agents. The entities are considered passive objects which follow rules on a system level. The difference between the two modeling approaches lies in the incorporation of entity behaviors. Particularly, one benefit of ABMS is that additional behaviors can be added to the model to capture or incorporate details on an individual level which may not be possible in DE modeling. In some cases, when interfacing between the two modeling methods, a "dispatcher" may be needed to coordinate agents' access to the resources available. This dispatcher would be considered an element of the environment from which the agent draws behavior rules a systems data table.

Unlike ABMS where the agents are autonomous and can therefore go through the system based on their interaction with each other and the environment, discrete event simulations' entities do not have a choice and so they travel through the systems' flowcharts via processes such as queue, seize, delay, and release. As such, ABMS is general approach, allowing for the expansion into more dynamic and complex structures. It also provides the ability to construct a model in the "absence of knowledge about the global interdependencies" (Borshchev 2004). This means that if little is known about the aggregate relationships and perception about how the entities or participants behave, you will be able to develop an understanding of the global behavior.

ABMS are governed by individual entities that possess some level of autonomy. These autonomous entities (agents) contribute to the overall evolution of the system in question (Bandini 2009). This differs from the approach of other modeling techniques, particularly DE, in that the dynamics of the system is a result of the overall individual interactions and actions rather than a global function definition. The geo spatial location or environment also plays a prominent role as it influences the behaviors of the simulated entities or agents and the subsequent agent actions.

The goal of a model of this nature is to observe some aggregate level of behaviors such as "the density of certain types of agents in an area of the environment, the average length of a given path for mobile agents, the generation of clusters of agents, etc." hence, they require the context of the environment to be meaningful. It is observed that despite a few common elements, agent based modeling is dramatically different in the way agents are defined as well as the impact and role of the environment. Agent based

models can be considered systems of significant complexity which may be the result of interactions between agents and environment. Some agents are defined as being reactive in the sense that the behavioral actions are a result of input or perceptions from their interactions with the environment or with other agents. This is usually set up in a way that defines the agents' condition-action rules as well as an accompanying selection strategy for the rules or actions lists. To the contrary, deliberative agents are defined by more complex rules and action selection process. Specifically, the behavior rules are often time dependent and are derived from a memory bank of cause-effect relationships and individual perceptions of the environment around the agent. Some models will inherently utilize a hybrid architecture consisting of layers of reactive and deliberative behavioral structures. "There are many possible dimensions and aspects of agent interaction models that can be chosen and adopted in order to define a possible taxonomy (Bandini 2009)."

When defining the autonomy of an agent, often times the agents are set to perform an action as a reaction to an external call. However, an agent may also decide not to perform an action that was required by another agent or entity. "Agents are considered in general to be temporally continuous and proactive (Bandini 2009)." In order for the structure of agent based models to function, in some cases it is necessary to have the agents effectively exchange knowledge or share ontology. This means that agents or entities must have meaning, properties, or framework that are uniform across the system. Agent based modeling and simulation approaches are still considered relatively young, yet vastly diffused approach to systems analysis. The vague and diverse

definition of the agent based modeling parameters makes it difficult to clearly state what an agent based model is and what is not. There is however a shared understanding that it is a bottom up modeling structure that provides insight and predictability of the overall complex systems (Bandini 2009).

According to a symposium on Operation Research (Siebers 2010), the question was posed as to why ABMS are not widely used in operations research as it is in economic or social sciences? The panel discussion agreed to a point made by Peer-Olaf Siebers that, "true ABS models in operations research (OR) do not exist. Instead, in OR we have combined DES/ABS models where we represent the process flow as a DES model and then add some active entities (to replace the passive DES entities) that are autonomous and can display proactive behavior". Next we will consider some applications of ABMS to related sociological research problems.

2.4 Related Problems Approached Using Agent Based Models

In this section we will consider agent based models related to non-communicable diseases, social behavior considerations and water systems. In some cases there is necessity to model agents in social context where geographical location is an element of consideration. An example of such technique was presented in an article utilizing agent based modeling to identify economic segregation patterns that affect health (diet) (Auchincloss 2011). The objective was to examine inequalities in diets and health outcomes by income and residential segregation. The approach was made to preference

i.e. high income households prefer healthy food options and thus live in areas where there are more healthy food options available and the opposite is the case for low income households. The argument is made that health food stores are situated near their target market customers and thus end up in areas of higher mean income levels or socioeconomic status. One may argue that the higher cost of healthy foods exaggerates the disparity between options and preference, placing healthy foods beyond the reach of poor households. Residential economic segregation also plays a big role in healthy food availability, and is a reflection of the income differences and customer base of healthy food providers. There is a tendency of these stores to be located in areas with a higher average income thus indirectly influencing the health outcomes of residents in the area.

Translating this scenario to agent based model, the role that segregation plays in defining dietary behaviors as indicated above is explored. This exploratory model is set to provide insight into why the observable phenomenon of income inequality and geographical segregation of food options exists. It is intuitive that if a household shopped at a healthy food store, then their diet followed a healthier lifestyle. The model aims to address the argument that contributing factors of income inequality and spatial access to healthy food plays in supporting these inequalities. If low-income households alter the preference in support of healthier foods, the result would be a reduction in the segregation of healthy resources and the income differential would begin to disappear. Favorable preferences of healthy foods as well as equally favorable prices both needed to be present in order to improve the health outcomes across income levels. The variables that contribute to the disparity are a part of a complex system of related

processes that are not clearly understood. The benefit of utilizing agent based modeling in this context aid in a deeper understanding in how health disparities develop and emerge in economically segregated environments by defining agent behaviors as a function of geospatial location and inherent income differences.

There are many levels of incorporating behaviors in agent based simulations, where they are commonly associated with a goal orientation as well. This goal orientation is essential to drive the selection of underlying behaviors that are to be examined in the model. Akhbari (2013), introduces a framework that was used to manage water resource conflicts. This framework considers behaviors of agents (stakeholders) that are hierarchical in nature and the interactions between them (Akhbari 2013). The goal of their paper is to find out effective strategies and water resources management policies that may encourage parties to cooperate.

In this paper, most of the decision logic for the agents is based on cooperate or no-cooperate decisions and remove the individual self-preservation position present in the Prisoner's dilemma game theory. This assumption indicates that the Pareto optimal solution is much lower in the non-cooperative structure than the cooperative structure (Ghotbi 2014). According to Akbari et al. 2013, the cost of "non-cooperation", either decision or time based, (for instance when applied to the San Joaquin Delta) is detrimental to all parties involved. This time dependent cost is related to the conditions of the water table deterioration as a result of time spent by the non-cooperating agents. The challenge of trading off time and cost validates the need for ABMS with goal-oriented behavioral structures. Since a collapse of the system can impose significant costs to both the

governing units and water users/stakeholders, the sooner the parties cooperate, the less damage may occur. This can be applied to many situational type decisions such as market analysis, health and goal orientation in ABMs. The basics of behavioral motivation in agent based modeling should follow this same logic.

Agents are driven by a goal; either overall goal or a series of sequential goals, that defines their decision making. Drawing from the two examples, the overall goal of the agents in our model is to get well from their illness. Thus this goal drives their action to adhere to medication. Similar to the ensuing examples, not adhering medication only exacerbates the agents' future health status. The longer the individual waits to adhere, the distance from the goal (deteriorating health) is also increased accordingly in health outcomes.

The American journal of public health published a review article of agent based modeling of non-communicable diseases (Nianogo 2015). There is a growing interest in utilizing systems science approaches to gain a better understanding of complex public health issues. As such, ABMS have been used to analyze such complexities of non-communicable diseases, given that they represent a leading cause of mortality worldwide.

Although ABM's is most widely used in ecology and public health to evaluate epidemics and infectious diseases, they consist of three key elements that allow for their use in analyzing non-communicable diseases. First, a set of agents is defined, and then characteristics of the agents are defined (attributes) such as age and gender. Agents in

the model can assume different identities, including individuals, organizations, particular groups and communities. The agents should be autonomous, goal orientated and capable of making decisions. The second element is a set of decision rules outlining how agents can interact with each other or with the environment. The third is the geospatial or environmental relationships. The environmental factors in ABM's differ by application and are often times considered passive (i.e. low relevance) to the processes under study.

Of the studies reviewed in this publication, it was found that higher proportions were set up to assess the impacts of health outcomes or the efficacy of interventions. "Physical activity, diet, and diabetes related complications and management were the most studied outcomes." An example of this is examining the progression of diabetes and diabetes related complications. Between 2003 and 2014, 22 relevant articles related to non-communicable diseases were identified, an indication of continued developments in employing agent based models in the realm of epidemiology. There exist some conceptual commonalities that govern the state changes in the model structure of agent based designs as can be seen below in Figure 6.

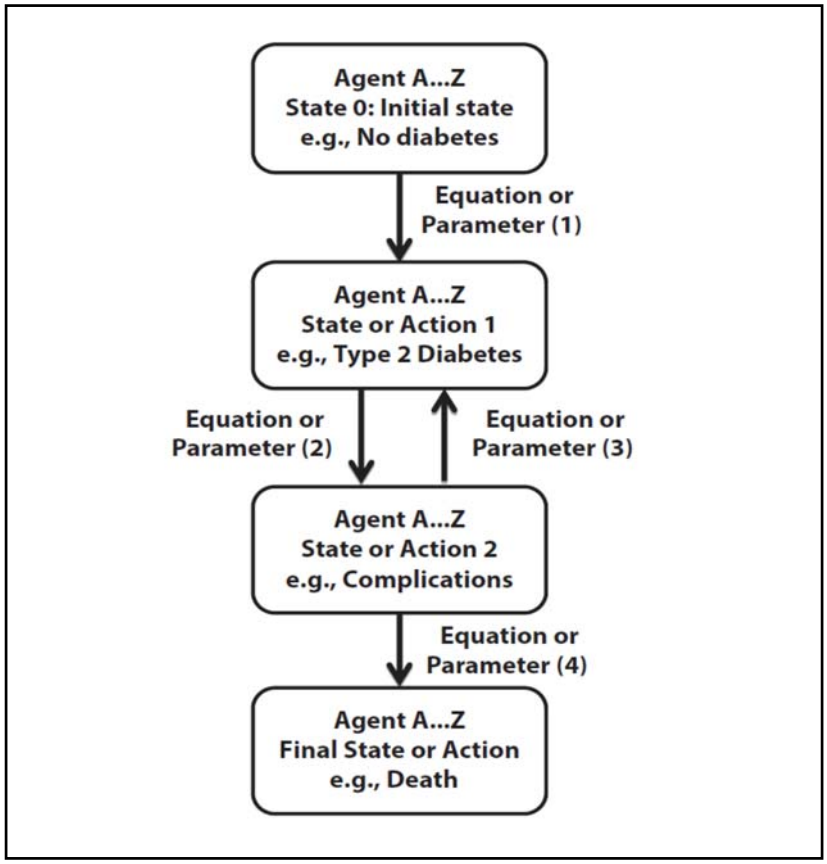


Figure 6: State changes example in agent based modeling (Nianogo 2015)

An article in the journal Ecological Modeling discusses the application of ABMS in the process of human decision making within the natural environment (L. An 2012). In preference or experience based decision processes, model developers often utilize artificial intelligence algorithms and fuzzy logic to allow the defined agents decision rules that mimic reality (Holland 1989), (Roberts 2002), (L. M. An 2005) and (Wilson 2007). When developing heuristic or empirical based models, the behavior rules that the agents are assigned are developed from observation or empirical data that does not necessarily have a strong theoretical background or basis. This method of data sourcing is sometimes

referred to as a “heuristic rule-based model”. These models require complex data compilations, calculations, derivation as well as statistical analysis to develop the rules. In this regard when the data sources are limited, it becomes practical to group agents according to specified sources such as survey data where there exist differences between groups in decision making, behaviors, perceptions and the like. It is important to also derive the foundation of these rules in the manner of preferences, motivations, and incentives (also known as defined agent goals). It is often necessary to develop hypothetical assumptions or “educated guesses” in order to enhance the model and agent behavior especially in areas where there is insufficient data. An example of this would be in modeling the epidemiology of infectious diseases. It would be important to define the parameters of susceptibility by assuming that individuals may be exposed, in the amount of time an individual spends on activities out of the home. The wide individual variability makes it hard to determine a universal range to be applied to a population. In order to provide useful model parameters, a general assumption is made that is within the realm of reality that would represent a large portion of the big picture. For example this can be set as 10 hours where 2 hours for transportation and 8 hours for work or leisure activities (Dragicevic and Perez 2009). These “untested” hypothetical assumptions are accepted to allow the model to function and test.

In modeling agents in a geospatial context, it is important to consider the mobility patterns associated with the agents to account for the movement within areas to determine how the model might be affected by population movements. This is difficult to determine from real world data as the accuracy of the data is questionable. In 2008 a

study was developed to gain a better understanding of the mobility patterns from anonymized mobile phone users tracked for six months (Gonzalez 2008). It was determined that humans and the associated travel trajectories, show a “high degree of temporal and spatial regularity.”, and hence significant probability to return to “a few highly frequented locations (Gonzalez 2008).” Thus the travel history of individuals over a period of time indicate that there is a high probability that humans follow simple reproducible patterns of movement. This is an important study in that it provides data that can be useful in modeling phenomenon that has human mobility at its base such as epidemiology, urban planning, and emergency response scenarios. It was determined that the majority of the time, the individuals traveled only short distances, for instance between home, work and school, with only the occasional longer trip. The individuals under study indicated significant regularity, returning to a few highly visited locations such as work or home. This provides a strong basis for realistic agent based modeling, with geospatial variation and introducing an agent size that is proportional to the actual population density. This aids in the quantification of network development and evolutionary movement patterns.

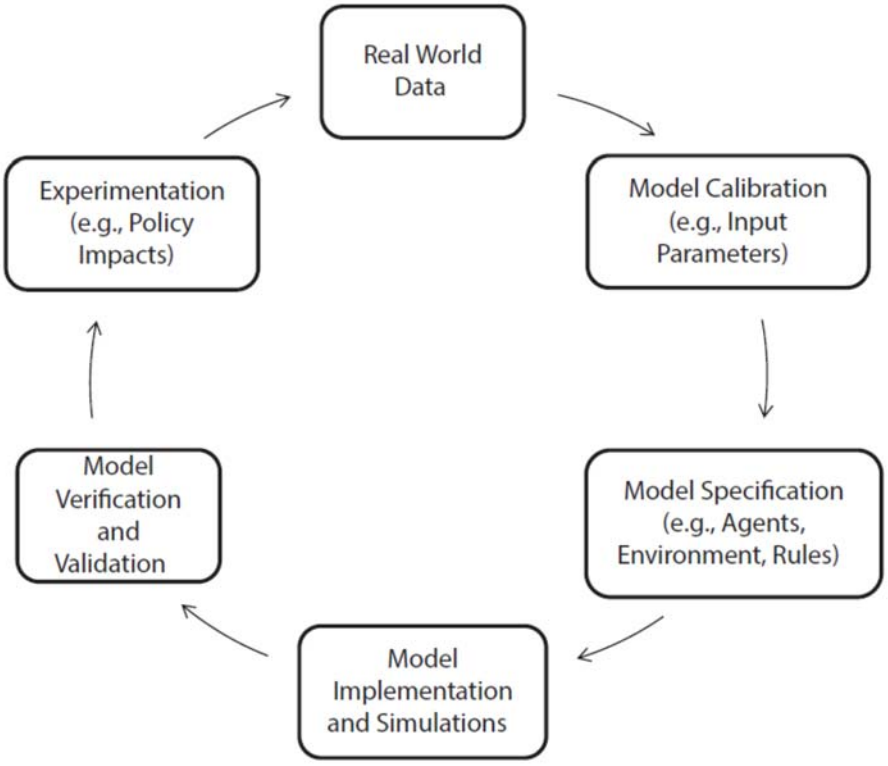


Figure 7: Steps of building ABMS (Nianogo 2015)

Figure 7 represents the general summary steps of building ABMS. Although slight deviations exist in defining ABMS in different disciplines, the general applicability and key elements are presented in Figure 7. We will note that many of the steps are common with other simulation modeling methods such as DES. These are the basis for development of our ABMS in the case of non-communicable diseases.

2.6 Literature Gap and Research Contributions

The literature review presented in the preceding section of this study indicates substantial application of ABMS in a wide variety of health, epidemiological, socio-economical and well as ecological disciplines. According to our knowledge, this study is the first if its kind that provides a holistic systematic approach to analyzing the problem of pharmaceuticals in the water network from a point source perspective.

In this study, we would like to draw parallels between the characteristics of prescription drug data (metformin) and specific illness information (type 2 diabetes mellitus). This is dependent on the ability to obtain individual health information, which is unfortunately not readily available or publicly accessible, being protected under privacy laws and HIPA standards in the United States. Thus drug usage and sales data is unavailable, which necessitates monitoring of pharmaceuticals concentrations through indirect indicators only. Studies show that regardless of the type of drugs used, that wastewater analysis is a valid source of information regarding population drug consumption as a whole, assuming that the drug is measurable in the wastewater streams (Prichard 2009) and (O'Brien 2013). This notion is further supported by a study that also confirms that quantitative analysis of wastewater concentrations can be directly correlated to the population from which it is drawn (F. Y. Lai 2013). The authors in this case utilize an average dose concentration divided by the total mass load concentration measured to determine the estimated number of doses measured, and thus the approximate number of users contributing to the mass load by drug consumption.

Ruhoy, 2007 confirms that wastewater monitoring is useful for drug market surveillance systems in parallel to traditional epidemiological methods. They assert that "an improved ability to predict the types and quantities of APIs that have the potential to enter the environment would certainly help guide the targeting of APIs to monitor in the environment. Access to real-time, geographic usage data is the major limitation to quantifying the scope (types, amounts, and locations) of API sources (Ruhoy 2007)." Now that we know that the measured concentrations in the wastewater stream can be correlated to the population, we will start to identify the sources of these pharmaceutical concentrations (namely metformin) in the model development. Next we will discuss the development of the model, the model parameters as well as the results and analysis of the outputs.

Chapter 3: Research Methodology

In this chapter we will present the sources and technique used to structure the model to reach our stated objective. This will include demographic data on the community and individual zip codes as well as some of the important characteristics of the prescription drugs to be examined. The majority of the structure of the model is in defining the source and pathway of information necessary to reach the goals and objectives of the model. The pre-process information makes up a large portion of the model development; and data selection must be made carefully to ensure that the level of detail and direction is well defined and present.

3.1 Data Sources and Pre-Process

In this section we will discuss the problem and objective of the model in identifying the source of the contribution of metformin into the water system. The scope and sources of the data are important parameters in preprocessing data to be able to form the model. The drugs and pollution in the water systems represent a waste that needs to be eliminated as the impact of the presence of this pollution in the water systems is of growing concern. In this study, we seek to employ an industrial engineering tool, simulation methodology, to assess the point source contributions to PPCPs in Milwaukee County's wastewater. Although this approach does not define an implicit solution to the problem, i.e. suggest methods of PPCPs removal, it does provide a test bed on which population-related solutions to the problem can be attended to at the source of

introduction (individuals). Such solutions include drug disposal (drug collection) and reduced dosage and change of lifestyle to reduce disease prevalence. Through the geo-spatial information from our solutions, we are able to determine likely target communities.

In addition, important secondary results can be drawn from the model, which include the extent by which mean income, geographic location as well as age and race affect the number of estimated PPCP contributors.

The model development procedure is reliant on the preprocessing of data and the understanding of the problem. We know that PPCPs' concentrations have been measured in Milwaukee County on a few select dates (Blair 2013). As discussed in chapter 2, the main ways though which medications enter the waste water system is through individual excretion or disposal. Therefore, the source of the drugs becomes the local population serviced by the water treatment facilities. A profile of the contributors for management of source contribution of the drugs is useful information. Surveys although potentially useful, are arguably not as complete or reliable as empirically measured sources. To eliminate the additional variables and uncertainty of the flow and treatment facility efficiencies, the measured concentrations at the raw sewer influent stream are targeted for comparison. Given the broad family of pharmaceuticals in Milwaukee waterways (Figure 7), the scope of this is narrowed down to the drug with the highest persistent concentration throughout the treatment process. This drug is metformin—an oral medication that helps to control blood sugar levels in patients with type 2 diabetes. The rationale behind the choice of metformin is

that of all the PPCPs prevalent in Milwaukee County's water treatment effluent, metformin has the highest trace levels at the influent and effluent streams (Blair, 2013).

The following list subsumes aspects of available secondary information enabled us to develop the methodology in this study:

- Subsistent recorded metformin concentrations found in water system, namely the treatment influent stream.
- Metformin is prescribed to treat type 2 diabetes.
- The prevalence of type 2 diabetes is determined by population factors.
- The profile and characteristics of individual agents (population) in the system is available.
- Demographic information is publicly available down to zip code level.
- Geospatial profile is available to add location concentrations to the model output.
- Illness profile information is available down to county level.
- Illness profile includes age and ethnicity information.
- Individual agent behavior rules that account for adherence to improve accuracy of results and estimates.
- Potential future contributors can also be incorporated into model for consideration
- It is possible to identify sources of metformin by race, age and location with mean income level.

3.2 Metformin

Metformin is widely used as the first go to drug for type 2 diabetics (adult onset). Current guidelines from the American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommend early initiation of metformin as a first-line drug for monotherapy and combination therapy for patients with type 2 diabetes mellitus. This recommendation is based primarily on metformin's effective glucose-lowering, relatively low cost, and generally low level of side effects, including the absence of weight gain. Metformin differs from sulfonylureas (a class of antidiabetic drugs that act by increasing the release of insulin by beta cells), in that it is not commonly associated with hypoglycemia or weight gain. With metformin, it is common for patients to maintain if not lose weight, which is important since obesity is related to type 2 diabetes diagnosis. "The initial use of metformin was significantly associated with a lower risk of subsequent treatment intensification compared with other oral agents (Berkowitz 2014)."

Studies have shown that patients who are given metformin as a first treatment for type 2 diabetes, are less likely to need additional medications to supplement treatment as compared to when other treatment options taken initially. Type 2 diabetes mellitus has become an epidemic in the past several decades. Metformin, taken orally is the most widely used drug for type 2 diabetes treatment (Graham 2011). Graham also makes the point that Metformin is excreted through the urine unchanged. The main method of

elimination is through the urine. Professional information listed on drugs.com for metformin states that, “Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours.” According to the drug fact sheet, metformin is soluble in water to 100mM (millimoles).

3.3 Type 2 Diabetes Mellitus

Type 2 diabetes is usually adult onset and represents the most common form of diabetes. The increase in prevalence and ubiquity of type 2 diabetes accounts for almost 95% of all diagnosed diabetes cases, yet is largely preventable. The risk of developing Type 2 diabetes grows with age and is a lifelong illness with no current cure. Type 2 diabetes usually develops slowly over many years and occurs when muscle, fat, and liver cells do not respond properly to the actions of insulin. Children diagnosis has also increased recently mainly due to being overweight. However it is considerably less common in children than in adults.

The underlying causes of diabetes remain unclear, though the question is the subject of extensive scientific study. What is known is that both genetics (family history) and environment (such as excess weight and inactivity) appear to play significant roles. Although men have a slightly higher risk of type 2 diabetes compared to women, this may be associated with lifestyle factors and body weight than innate gender differences. Although one’s genetics, lifestyle factors and age can be

predictors of risk, certain ethnicities in the United States have greater rates of pre-diabetes and type 2 diabetes even after adjusting for the other risk predictors. The main risk factors for type-2 diabetes include:

- Obesity
- Physical inactivity
- Family history of diabetes
- History of gestational diabetes
- Older age
- African American, Hispanic/Latino American, American Indian, or Native Hawaiian

We will now look at studies available that will provide enough of a demographic profile of the disease prevalence in the community.

3.4 Community data

In this section we will identify data sources that provide information on the probabilities of the prevalence as well as the demographical differences incorporated into the model for diabetes. We will now turn to the Wisconsin Department of Health which, in a 2012 study, identifies the prevalence of diabetes in Milwaukee County (DPCP 2012). The information in this study provides prevalence data among age groups of adults and

racial ethnicity as well as a county breakdown. The breakdown includes variation in prevalence among differing ethnic groups as shown in Table 1. In addition, the prevalence of other health indicators and conditions associated with type 2 diabetes are also presented. After identifying the rate of diabetes, we wish to apply this to the population of Milwaukee County. We would like to determine some geospatial information to those afflicted and diagnosed with diabetes based on the information available. In order to achieve this we opted to divide Milwaukee County into its composite zip codes.

The zip codes provide another layer of information including population, ethnic diversity, age and average zip code income. Although median values are recognized as being better central estimators, the source of data reported average values. The mean values will be incorporated, since the income is a secondary data source and will be used to enhance the results. This will allow us to identify the number of type 2 diabetics in each zip code by race, age, with supporting mean income and location which are to be considered the contributors of metformin. Once we have identified the contributors of the drug, we must further consider the pharmacokinetics of the drug metformin as well as the adherence rates of the contributors to determine the total real world adjusted contribution. We can then multiply this value to the mean dose of metformin to determine the quantity or concentration of metformin contributed. This will then allow us to determine the amount of metformin introduced into the system. Then by dividing by the volume of water entering the treatment facilities, we can validate our model by comparing to the concentrations determined by those found at the influent at the wastewater treatment facility of Milwaukee County (Blair 2013).

The concentrations reported in Blair's study were taken as a "snapshot" of the concentrations in the water system at the time the treatment water samples were obtained. Hence, the results of this study will be used as proof of concept that are generalizable following appropriate seasonal and demographic adjustments. Since metformin is a medication taken daily, the population estimates and model output should provide the same level of results while providing a consistent (does not vary greatly over specified time) estimation of the contributors of the system per zip code which is the objective of this model.

Next we will discuss the considerations of the autonomy of the individual diabetics and the basis for the behavior rules used in the model. In our case the variability lies with the persistence in taking medication, referred to as adherence.

Table 1: Hierarchical probabilities of afflicted age group by ethnicity/race

	18-44 years	**45-64 years**	**65+ years**
American Indian	0.216	0.533	0.251
Asian	0.092	0.3622	0.563
Black	0.0961	0.3622	0.542
Latino	0.08	0.3965	0.523
White	0.0559	0.3112	0.633

3.5 Medication Use and Adherence

For non-chronic cases, two out of three dispensed medications prescribed remain unused, with national projected costs ranging from $2.4B to $5.4B (Law 2015). This waste raises concerns about adherence, cost and safety; pointing to the necessity for public awareness and policy to reduce waste (Law 2015). There exists a difference in adherence rates between chronic and non-chronic illnesses as well as differences between the underlying conditions being treated (DiMatteo 2004). According to a review of adherence studies related to diabetes, 23 studies indicate a mean adherence of 67.5% (min: 58.5%; max 75.8%). According to a study examining the link between race and medication adherence among diabetes patients, Blacks/African Americans, Latinos, and Native Americans experience a higher burden of mortality and illness related to diabetes than do white Americans by as much as 50-100% (Shenolikar 2006).

Classification, minimum detection limit (MDL), minimum quantification limit (MQL), range and median values for compounds assessed at SSWRF. Below detection limit (BDL) values are below the MDL.

	Classification	MDL	MQL	Raw influent	Primary effluent	Secondary effluent	Final effluent
				Min–max, median	Min–max, median	Min–max, median	Min–max, median
		ng L^{-1}	ng L^{-1}	ng L^{-1}	ng L^{-1}	ng L^{-1}	ng L^{-1}
17,20-Dihydroxyprogesterone	Sex hormone	1.4	4.2	BDL–3.8[a], BDL	BDL–2.9[a], BDL	BDL–BDL, BDL	BDL–BDL, BDL
17-Alpha-estradiol	Sex hormone	1.2	3.5	BDL–10,000, BDL	BDL–760,000, BDL	BDL–2900, BDL	BDL–4700, BDL
17-Beta-estradiol	Sex hormone	1.3	3.8	BDL–9.4, BDL	BDL–11, BDL	BDL–BDL, BDL	BDL–2.8[a], BDL
4-Androstene-3,17-dione[b]	Sex hormone	0.5	1.4	BDL–150, 12	BDL–73, 0.8[a]	BDL–1.9, BDL	BDL–2.3, BDL
5-Alpha-androstane-3,17-dione	Anabolic agent	2.3	6.9	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL	BDL–24, BDL
Acetaminophen	Antipyretic, analgesic	2.5	7.5	5900–150,000, 18,000	8000–150,000, 14,000	BDL–22,000, 29	BDL–650, 39
Albuterol	Antiasthmatic	1.4	4.2	BDL–23, 6.3	BDL–69, 7.2	BDL–12, BDL	BDL–2.6[a], BDL
Azithromycin[b]	Macrolide antibiotic	3.7	11.0	BDL–280, BDL	BDL–340, 6.9[a]	BDL–47, 6.5[a]	BDL–350, 110
Boldenone	Anabolic steroid	1.3	4.0	BDL–170, 13	BDL–16, BDL	BDL–BDL, BDL	BDL–BDL, BDL
Caffeine[b]	Stimulant	3.1	9.3	3300–130,000, 9200	4200–110,000, 9400	34–7800, 1000	BDL–1400, 310
Carbadox[b]	Quinoxaline antibiotic	3.4	10.1	BDL–44, BDL	BDL–68, BDL	BDL–BDL, BDL	BDL–15, BDL
Carbamazepine	Anticonvulsant	2.7	8.2	21–310, 72	24–310, 73	33–170, 88	27–340, 180
Cimetidine	Anti-acid reflux	1.3	3.8	BDL–39, BDL	BDL–120, BDL	BDL–18, BDL	BDL–BDL, BDL
Ciprofloxacin	Quinoline antibiotic	3.3	9.9	BDL–87, BDL	BDL–19, BDL	BDL–16, BDL	BDL–BDL, BDL
Clarithromycin	Macrolide antibiotic	3.2	9.6	BDL–5.6[a], BDL	BDL–BDL, BDL	BDL–BDL, BDL	BDL–19, BDL
Codeine	Opiate	3.6	10.7	15–540, 45	15–460, 43	9.6[a]–170, 62	BDL–230, 100
Cotinine	Nicotine metabolite	3.5	10.6	BDL–130, 18	BDL–810, 28	BDL–810, BDL	BDL–BDL, BDL
Digoxigenin	Cardanolide steroid	4.4	13.2	BDL–850, 26	BDL–710, 34	BDL–68, BDL	BDL–BDL, BDL
Diltiazem[b]	Antihypertensive	3.5	10.4	20–640, 52	17–720, 41	BDL–160, 38	BDL–510, 45
Diphenhydramine[b]	Antihistamine	3.6	10.9	11–420, 35	7[a]–420, 24	5.8[a]–140, 22	BDL–360, 54
Estriol	Sex hormone	2.0	6.1	BDL–22, BDL	BDL–44, 3[a]	BDL–6.1, BDL	BDL–BDL, BDL
Estrone	Sex hormone	2.2	6.7	BDL–350, 64	BDL–290, 26	BDL–BDL, BDL	BDL–BDL, BDL
Fluoxetine	SSRI antidepressant	3.5	10.5	6.1[*]–95, 20	4[a]–120, 11	5[a]–25, 8.3[a]	BDL–96, 28
Gemfibrozil	Antilipemic	1.6	4.8	29–1200, 180	62–1100, 500	85–1100, 420	30–1100, 170
Ibuprofen	Analgesic	4.7	14.0	670–11,000, 2100	BDL–14,000, 260	BDL–4000, BDL	BDL–BDL, BDL
Lincomycin	Lincosamide antibiotic	3.1	9.3	BDL–25, BDL	BDL–29, BDL	BDL–BDL, BDL	BDL–15, BDL
Lomefloxacin	Quinoline antibiotic	4.7	14.2	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL
Melengestrol	Steroid hormone	1.3	4.0	BDL–43, BDL	BDL–49, BDL	BDL–BDL, BDL	BDL–BDL, BDL
Melengestrol acetate	Steroid hormone	0.6	1.7	BDL–1300, BDL	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL
Metformin[b]	Anti-diabetic drug	0.5	1.5	3200–100,000, 55,000	9800–92,000, 42,000	800–33,000, 27,000	640–47,000, 26,000
Miconazole	Tetracycline antibiotic	2.7	8.1	BDL–81, BDL	BDL–69, BDL	BDL–6.4[a], BDL	BDL–25, 3[a]
Naproxen	NSAIDs	1.0	2.9	780–9400, 3000	260–11,000, 3000	19–4000, 520	8.3–580, 140
Norfloxacin	Quinoline antibiotic	5.1	15.3	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL
Ofloxacin	Quinoline antibiotic	3.9	11.7	BDL–980, 16	BDL–530, BDL	BDL–220, 11[a]	BDL–670, 44
Oxacillin	β-Lactam antibiotics	2.5	7.4	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL
Paraxanthine	Caffeine metabolite	6.1	18.2	740–15,000, 3800	1500–13,000, 3000	25–2700, 540	BDL–770, 120
Progesterone[b]	Sex hormone	0.7	2.0	BDL–23, 3.7	BDL–8.7, BDL	BDL–0.8[a], BDL	BDL–2.9, BDL
Ranitidine	Anti-acid reflux	0.9	2.6	BDL–130, 16	BDL–330, 53	BDL–29, BDL	BDL–13, BDL
Roxithromycin[b]	Macrolide antibiotic	4.3	13.0	BDL–1500, BDL	BDL–88, BDL	BDL–BDL, BDL	BDL–110, 9.2[a]
Sarafloxacin	Fluoroquinolone antibiotic	5.4	16.3	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL
Sulfachloropyridazine	Sulfonamide antibiotic	4.1	12.3	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL
Sulfadiazine	Sulfonamide antibiotic	2.8	8.5	BDL–2.8[a], BDL	BDL–BDL, BDL	BDL–3[a], BDL	BDL–5.7[a], BDL
Sulfadimethoxine	Sulfonamide antibiotic	2.4	7.1	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL	BDL–13, BDL
Sulfamerazine	Sulfonamide antibiotic	2.1	6.2	BDL–BDL, BDL	BDL–BDL, BDL	BDL–3.2[a], BDL	BDL–BDL, BDL
Sulfamethazine	Sulfonamide antibiotic	4.0	12.1	BDL–BDL, BDL	BDL–48, BDL	BDL–BDL, BDL	BDL–BDL, BDL
Sulfamethizole	Sulfonamide antibiotic	4.2	12.7	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL	BDL–BDL, BDL
Sulfamethoxazole	Sulfonamide antibiotic	4.1	12.4	54–1200, 140	21–1300, 93	34–300, 67	17–810, 180
Sulfanilamide	Sulfonamide antibiotic	2.9	8.6	BDL–900, 57	BDL–2500, 21	BDL–68, 42	BDL–900, 25
Sulfathiazole	Sulfonamide antibiotic	2.6	7.8	BDL–3.8[a], BDL	BDL–5.0[a], BDL	BDL–BDL, BDL	BDL–BDL, BDL
Testosterone[b]	Sex hormone	1.1	3.2	BDL–25, 1.7[a]	BDL–13, BDL	BDL–BDL, BDL	BDL–BDL, BDL
Thiabendazole	Fungicide	1.8	5.3	BDL–26, BDL	BDL–19, BDL	BDL–9.5, BDL	BDL–16, 6.8
Triclocarban	Antimicrobial	0.5	1.4	3.3–5900, 120	17–2800, 260	61–120, 74	27–980, 120
Triclosan[b]	Antimicrobial	0.5	1.6	89–9100, 650	250–5700, 440	24–350, 120	BDL–850, 97
Trimethoprim	Pyrimidine antibiotic	3.4	10.1	18–590, 49	19–510, 44	21–260, 41	BDL–660, 120

[a] Value above MDL, but below MQL.
[b] Compound where values above the MDL were found in the method blanks, see supplemental information for values.

Figure 8: 54 PPCP concentrations measured as SSWRF - Milwaukee County (Blair 2013)

3.6 Simulation Methodology

The Agent Based Model in this study was developed using the Simio software. Simio is a simulation modeling framework based on intelligent objects. The intelligent objects are built and can be incorporated into multiple modeling projects. These objects can be stored in libraries and used in a hierarchical model structure. The flexibility of these intelligent objects is that an object can be defined as being machines, processes, customers, agents or other such autonomous model entities. The model is structured so that a number of defined objects can be combined together in different ways by defining the relationships and components within the aggregate model system. This flexibility allows Simio to provide complexity to mimic a real system. The structure of the logic (rules) can be assigned to the objects as well as global model logic (environmental rules). A Simio model is designed to look like the real system. In Simio, there is an added benefit of building animation alongside model development to visualize emergent behavior, especially if it is an important aspect of the model output.

Simio is designed from the ground up to support the object modeling paradigm; however it also supports the utilization of multiple modeling paradigms including process orientation and event orientation. It is also capable of supporting both discrete and continuous systems, as well as large scale applications reliant on agent-based modeling techniques. These modeling paradigms can be freely mixed within a single model to form a “hybridized” model. Simio is a good choice for industrial engineers who are familiar

with building process simulation in programs such as ARENA. The familiarity will allow for an easy way to incorporate intelligent objects among others into your model quickly.

3.7 Procedure of building the model

In this section we will discuss the development, objective and structure of the model. In order to begin building the system, we will follow the seven steps discussed in a Seminar on Simulation and Modeling held at the Argonne National Laboratory on the topic to begin by identifying the agents in our system (Macal CM 2006).

1. Identify agents

2. Accurately specify the distinct behaviors

3. Define the environment that the agents live in and interact with

4. Identify agent relationships and develop a theory about their interactions with each other and the environment

5. Develop essential agent related data

6. Appropriately represent agent to agent interactions if applicable

7. Validate the agent behavior model

The amount of information that agent needs to make decisions are characterized by their attributes, behavior rules, memory decision making sophistication and resource flows. Agents can be represented as individuals, groups or organizations (Macal CM

2006). In our case the agent represent the diverse population for each of the 34 zip codes in Milwaukee County. These are all of the potential contributors of the drugs entering the water system. Drug pathways into the water system are numerous, but the most prevalent is through consumption and excretion of the drugs. These drugs can be excreted through the kidneys as well as through the skin. In our model, we will need to account for the subset of the population that is in possession of the drugs, who will be the direct contributors of the drugs to the system.

We know from several studies on medication adherence that many prescribed drugs are not taken in their entirety and that the consumption rates vary greatly under conditions such as acute, chronic illnesses, short term illness, and due to external conditions. This variability must be introduced into the model system and attributed to the agents as part of their decision making process. This decision process is defined by the agent goals, which we will define as the prime motivator of the underlying agent decisions. The agent's decisions are evaluated against the agent's objectives and the actions of the agent are in a manner that moves to fulfill the stated goal. The agent's asses their situation and goal objectives and take action that will have an influence on the environment as well as on the agent themselves.

In our case, the goal of the agent has to be in a manner that will give the agent direction, however does not guarantee that the agent will have a defined goal that acts in the best interest of the agent or environment. By defining the goal as "be healthy", the agent may not always move to fulfil this goal, as in our case taking the medication may present a conflict to the agent as potential side effects can cause the agent to feel ill thus

discontinuing the pursuit of the goal of being healthy by taking the medication necessary to control the illness or condition. In addition, there is a potential for agents with certain medication that can be abused to be taking the medication in doses greater than prescribed or for longer than prescribed. This can have a detrimental effect on the agents and is in conflict with the health goal.

Due to this wide range of adherence variation and behaviors that are not in line with the stated goal, it becomes apparent that a revision of the defined goal is in order to best serve the agent motivations in a realistic manner. This is an important factor with the scalability of the model to include additional medications that are more prone to abuse as well as temporal illness that are affected by the perception of the agent towards their health outcomes that could potentially be expanded and incorporated in future work and applications of this model. After careful consideration, the goal definition best suited to the model purpose as well as the most realistic perspective on social agent behaviors in the author's opinion is "feel better". By adjusting the goal objective to be defined as "feel better", the agent's motivation is better served and accounts for the individual perception and actions associated with the agent's behavior. The main goal of prescribing medication to an agent is to improve their health making them "feel better" and as such the contributing agents in our model are limited to those who have seen a healthcare professional and are diagnosed with the condition as well as being prescribed medication for said condition. In reality, the goal of being healthy is the prime objective of healthcare providers and may not be shared by the agents being treated as the perception of treatment may differ. The agent who is prescribed medication to treat a

chronic condition may suffer from side effects that may make the agent feel sicker, thus abandoning the medication. This phenomenon is one that plays into the behavior of the agent who may decide to take the prescribed medication when the chronic illness has a greater detrimental effect on the agent health than does the side effects associated with the medication. This will cause the agents contribution to fluctuate in accordance with the perceived personal goal of feeling better.

The short term implication is that the agent is relieved from the short term side effect of the drugs but the underlying condition is not treated, which will result in negative long term health complications. This brings into the model a factor of education related to treatment of the underlying health conditions. Perhaps the agent is unaware of the severity or the long term mechanism of impact associated with not taking the prescribed medications. The lower level of education will impact the long term health impact of the agent detrimentally which could have been mitigated with the agent's better understanding of the diagnosed illness and associated long term health complications.

The ability to define agents' goal as "feel better" in the model also has the added benefit of incorporating the abuse of drugs among those who are not prescribed medication. Abuse is especially prevalent in drugs such as pain killers where the pursuit of the medication in a social construct is driven by the abuser's motivation to "feel better" while having the opposite effect on the overall agent health. An agent may be prescribed a regimen of medication and may skip a dose or stop taking the medication because the objective goal in the perception of the agent has been met. This is true in situations of temporal illness where an agent may be prescribed a cycle of antibiotics for example, and

the agent will continue to take the medication until the goal of “feel better” is reached and the remaining doses in the cycle are not consumed, stored or discarded. Another example may be in cases of personal injury where the agent is prescribed medication and may be reluctant to take the medication after the “feel better” goal is reached. Another contributor is of emotional decision making where the agent is not adhering to the medication because of associated expense and the acceptable level of comfort is adjusted to account for the economic considerations of not being able to afford the medication or the priority of obtaining the medication is lower due to economic constraints being greater than the level of discomfort.

In order to develop a model that will account for the measured concentrations of the drugs found at the wastewater influent stream at the wastewater treatment facility, the measured concentrations of the drugs found in the flows are considered a mass load contributed by the population feeding the influent stream and no further detail is available to point to the sources of the contributions. Although affecting wastewater treatment by the mass load concentrations found in the stream is reactionary at best. By not isolating the source of the drugs found in the system, an understanding of the dynamics involved in individual source contributions can be identified and the associated fluctuations in the excretion of the drugs finding their way to the water system. Not only can the sources of the contributions be identified, in the case of metformin and the prevalence of type 2 diabetes among the population at the current point in time with the available demographic data; the risk factors of those with pre-diabetes who may become future contributors can also be identified. This allows for the current impact of the

contributions and population health risk factors to be included in the process and forecast the future increase in the contributors and the associated increase in mass load concentrations to be identified. This will aid in ensuring that any steps taken to address these active pharmaceutical ingredients in the water treatment process are adequate in meeting the current and future volumes needed in order to account for the expected higher future concentrations.

This level of results detail provides an accounting of the prevalence of diabetes by race and age level of each of the boundary zip codes and the mean income range of the population in that zip code. This level of detail goes beyond the reactionary steps to treat these concentrations at the wastewater level but also provides information to improve the efficacy of social health campaigns that aim to improve the population health and reduce the number of contributors to the system. In the case of diabetes there are many factors that can be addressed to mitigate the number of agents that are at risk to becoming contributors of the drug used to treat the onset of type 2 diabetes. One of the biggest indicators of the prevalence of type 2 diabetes with available data is the connection between obesity and type 2 diabetes. A staggering 87% of type 2 diabetics are considered overweight or obese according to the Wisconsin department of health study on the burden of diabetes in Wisconsin compared to approximately 30% of the population as a whole (WDHS 2011). Diabetes and associated health complications account for a large portion of medical expenses related to hospital visits with a 14.9% of all hospital related visits representing 16% of total hospital charges. In Wisconsin there are several factors that contribute to the level of obesity including sedentary lifestyle,

decreased level of activity especially during the cold winter months as well as poor access to healthy food choices in lower income urbanized environments.

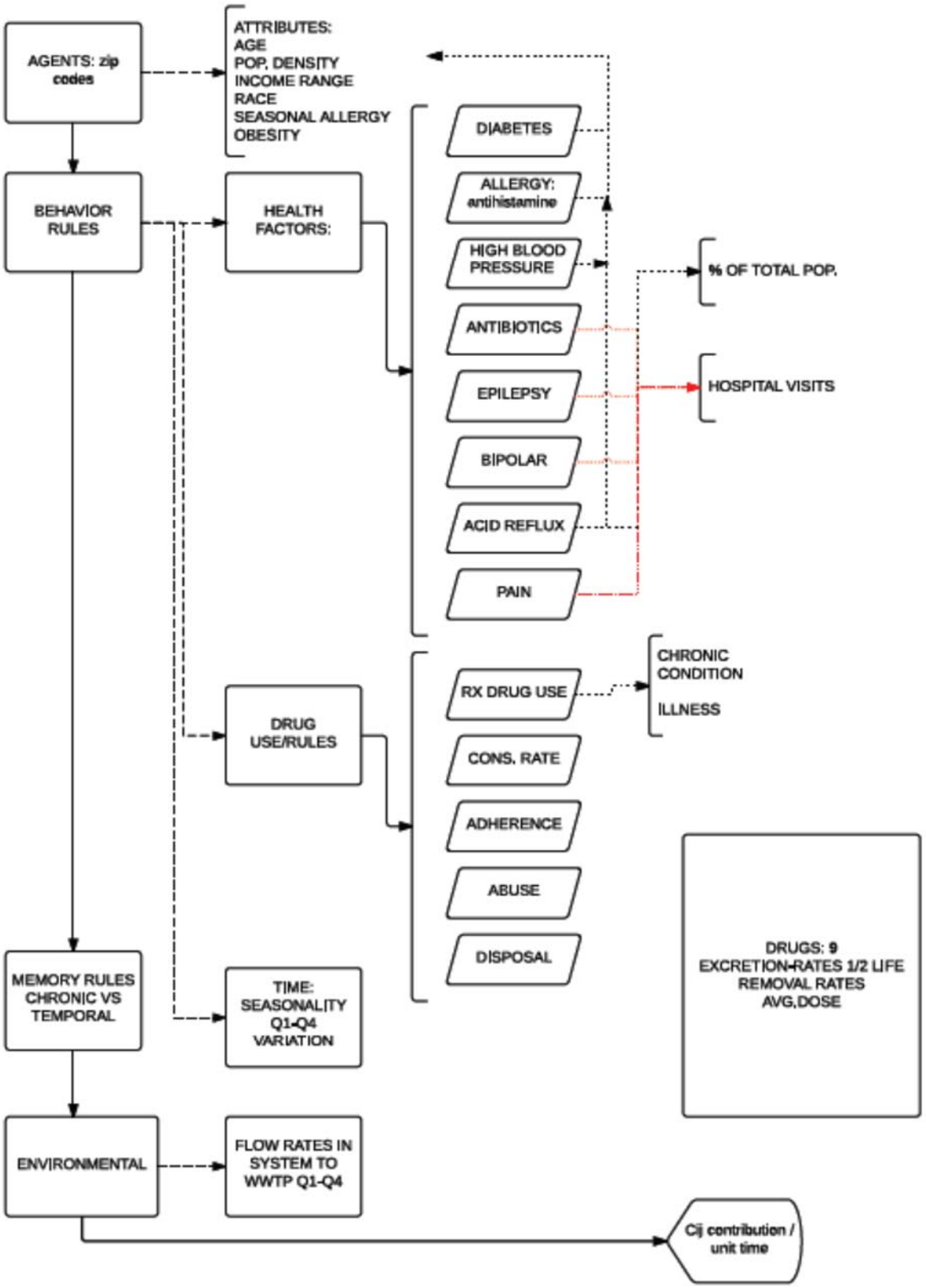


Figure 9: PPCP point source identification modeling structure

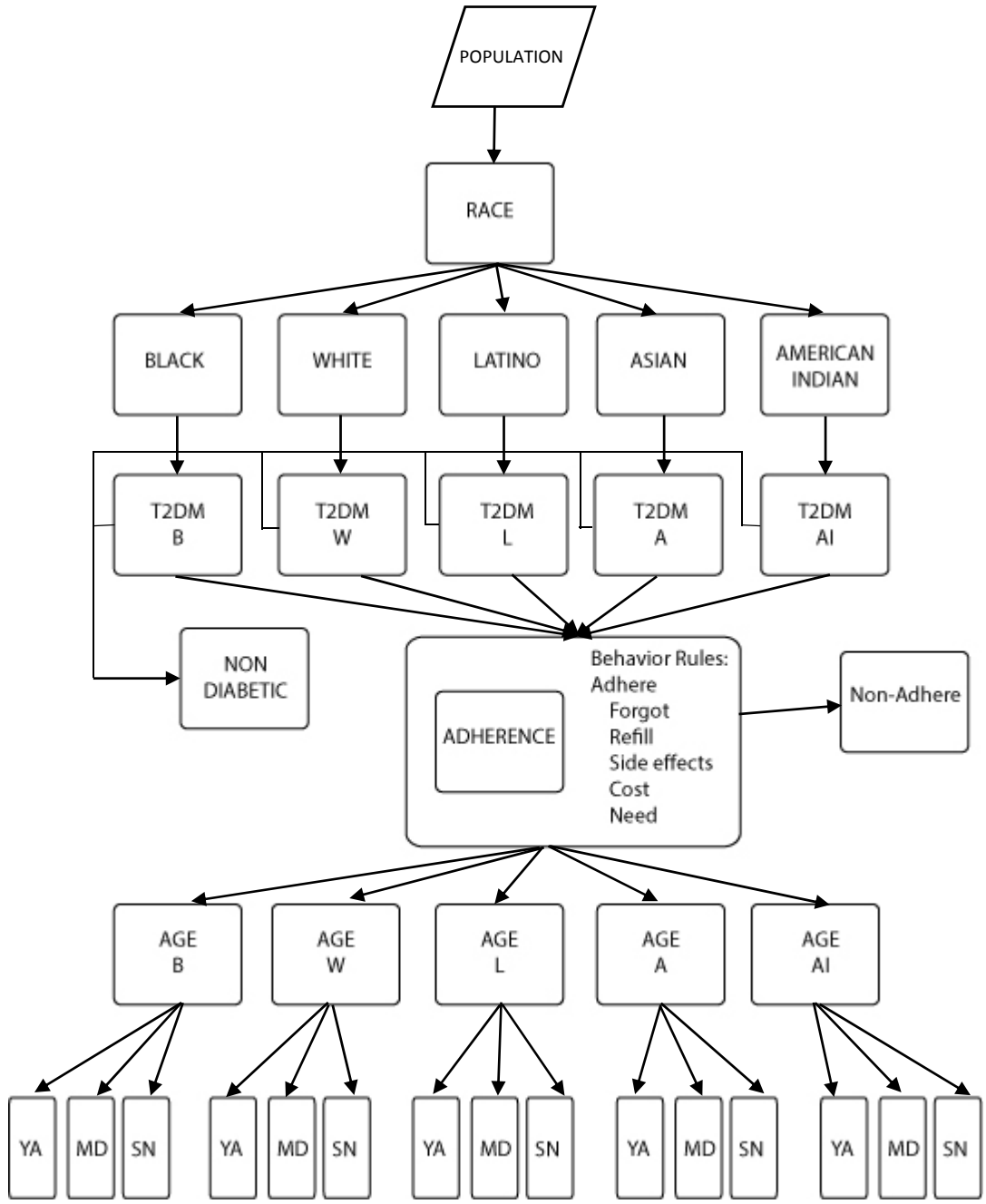


Figure 10: Metformin Source identification model Milwaukee County

3.8 List of inputs in model – Simio

In this section, we will discuss the inputs of the model necessary to develop our output. The study of diabetes in Wisconsin indicate that the prevalence of type 2 diabetes is greater in some ethnicities than others in Milwaukee County. To incorporate this into the model, the specific zip code racial profile is included to determine the zip code composition from the United States Census Bureau website (USCB 2010). Zip code specific population information also includes racial demographics composed of the following:

Black

White

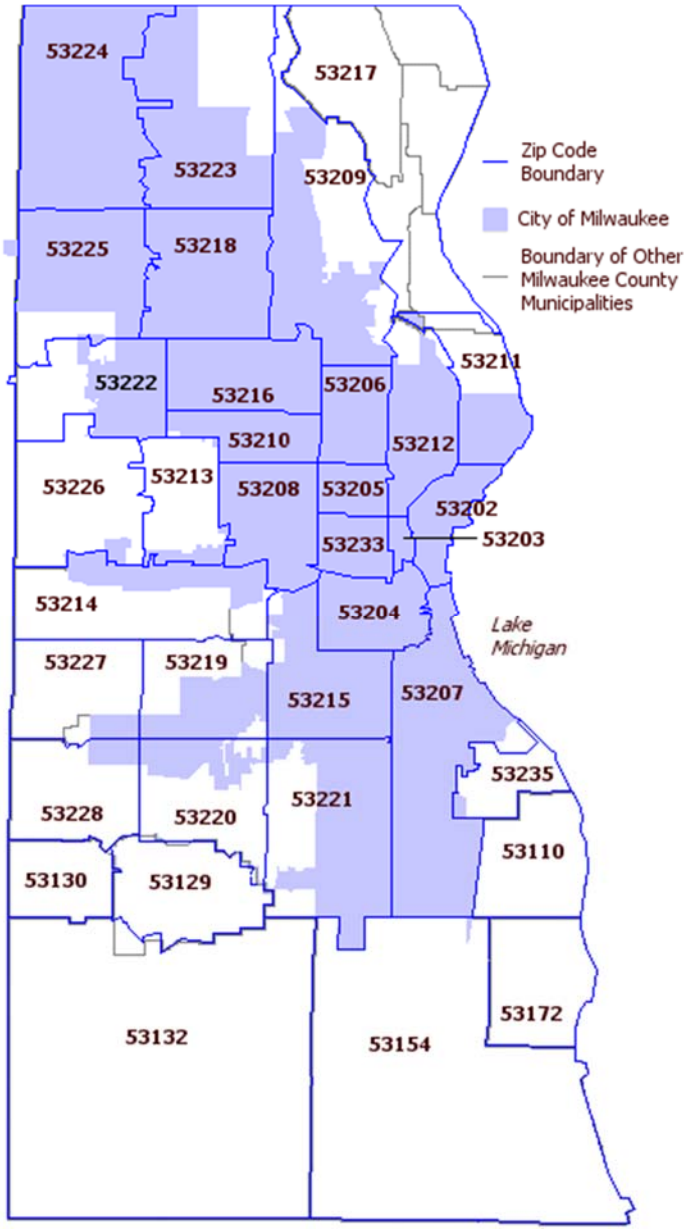
Latino

Asian

American Indian

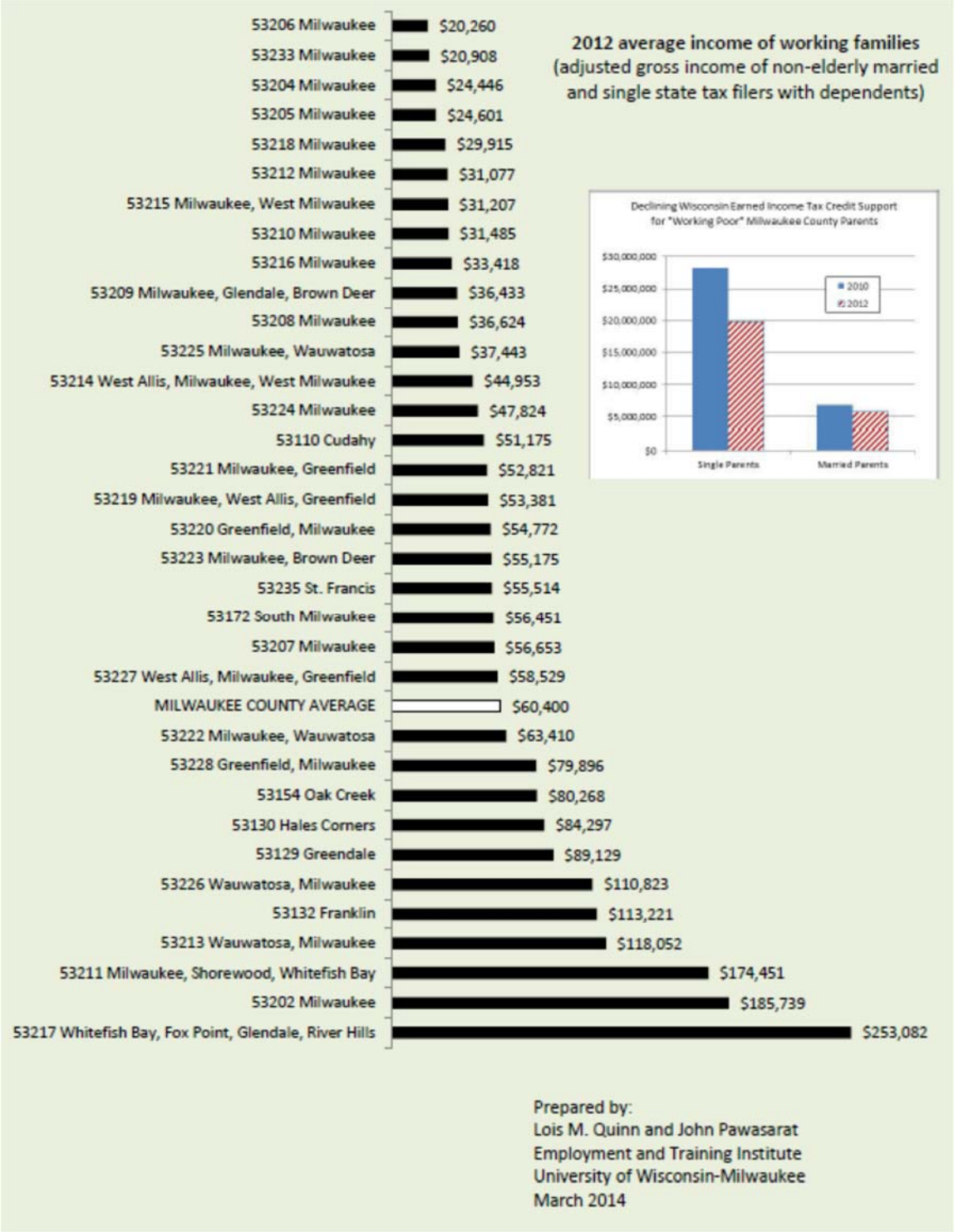
From the initial racial breakdown the race specific diagnosed diabetes prevalence is applied. The undiagnosed estimates listed in the Wisconsin health report are not utilized in the model because although they may be diagnosed in the future, they are not currently being treated for the illness and thus do not contribute to medications consumption entering the water system. Since the rates of illness differ by ethnicity, as well as the age profiles within ethnicities, it is necessary to account for this in order to obtain a good estimate of the numbers contributing among each racial group. This is

important because although certain races may not have a large population in a given zip code, the higher percentage of those afflicted will need to be reflected in the overall zip code contribution of medications in the waste streams. Figure 11 is a map of Milwaukee County, showing the zip code boundaries, and Figure 12 is a graph of the 2012 average income for working families in each zip code, which were used as input in the simulation model.



Source: http://www.city-data.com/forum/attachments/milwaukee/80428d1306619341-milwaukee-metro-photo-thread-zip.gif

Figure 11: Milwaukee county zip code map



Source: https://www4.uwm.edu/eti/2014/IncomeInequality.pdf

Figure 12: Milwaukee County mean income by zip code

Once the total number afflicted in the zip code population by race are determined, we will need to adjust the total contributors by the adherence rates. The adherence rates were examined to determine the effects if any of race on the rates of adherence to medication. In addition, since these are chronic or acute illnesses, it was determined that rates of adherence differs from short term illnesses to chronic illness (DiMatteo 2004). It was determined for use in the model that the research on ethnicity variation in adherence is minimal, non-uniform and unclear and will not be a consideration included in the model. If greater accuracy is needed, the sensitivity of the model can be expanded to include greater level of detail and modify the individual adherence rates determined. The adherence rates were developed to include variations in adherence selections based on defined criteria. According to a review of adherence studies related to diabetes, 23 studies indicate a mean adherence of 67.5% with a minimum of 58.5%; and maximum of 75.8% (DiMatteo 2004). This will be modeled as a triangular distribution. The criteria will include considerations for the following agent behaviors as shown in Table 2.

Table 2: Adherence Behavior Rules

Individual Agent Behavior Rules	Rate of occurrence (%)
Take Medication	Triangular (0.585, 0.675, 0.758)
Not taking	
Forgot	Triangular (0.33, 0.34, 0.36)
Feel Better	Triangular (0.15, 0.16, 0.17)
Ran Out	Triangular (0.36, 0.38, 0.39)
Cost	Triangular (0.07, 0.08, 0.09)
Side effects	Triangular (0.03, 0.04, 0.05)

Triangular distributions:

The triangular distribution provides a representation of the probability distribution when sample data is difficult to obtain or is not available. When inadequate empirical data exists, models will turn to triangular distributions to define a range of the data. It is used as an estimate or approximation of some underlying stochastic variable in the absence of system data, or when data is difficult to obtain (Kelton 2003). Its parameters are the minimum or the lower limit (a), maximum or the upper limit (c), and mode of the data also known as the peak location or most likely (b).

Triangular distribution data is commonly estimated using reasonable values based on sample data. The lower and upper limit parameters ***a*** and ***c*** can be estimated using the minimum and maximum values of the sample data, respectively The peak location parameter b, often referred to as the most likely can be estimated using the sample mean, median, mode, or some reasonable estimate of the population mode.

The Probability Density Function (pdf) of the triangular distribution is given as:

$$f(x \mid a,b,c) = \begin{cases} \dfrac{2(x-a)}{(c-a)(b-a)} & ; \quad a \le x \le b \\ \dfrac{2(c-x)}{(c-a)(c-b)} & ; \quad b < x \le c \\ 0 & ; \quad x < a \,, x > c \end{cases}$$

while the Cumulative Distribution Function (cdf) of the triangular distribution is:

$$F(x \mid a,b,c) = \begin{cases} 0 & , \quad x < a \\ \dfrac{(x-a)^2}{(c-a)(b-a)} & , \quad a \le x \le b \\ 1 - \dfrac{(c-x)^2}{(c-a)(c-b)} & , \quad b < x \le c \\ 1 & , \quad x > c \end{cases}$$

(Source: http://www.mathworks.com/help/stats/triangular-distribution.html)

For some of the behavioral rules options, such as “forgot” and “ran out”; the lapse will be temporary and thus the agent eventually feeds back into the contributor stream. A “feel better” agent will also be subject to a feedback loop though in this case it will be less proactive than the previous options. In this case the behavior will remain unchanged until a drift from the goal of feeling better is enough to drive the agent towards a more active pursuit of the goal objective. “Can’t afford” option is one that will not add to the

current stream of contributors until the underlying issue is resolved. This would require a time delay that is reflective of the adherence of medication due to socioeconomic limitations that is beyond the scope of this initial model timeframe (snap shot) and thus will not be contributors in this case. They will be collected into the non-adhere group. The "side effects" options is a result of the side effects exceeding the positive effects of the medication. Until the effects of the underlying illness are worse than the perceived or experienced side effects of the medication, the goal of feeling better (taking medication) remains in conflict between these two objective behavior options. It may be considered that this behavior will be persistent until the side effects are not a deciding factor, such as temporary side effects, health deterioration, or until the medication can or will be substituted for another option; thus removing this agent from the potential contributors over time. The model will include a count for those either undiagnosed diabetics or those diagnosed but are not currently adhering to medication. This count could be a representation of the medication that may find its way into the system as a mass disposal in the future if not removed through efforts such as drug take back programs. There is also the potential for the non-adhere group to be diagnosed and placed on metformin, making them future contributors.

The adherence rates are included for each of the agent groups after the rates of affliction are determined for each group. The next step is to determine the age groups of the agents in the model as shown in Table 3.

Table 3: Adult age groups identification

Young Adult	18-44
Middle Age	45-64
Senior	65+

The total number of actual contributors for the medication are determined for each zip code broken down into ethnicity and associated age groups. The total number of active contributors can now be used to determine the concentration by multiplying the number of active contributors by the excretion rate and the mean dose range of the prescribed medication.

We have so far compiled a framework for reaching our model objectives as well as the sources and level of information to be incorporated into the model. Figure 12 is a snapshot of the ABMS visual interface. In the following section of the model results, we will examine the results and provide an estimate for the total number of contributors in Milwaukee County as well as the associated concentrations of Metformin being introduced into the system.

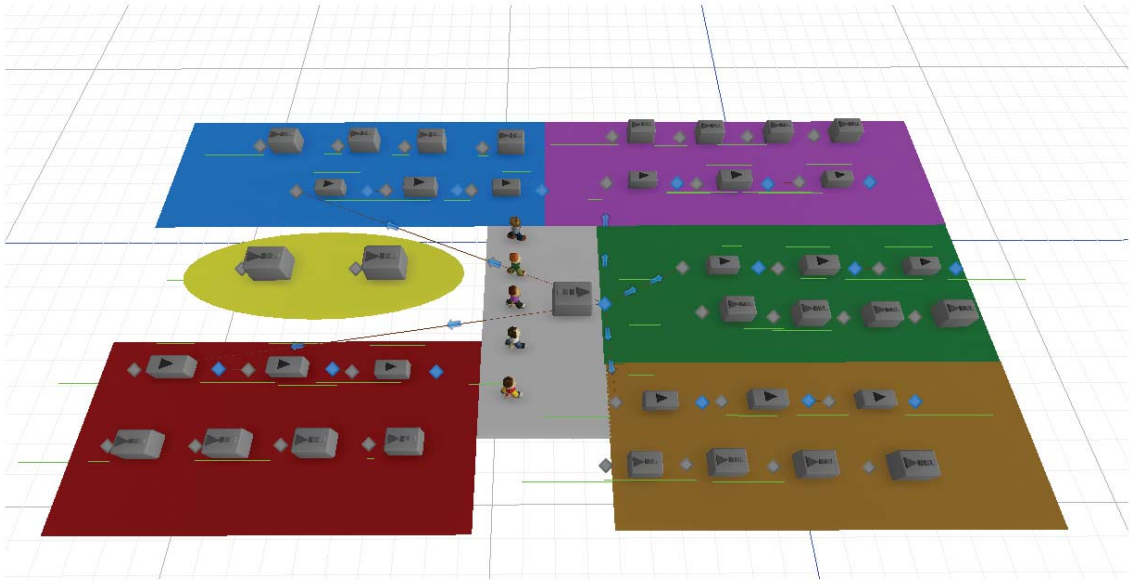


Figure 13: Visual user interface of the model in Simio

3.9 Assumptions

In this study, adherence rates are assumed to have a triangular distribution. Although some studies indicate that there is a difference in adherence to medication based on race, this difference is generally only available comparing black and white populations. This difference however, although statistically significant only represents a 5% difference in adherence rates (Shenolikar 2006). There have been subsequent studies that indicate adherence rates are a function of health education and could potentially remove the racial differences in adherence alone (Osborn 2011) and (Adams 2008). Considering this as well as the adherence range represented in (DiMatteo 2004); the 5%

difference is within the range incorporated in section 3.5 above. This assumption will account for this potential 5% difference reported in Shenolikar (2006). It was found that reported adherence rates differ significantly between studies and the range presented by DiMatteo (2004) is a reasonable representation of adherence considering it is based on a large number of studies and includes diabetes specifically. Since racial differences of adherence in the Asian, Latino, and American Indian groups were not found to be reliable or non-existent, it would be prudent to keep the adherence rates as a triangular distribution as discussed above and assume that any differences or deviations are represented in the range used in our model. Although there are numerous reasons for non-adherence, the world health organization (Sabaté 2003) identifies 5 major elements or dimension related to patient adherence and long term therapies. These are the basis for the adherence rules used in the presented in this thesis.

Figure 14: dimensions of adherence World Health organization 2003

The racial profiles of the populations were taken to be one of 5 options presented as the reported values of White, Black, Latino, Asian and American Indian. The Latino

proportion was taken as the sum of the white, black, Asian, and American Indian proportions of the population and then subtracted from 100. The reason being that some of the Latino population may self-report as being one of the other racial profiles or be included in 2 of the racial profiles (such as White or Black and Latino-White or Latino-Black) and thus will sum to greater than 100. This assumption will allow the proportions of the racial profile to sum to unity while not misrepresenting the population demographics.

The estimate of the average dose of metformin was made to be 1300mg per day. This assumption was made following the data that the minimum and maximum dosage levels are 500mg and 2500mg respectively, and at times the minimum dosage can be ramped up to 850 mg. Since this is the first study that simulates the prevalence of metformin from a community perspective, actual dosages could easily be personalized to each agent, as mentioned in the future studies section of this Thesis. The last assumption that was made is that the excretion of metformin was assumed to be 90% of average intake dose estimate (also known as the metabolic residue percentage).

Chapter 4: Results

4.1 Results and Analysis

The following sections presents the model input and output of each of the 34 Milwaukee zip codes along with the mean income values as determined by a UWM community study (Quinn 2014). Tables 4 and 5 have been included in this section to give comparative perspective of the model outputs as well as population demographics between the zip codes with the lowest and highest average income respectively. The model outputs and demographic information for the rest of the zip codes are given in the appendix section of this Thesis, presented in order of lowest mean income zip code to the highest with the accompanying age and racial profile.

The Non-adhere group is the number of estimated undiagnosed diabetics and the population of diagnosed diabetics not adhering to medication. These are important figures as these are guaranteed to be future contributors as the side effects of the untreated underlying condition worsen or diagnosis is made. The name of non-adhere was used as a means of differentiating the diabetic group from the non-diabetic population.

The following notation will be used to define the proportion of the population for each of the 5 ethnic groups, namely, Black, White, Asian, Latino and American Indian in the results analysis:

Table 4: notation for calculation of contributors

Notation	Description
$(\boldsymbol{u_i})$	Proportion of the zip code specific population of specific racial group *i* – Black, White, Latino, Asian, American Indian
$\boldsymbol{DA_i}$	Count of contributors of race *i* per zip code
$\boldsymbol{W_{ij}}$	Matrix representing the proportion of contributors of age group *j* for each race *i*
$\boldsymbol{M}$	Population of zip code
$(\boldsymbol{P_{di}})$	Prevalence of diabetes in the population for each race *i*
$\boldsymbol{AD_{ri}}$	Adherence rate as a triangular distribution for each race *i*
$\boldsymbol{N_{pi}}$	Adult age profile for race *i* represented as a uniform distribution (proportion value); where r_i is the age group proportion of the race group. (Table 2)
$\boldsymbol{DAC_{ij}}$	Stratified diabetes afflicted contributors for race *i* and age group *j* for each zip code
DAX	Diabetes diagnosed non-adhere

Equations 4.1 through 4.3 are used to determine the number of contributors by race and age profile for each zip code. Equation 4.4 is used to determine the total number of non-adhering diabetics and undiagnosed diabetics in the population.

$$DA_i = M \times (u_i) \times (P_{di}) \tag{4.1}$$

$$DAC_i = DA_i \times W_{ij} \times AD_i \tag{4.2}$$

$$N_{pi} = (r_i YA, r_i MD, r_i SN) \tag{4.3}$$

$$DAX = \sum_{i\in(B,W,L,A,AI)} DA_i - \sum_{j\in(YA,MD,SN)} DAC_{ij} \tag{4.4}$$

Table 5 and 6 below represent the zip code profile and the model output by race for the zip code with the lowest income (53206) and the highest income (53217) respectively. Tables for all 34 zip codes in Milwaukee County can be found in the appendix section at the end of this paper.

Table 5: data and results – 53206

Zip Code	**53206**				
Mean Income	$20,260				
Population:	**28,210**				
American Indian	0.3%				
Asian	0.4%				
Black	95.1%				
White	1.6%				
Latino	2.6%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	130	639	2092	1387
	White	0	2	16	10
	Latino	2	18	44	32
	Asian	0	2	4	1
	American Indian	4	4	3	12
Total contributors	**2960**				
Total undiagnosed T2DM and Non-adhere					**1442**

Table 6: data and results - 53217

Zip Code	**53217**				
Mean Income	$253,082				
Population:	**29,192**				
American Indian	0.2%				
Asian	4.1%				
Black	4%				
White	89.3%				
Latino	2.4%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	5	30	94	48
	White	17	185	899	532
	Latino	3	14	36	30
	Asian	8	23	70	47
	American Indian	4	3	2	8
Total contributors	**1393**				
Total undiagnosed T2DM and Non-adhere					**665**

Table 7: Summary of results by zip code from lowest income to highest

	ZIP CODE	MEAN INCOME ($)	POPULATION	TOTAL CONTRIBUTORS	CONTRIBUTORS AS A % OF POPULATION	TOTAL NON-ADHERE
1	**53206**	20,260	28210	2960	10.49%	1442
2	**53233**	20,908	16453	1091	6.63%	541
3	**53204**	24,446	42355	2867	6.77%	1371
4	**53205**	24,601	10050	1053	10.48%	508
5	**53218**	29,915	40625	3743	9.21%	1817
6	**53212**	31,077	30416	2452	8.06%	1236
7	**53215**	31,207	60953	3879	6.36%	1870
8	**53210**	31,485	28126	2616	9.30%	1262
9	**53216**	33,418	32264	3149	9.76%	1525
10	**53209**	36,433	46917	4134	8.81%	1988
11	**53208**	36,624	27356	2960	10.82%	1442
12	**53225**	37,443	25706	2060	8.01%	316
13	**53214**	44,953	34725	1804	5.20%	866
14	**53224**	47,824	21284	1785	8.39%	850
15	**53110**	51,175	18320	889	4.85%	420
16	**53221**	52,821	37701	1998	5.30%	931
17	**53219**	53,381	33880	1710	5.05%	824
18	**53220**	54,772	26303	1315	5.00%	641
19	**53223**	55,175	29230	2252	7.70%	1126
20	**53235**	55,514	9270	469	5.06%	221
21	**53172**	56,451	21156	1031	4.87%	487
22	**53207**	56,653	35149	1776	5.05%	861
23	**53227**	58,529	23357	1131	4.84%	547
24	**53222**	63,410	25165	1540	6.12%	733
25	**53228**	79,896	14369	684	4.76%	311
26	**53154**	80,268	34451	1686	4.89%	804
27	**53130**	84,297	7755	374	4.82%	170
28	**53129**	89,129	13973	643	4.60%	298
29	**53226**	110,823	18370	867	4.72%	404
30	**53132**	113,221	34863	1699	4.87%	812
31	**53213**	118,052	26020	1257	4.83%	599
32	**53211**	174,451	35406	1677	4.74%	796
33	**53202**	185,739	23386	1167	4.99%	558
34	**53217**	253,082	29192	1393	4.77%	665
	TOTAL			**62,111**	**6.47%**	**29,242**

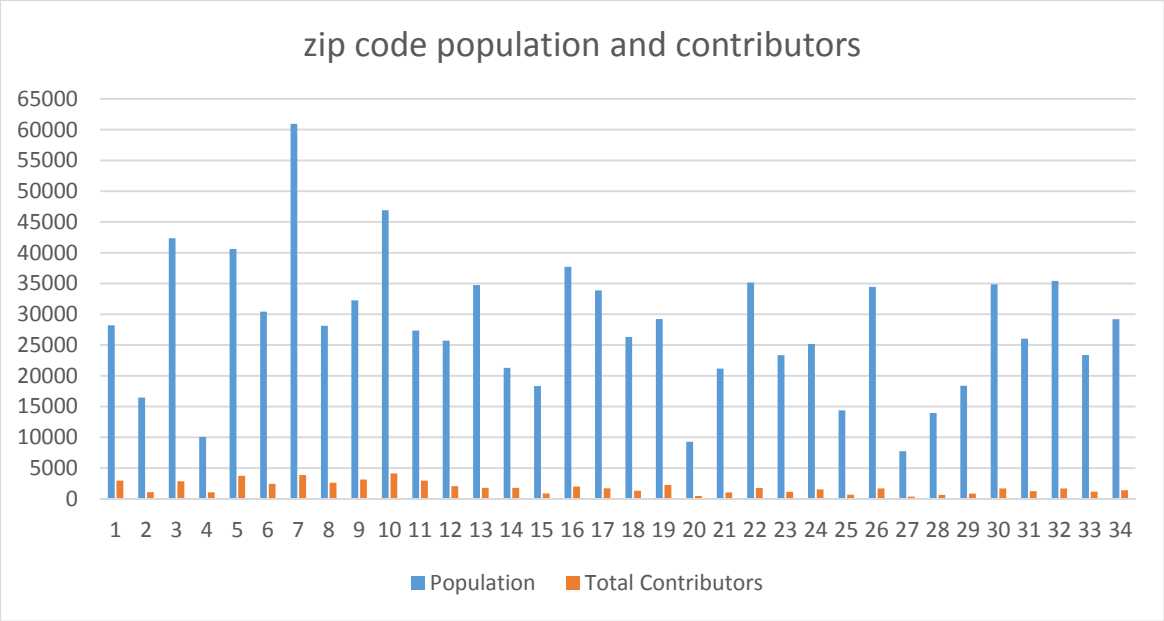


Figure 15: Zip code population and contributors

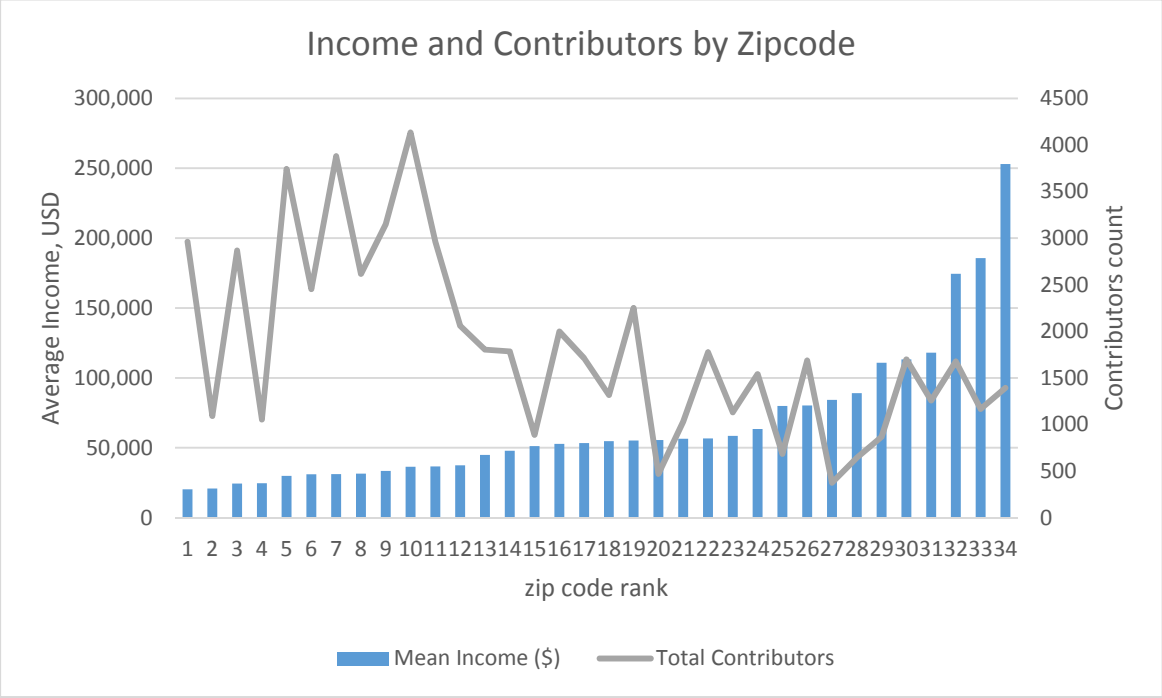


Figure 16: zip code Income and contributors

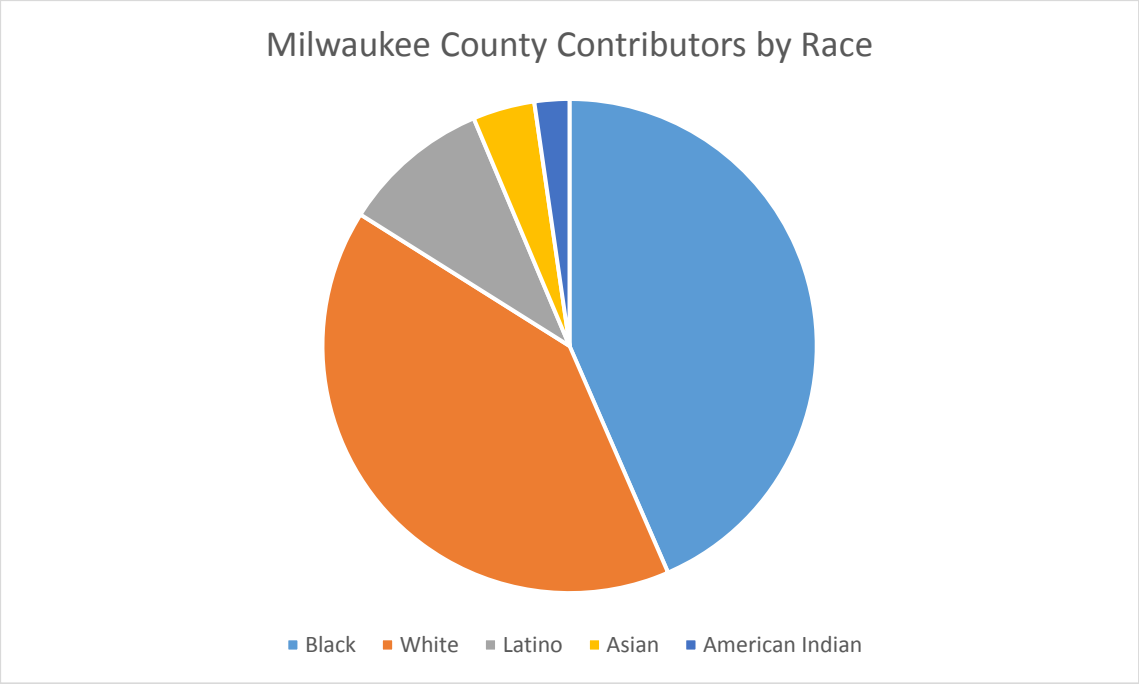


Figure 17: Milwaukee County contributors by race

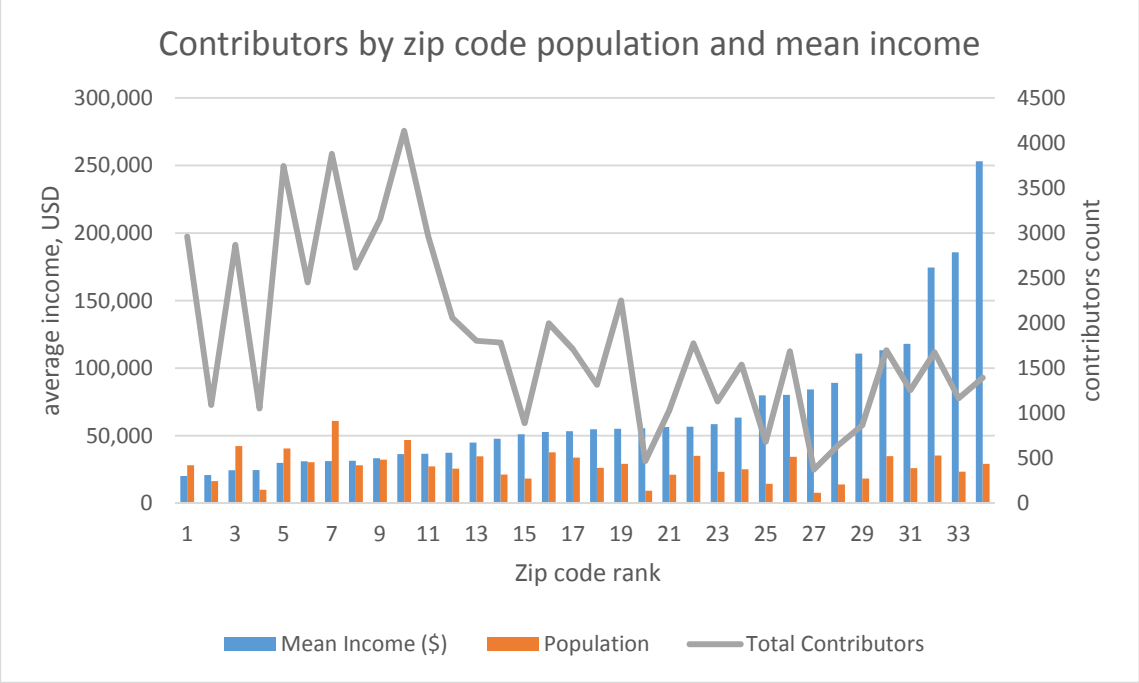


Figure 18: contributors by zip code population and mean income

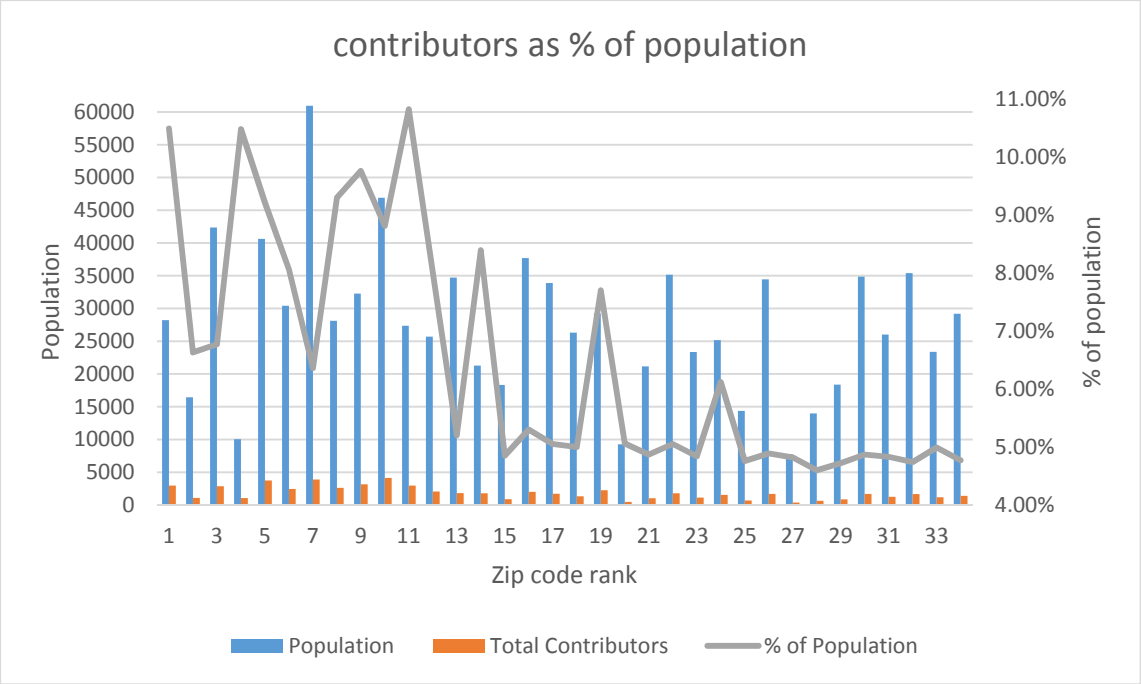


Figure 19: contributors as % of zip code population

From the above graph of contributors as a percent of the population in each zip code, it can be seen that there are several zip codes that are higher than 7.5% in terms of the population that are diabetics (T2DM). There are 9 of the 34 zip codes with a higher percentage of diabetics that are candidates for targeted reduction. From table 38 above, the average percent of the population for the 34 zip codes is 6.47%. Of the 34 zip codes that make up Milwaukee County, 14 of the 34 zip codes (or approximately 42%) have a higher than mean percent of the population with diagnosed type 2 diabetes. It is of note that all of these 14 zip codes have below $55,175 mean household income, indicating that health may be correlated to socioeconomic status in Milwaukee County. The following charts take a look at the population, contributors, percent contributors of the zip code population, as well as considering the zip code average income.

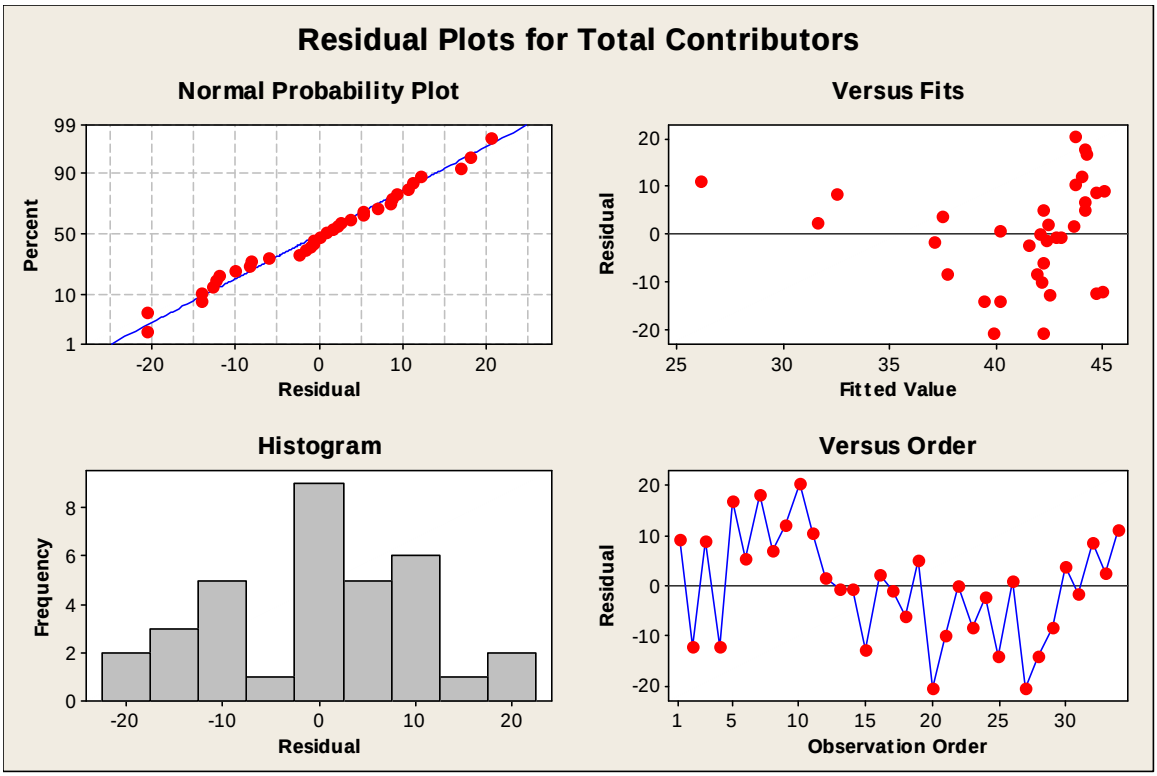


Figure 20: Residual plots for total contributors per zip code

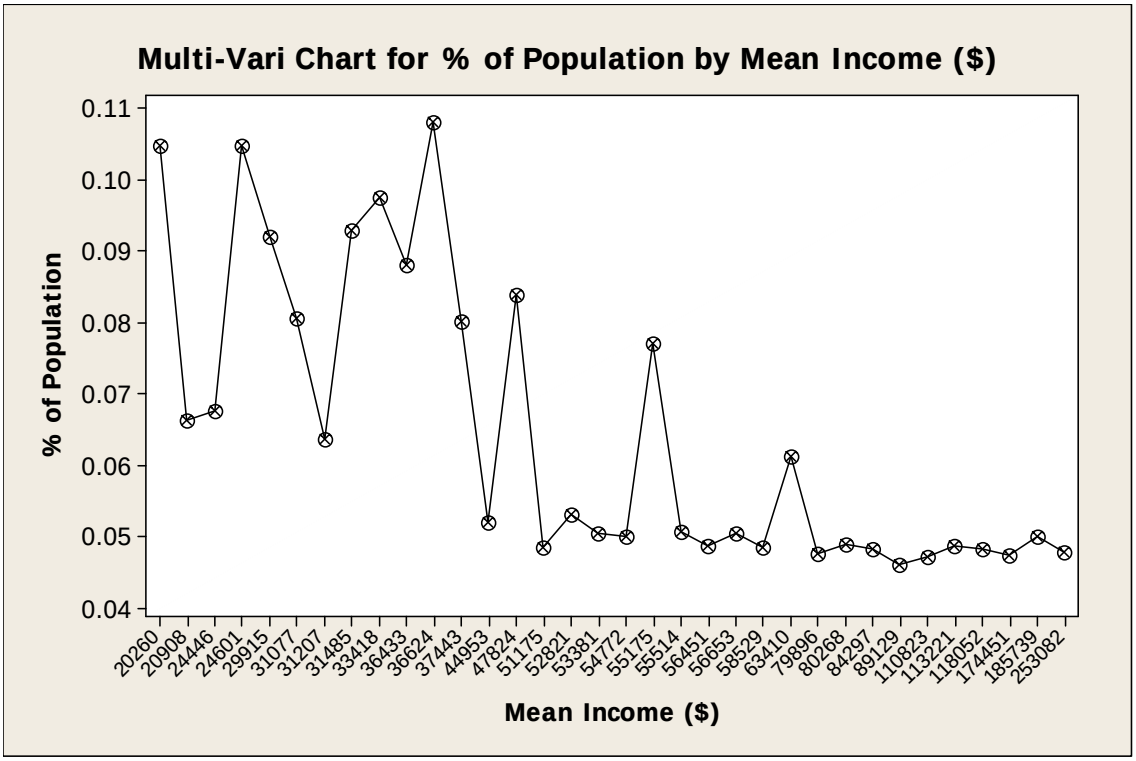


Figure 21: Population percent diabetic contributors vs zip code average income

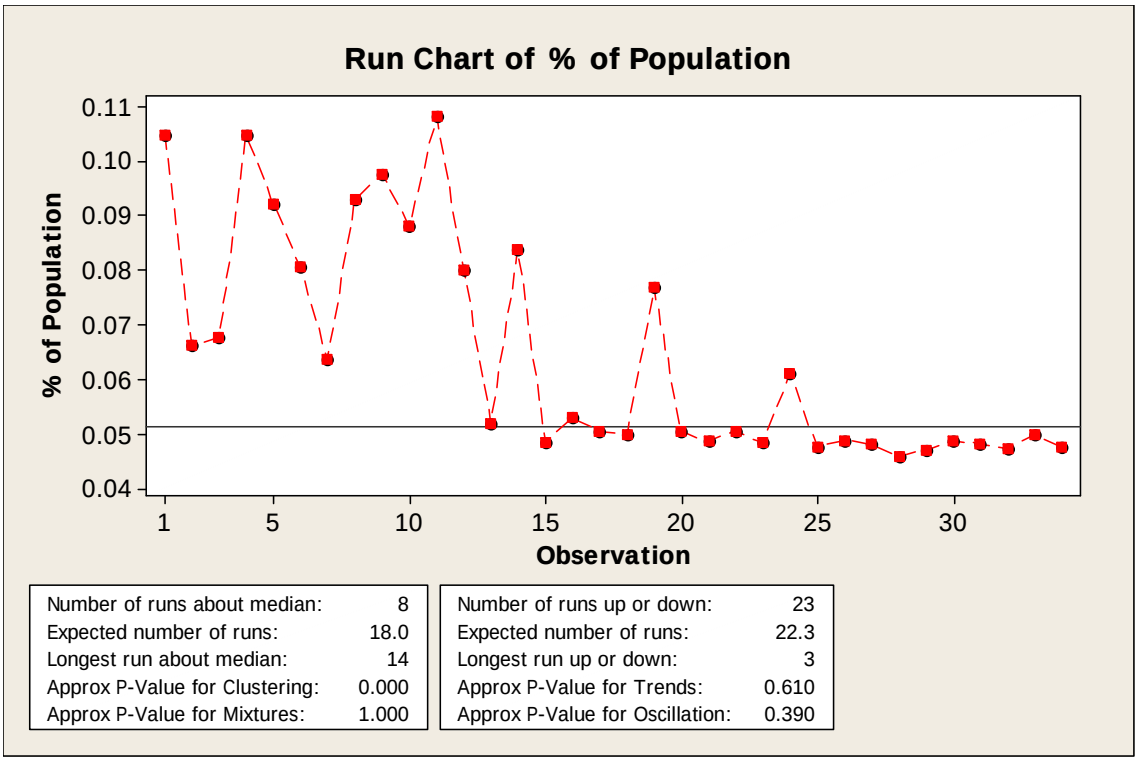


Figure 22: Diabetic contributors as % of population per zip code

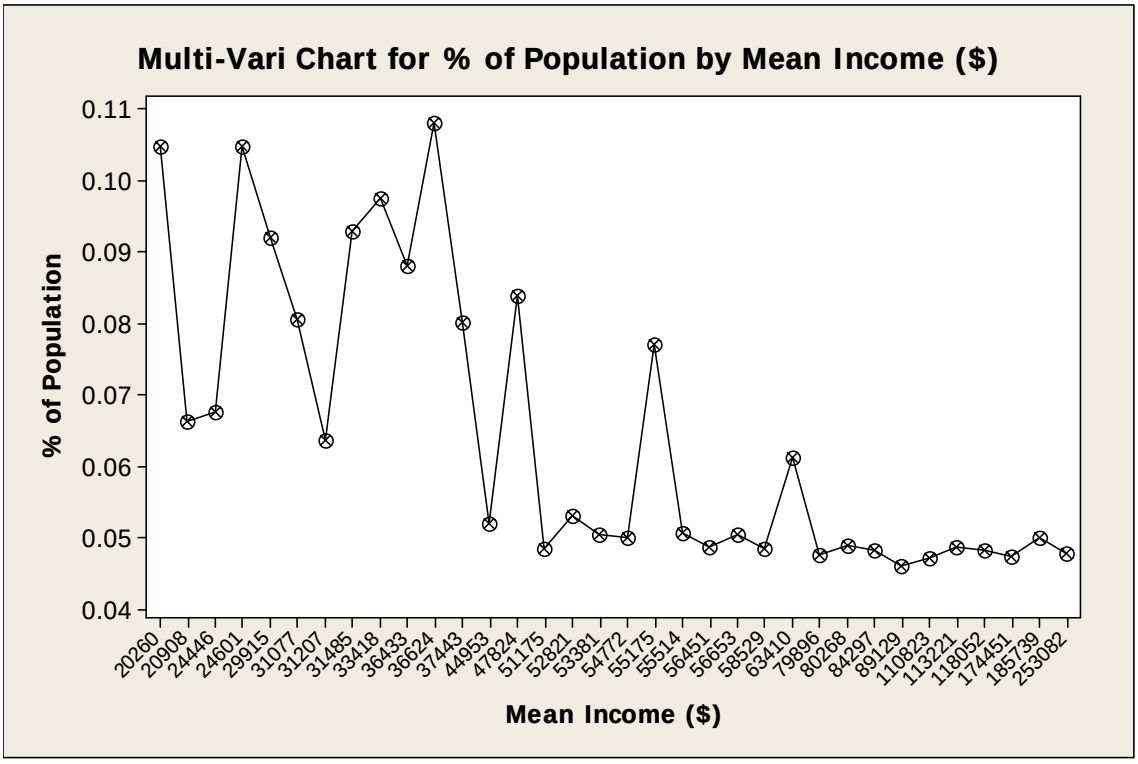


Figure 23: Multi-Vari chart for % of zip code population diabetic contributors vs. average income

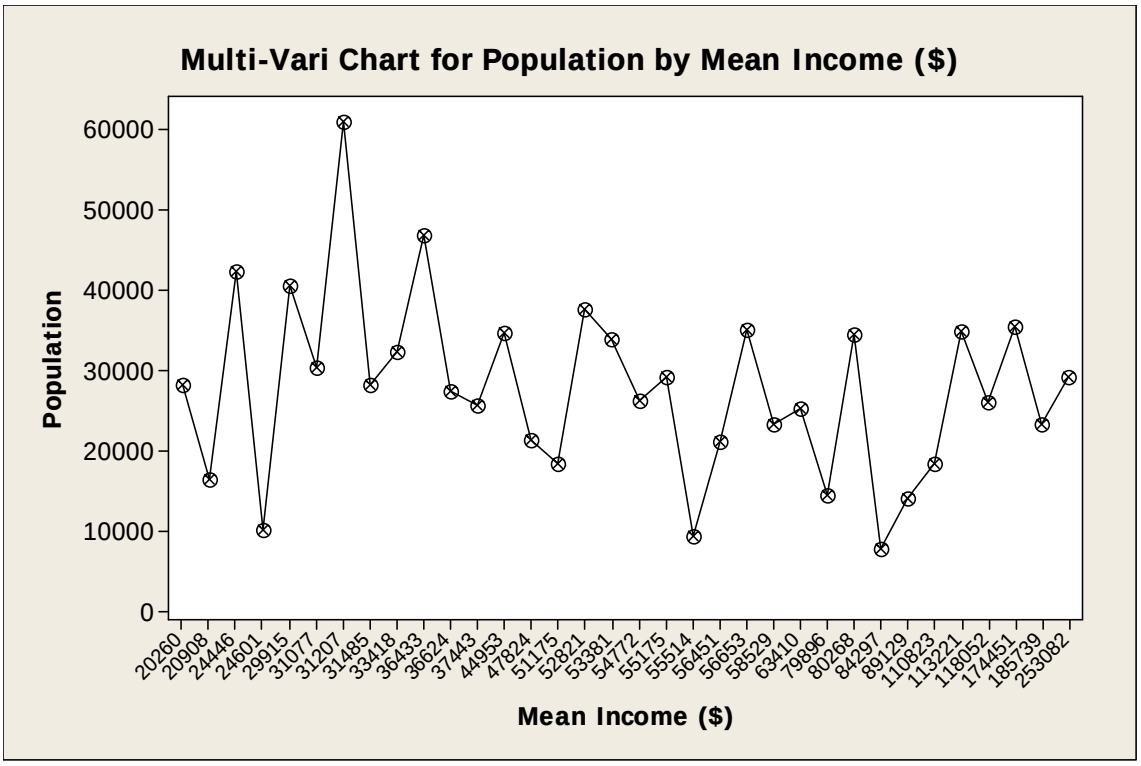


Figure 24: Total population per zip code vs average income

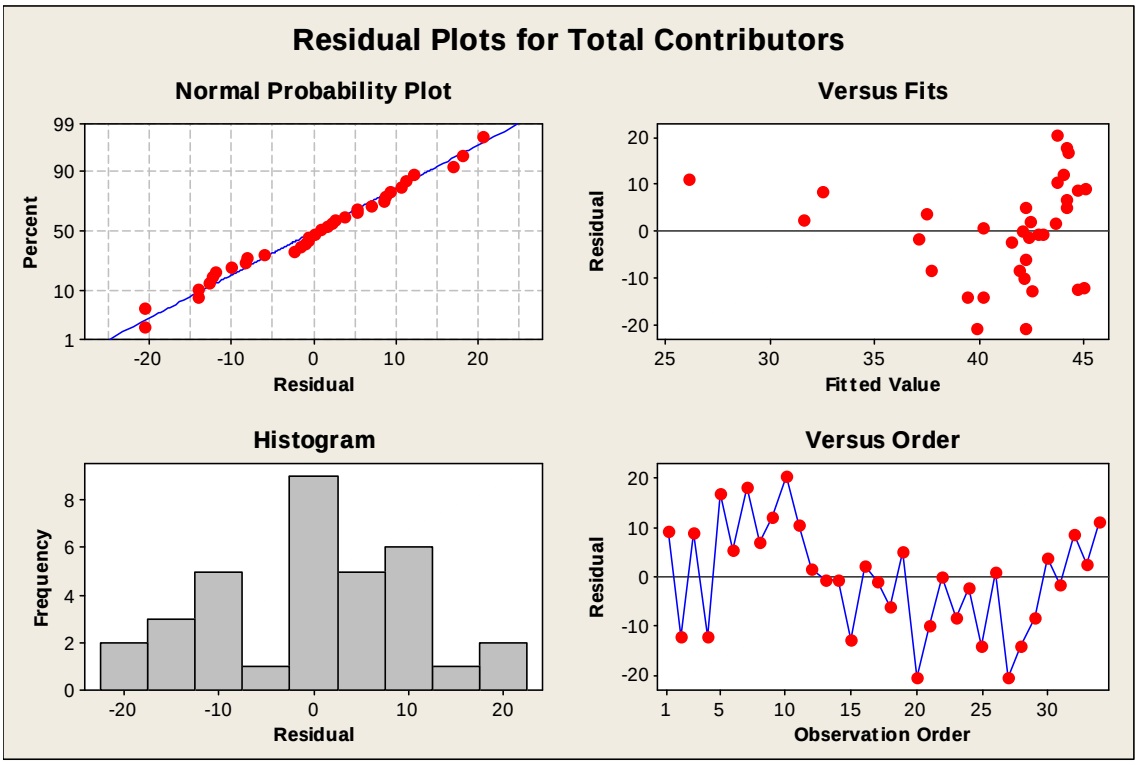


Figure 25: Residual plot of population per zip code

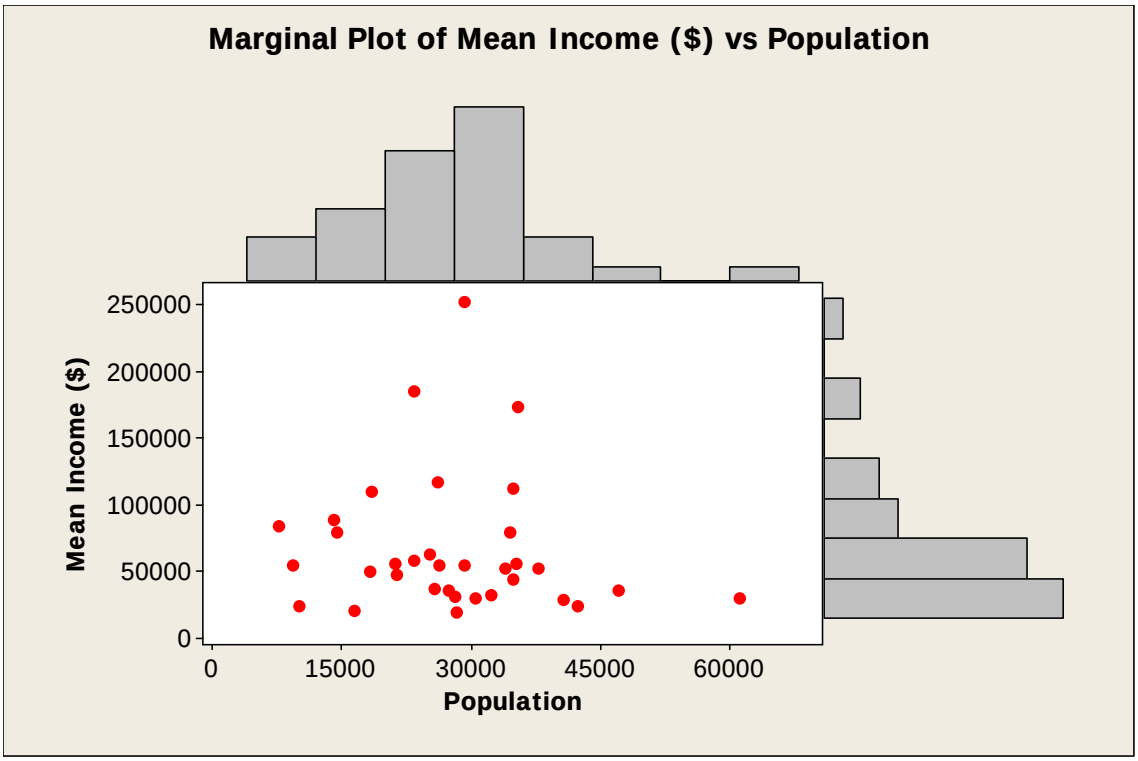


Figure 26: Marginal plot of zip code population vs mean income

This figure shows that population values of the zip codes follows a relatively normal distribution, however the income is heavily biased towards the lower income range for Milwaukee County. Table 8 below shows the number of contributors for each zip code by race for a single model run. Table 9 shows the same data however the number of replication of the model are set to 3.

Table 8: Demographic information of T2DM contributors by zip code and ethnicity

	BLACK	WHITE	LATINO	ASIAN	AMERICAN INDIAN
53206	2861	18	64	6	11
53233	551	396	54	73	17
53204	557	876	1207	74	153
53205	938	19	35	57	4
53218	3020	268	144	284	27
53212	1751	479	168	21	33
53215	465	1401	1616	147	250
53210	2219	238	90	41	28
53216	2821	182	93	40	13
53209	3441	494	123	49	27
53208	1651	429	156	241	35
53225	1403	423	103	106	25
53214	206	1226	225	51	96
53224	1279	298	111	72	25
53110	59	687	82	21	40
53221	177	1272	298	163	88
53219	139	1228	206	51	86
53220	95	983	114	58	65
53223	1482	518	98	136	18
53235	29	348	44	19	29
53172	48	841	70	27	45
53207	111	1291	229	46	99
53227	83	876	75	55	42
53222	593	771	84	69	23
53228	25	555	44	34	26
53154	117	1295	100	132	42
53130	6	319	12	12	25
53129	15	542	30	44	12
53226	64	693	43	52	15
53132	199	1272	60	153	15
53213	117	1007	65	50	18
53211	114	1342	81	130	10
53202	200	806	55	91	15
53217	129	1101	53	101	9
TOTALS	**26965**	**24494**	**6032**	**2706**	**1466**

Table 9: Diabetic contributor counts per zip code by ethnicity – 3 replications means

	BLACK	WHITE	LATINO	ASIAN	AMERICAN INDIAN
53206	2878	18	63	7	16
53233	574	411	52	66	15
53204	545	854	1218	61	148
53205	934	15	34	49	5
53218	3056	282	130	284	32
53212	1780	482	169	28	36
53215	437	1408	1661	124	231
53210	2247	243	89	40	27
53216	2827	183	90	39	16
53209	3480	511	125	49	35
53208	1700	426	158	225	41
53225	1430	421	108	96	25
53214	194	1255	219	48	94
53224	1282	305	116	79	22
53110	55	710	83	21	34
53221	164	1299	289	141	79
53219	127	1266	198	45	80
53220	85	1004	116	60	58
53223	1489	521	100	131	22
53235	27	364	40	15	21
53172	45	857	69	22	35
53207	106	1320	219	43	96
53227	83	907	79	52	38
53222	595	781	84	64	22
53228	24	575	36	29	21
53154	108	1319	112	115	47
53130	8	327	10	12	17
53129	16	569	25	35	12
53226	63	733	42	46	15
53132	190	1318	67	138	20
53213	117	1032	60	47	20
53211	109	1392	81	114	14
53202	204	966	68	111	24
53217	130	1146	52	92	11
TOTALS	**27109**	**25220**	**6062**	**2528**	**1429**

Although the African American demographic is approximately 27% of the population in Milwaukee County, it can be seen that the contribution is proportionally higher than the White demographic which makes up just under two thirds of the population in Milwaukee County on a whole. The Black/African American demographic is approximately half of the white demographic population yet its contribution and prevalence is greater overall. There is another layer of data to consider in our analysis, the impact of income on the contributors by race.

We would like to preface the following analysis with the following note on results from ABMS. Especially for exploratory studies, the results are best interpreted qualitatively rather than quantitatively. When considering the effects of race on diabetes contributors as a percent of population as well as income as a factor, the results of the regression analysis are presented in the Figure 26 below.

The independent variable in the regression analysis was taken as the square root transformation of normalized percentage of contributors for each zip code. We will note that the normalization was obtained as the estimated number of contributors divided by total population for each zip code. Next, the response variable was calculated as the normalized contribution for each zip code as a percentage of the total normalized contributors. The first explanatory variable was the natural log transformed income values, so as to remove the effect of scale differences from other explanatory variables. The second and third explanatory variables were the percentage of blacks and whites respectively for each zip code.

The regression was limited to black and white contributors as the percentages of the remaining ethnic/racial groups (Latino, Asian and American Indian) were comparatively small that their normalized values were well below the contribution and variation present in the black and white.

The race (black and white) and income had statistically significant effects on the number of persons with type 2 diabetes in Milwaukee County, with an overall R-squared value of 97.04%.

Analysis of Variance

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Regression	5	569208	113842	217.69	0.000
ln(income)	1	13942	13942	26.66	0.000
%B	1	20669	20669	39.52	0.000
%W	1	14358	14358	27.46	0.000
ln(income)*%B	1	21044	21044	40.24	0.000
ln(income)*%W	1	12959	12959	24.78	0.000
Error	28	14642	523		
Total	33	583850			

Model Summary

S	R-sq	R-sq(adj)	R-sq(pred)
22.8680	97.49%	97.04%	93.61%

Figure 27: Minitab multi-variate regression results of race and income

Overall, it can be seen that diabetes contributors as a percent of population is a function of race for our analysis. Income is also a factor however it is unclear whether the prevalence is associated with simply genetics alone or a result of the underlying

socioeconomic disparity as it relates to race in Milwaukee County. This is especially so, since the interactions between race and income are also statistically significant. Figure 27 below presents the results as a contour plot of the mean income vs. race. It can be seen that the results indicate a racial bias when considering race and income in Milwaukee County.

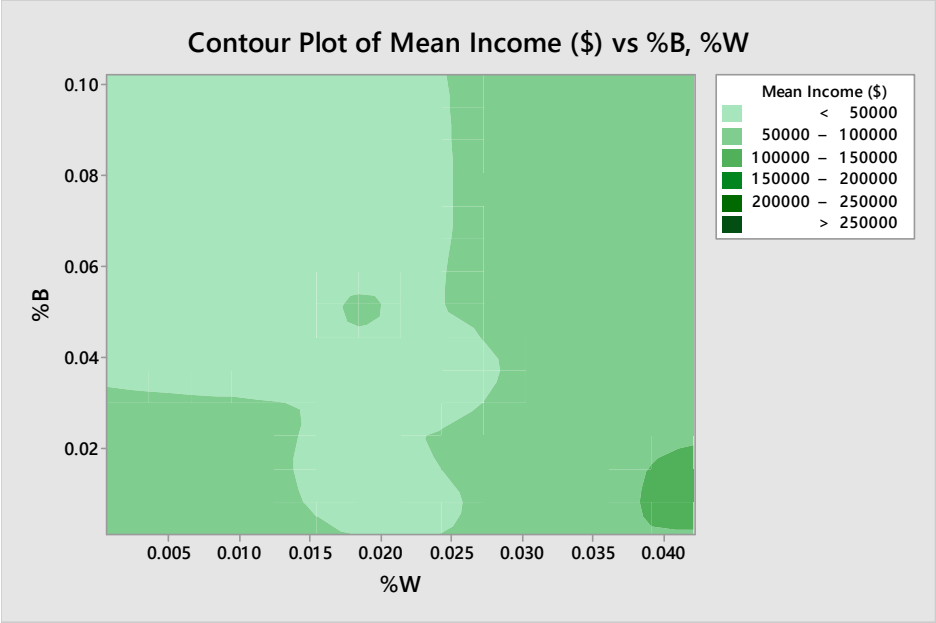


Figure 28: Contour plot of mean income vs race

4.2 Model Verification/Validation

It is often not practical (cost, time) to determine the absolute (100%) validity of a model in all areas that it may be applicable (Sargent 2013). It is important to assess the confidence in the model for its intended purpose. Figure 26 below is a graphical

representation of the relationship between the confidence level and the associated cost/value tradeoff.

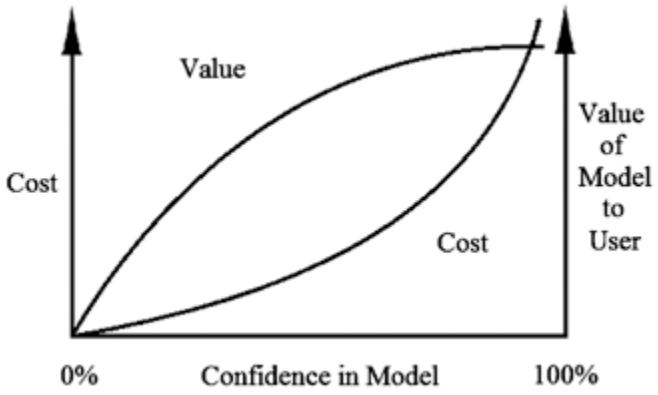


Figure 29: Confidence that a model is valid (Sargent 2013)

In order to validate our system we were able to confirm the process simulation and results with published studies related to the county health profile and a study on the measured concentrations of pharmaceuticals in the influent stream at SSWRF. In modeling our system we proceeded with the knowledge that "The most definitive test of a simulation model's validity is to establish that its output data closely resemble the output data that would be expected from the actual (proposed) system" (Kelton 2003). In addition authors Naylor and Finger (Naylor 1967) formulated an approach to the validation of simulation models following three steps:

Step 1. Build a model that has high face validity.

Step 2. Validate model assumptions.

Step 3. Compare the model input-output transformations to corresponding input-output transformations for the real system.

This 3-step approach is at the heart of many simulation modeling paradigms. The data validity of the model contributes to the overall simulation model validity, and is central to all aspects of the modeling process (Sargent 2013). This supports the importance of the pre-processing data phase of ABMS development.

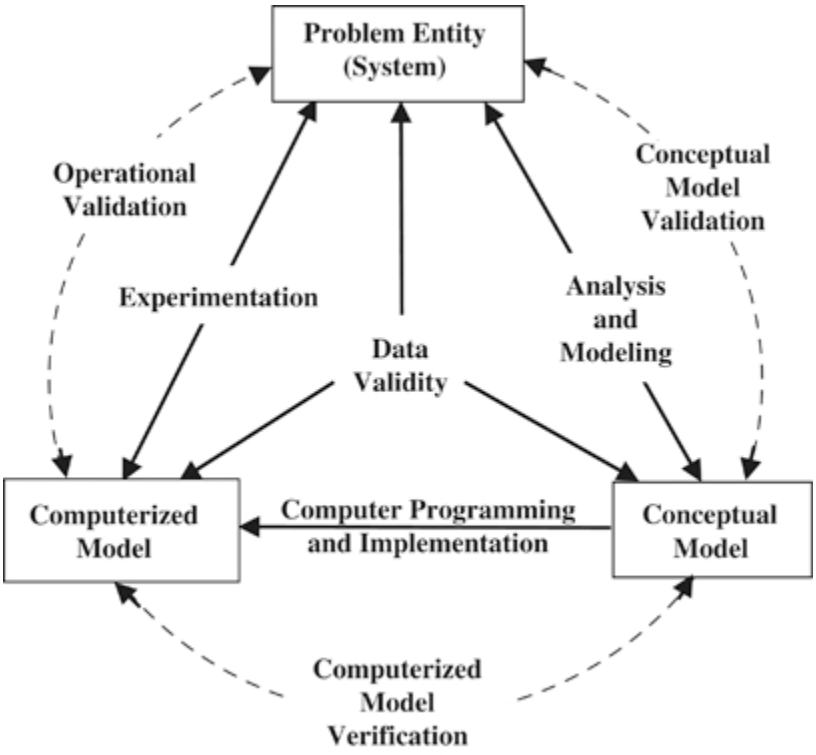


Figure 30: Process of model development (Sargent 2013)

By following these steps and performing verification and validation during the modeling process we were able to confirm the accuracy of the data sources utilized and the process assumptions made. The model is validated and the confidence interval of the results are examined. The output of the model does not include the standard

deviation (only half width) of the replication values, thus we will need to determine this from the output data. When considering data where the sample size is within 16-70 and is normally distributed, the best estimator of the standard deviation is considered range/4 (with a relative error of approximately 10%) (Hozo 2005). We will consider the confidence interval and number of replications necessary for statistical significance on our base model for the output of diabetes count for randomly selected zip code 53215:

Average count for Black/African American diabetic seniors contributing: 328
Maximum: 353
Minimum: 312
Range (max-min): 41
Standard deviation, σ (range divided by 4): 41/4 = 10.25
Base replications: 30
Z: from table for 95% = 1.96
H: mean*(0.05 margin of error) = 16.4

$$N = \mathbf{z}^2_{\alpha/2}(\sigma^2/H^2) \qquad (4.4)$$

$$= 1.96^2\ (10.25^2/16.4^2)$$

$$= 1.5 \text{ replications} \approx 2 \text{ replication}$$

Additional replications = N – n = 2 - 30 = - **28 (i.e. 28 surplus replications)**

No additional required, only 2 replication necessary for this significance

Confidence interval of count at 3 replications:
X: count simulated
Y: mean value from simulation

t: from table at 95% = 2.920

$$Y \pm \mathbf{t}_{1-\alpha/2} (\sigma / \sqrt{N}) \quad (4.5)$$

$$= 328 \pm 24.44$$

CI @ 95% for Black/African American population contributors:

(304 < X < 353)

We will take another example:

Average count for White diabetic seniors contributing: 1151

Maximum: 1179

Minimum: 1125

Range (max-min): 54

Standard deviation, σ (range divided by 6): 54/4 = 13.5

Base replications: 30

Z: from table for 95% = 1.96

H: mean*(0.05 margin of error) = 57.55

$$N = \mathbf{z}^2_{\alpha/2}(\sigma^2/H^2) \quad (4.4)$$

$$= 1.96^2 (13.5^2/57.55^2)$$

$$= 0.211 \text{ replications} \approx 1 \text{ replication}$$

Additional replications = N – n = 0.094 - 30 = **- 29.79 (i.e. 29 surplus replications)**

No additional required, only 1 replication necessary for this significance

Confidence interval of count at 1 replications:

X: count simulated

Y: mean value from simulation

t: from table at 95% = 2.920

$$Y \pm \mathbf{t}_{1-\alpha/2} (\sigma / \sqrt{N}) \quad (4.5)$$

$$= 1151 \pm 85.82$$

CI @ 95% for white population contributors:

(1066 < X < 1237)

We have selected to run the models for a total of 3 replications as this helps reduce the half width values.

We have validated that our model replicates the real world model as well as testing for statistical significance. Our model results represent a 95% confidence interval or 5% margin of error. The results are now considered against data available from a community health assessment study and the measured concentrations of metformin found in the water system.

In comparing the results to the results available from the studies and reports in Wisconsin, The total estimated number of diabetics in Milwaukee County (WDHS 2011):

Table 10: model results comparison with actual estimates from WDHS

	Department of Health Services (WDHS 2011)	**Model Result Estimates**	**Difference**
Diagnosed estimate of T2DM	67,780	62,111	8%
Undiagnosed estimate	25,240	29,242	15%
Total	93,020	91,353	1.7%

The model results for diagnosed contributing type 2 diabetics represents a smaller number than those estimated in the 2011 health study (WDHS 2011). The count that is for the undiagnosed estimate do include the total number undiagnosed regardless of age as well as the diagnosed adults who were not contributing at that time in the current model "snapshot". The difference in the numbers for the total is within 2% error and well within the acceptable range of 5% error for our model. The differences are higher for the adhering and non-adhering counts and can be attributed to the underlying difference of the model objective and the department of health study. The model is intended to consider the active contributors of metformin to the system and is thus "filtered" to supply a count of those actively contributing rather than a total of the diagnosed diabetics only.

Table 11: notation for concentration calculations

	notation	*Value*
Total Contributors from Model	***TCp***	62,111 total people
Mean dose range of prescribed Metformin		500mg to start and not to exceed 2500mg
Mean dose taken for calculation	***Md***	1300 mg per day
Metformin excretion	***Ec***	90% unchanged renal
Total raw concentration	***TCr***	
Total number of facilities serving area	F_t	2

To convert the model results of contributors to the concentration values measured in the wastewater influent (Blair 2013), we will now calculate the estimate of

the concentration of the drugs entered into the system. Total raw concentration of metformin in grams being introduced into the system is determined as follows:

$$TCr = TCp \times Md \times Ec \quad (4.6)$$

= 62,111 (1.3g) (0.9)

TCr = 72,669.87 g total

In order to compare the values to the measured concentrations we will need to divide the concentration into n, the number of treatment facilities serving the area. In our case there are 2 treatment facilities that serve Milwaukee County. The assumption here is that the same amount of waste water is directed to the two treatment plants. With further sewer routing information, this estimate can be adjusted to account for the actual sewer processing volumes by the two facilities. The South Shore Water Reclamation Facility portion of total flow is thus:

$$SSWRF_{FS} = \frac{TCr}{F_t} \quad (4.7)$$

= 72,669.87g / 2

$SSWRF_{FS}$ = 36,334.94g

A correction factor is included to account for error in line loss, i.e. the concentrations that would remain in the pipes or seep out of the system prior to the end of the line, as well as for fluctuations in the sewer flow rates (F. Y. Lai 2011). This has been presented as being in the range of 5-25% which is intended as a refinement of

estimations related to pharmaceutical wastewater analysis. This correction factor will be denoted as C_t. The value for C_t for our purposes will be set at 20% to account for flow uncertainties. Equation (4.8) below is used to determine the corrected loss applied to the contribution total to account for flow uncertainties through the water system inlet.

$$L_C = SSWRF_{FS} \times C_t \quad (4.8)$$

$$= 36{,}334.94\text{g} * 0.2 = 7{,}266.99\text{g}$$

$$\text{Corrected total, } T_C = 36{,}334.94\text{g} - 7{,}266.99\text{g} = 29{,}067.95\text{g}$$

This value will now be divided by the mean daily flow of 100M gallons per day (378M liters) to obtain the estimated concentration of metformin in the influent stream at SSWRF in Equation (4.9).

$$\text{Total Concentration Contributed, } TCC = T_C / MDF \quad (4.9)$$

$$= 29{,}067.95\text{g} / 378{,}000{,}000\text{L}$$

$$\text{TCC} = 0.0000768993\text{g/L or } \mathbf{76{,}899.3\ ng/L}$$

Where MDF is the Mean Daily Flow of the treatment facility. The raw influent concentration reported for metformin in Milwaukee County (Blair 2013) is as follows:

Table 12: model concentration estimate comparison

Measured	Minimum: **3200 ng/L**	Median: **55,000 ng/L**	Maximum: **100,000 ng/L**
Model	**76,899.3 ± 3844.97 ng/L**		

It can be seen that the models' 95% confidence limit of the traceable measures of metformin in the simulation is **76,899.3 ± 3844.97 ng/L, which** is within the range of measured concentration. The results are an acceptable estimate and falls within the specific detection range measured at SSWRF.

In reviewing the model result value, the correction factor C_t used at 20% is a reasonable estimate, noting that even at 15% or 10%; the resulting value is still within the actual measured concentration range of metformin. This indicates some flexibility of correction and that the range of correction discussed in previous studies (F. Y. Lai 2011) is a valid assumption for the purposes of variations present in sewer systems and concentration estimates.

Chapter 5: Conclusion and Future Work

5.1 Conclusion

The Thesis details a systems approach to point source identification of pharmaceutical ingredients in the water system for Milwaukee County. A novel holistic, agent based systems approach was utilized to aid in system modeling. In particular, this study considered metformin as a case study. Studies have found highest traceable amounts of metformin Milwaukee County waste water system, especially in the effluent that is directed back to Lake Michigan.

It is important to have a well-defined objective in place to be able to pre-process data to determine model structural suitability. Obtaining data sources to utilize in the model structure is of utmost importance in developing an appropriate level and results in the simulation. By utilizing publicly available data sources, the data can be paired with demographic information to obtain greater detail in the model output. By building the model, and verifying and validating the results with other empirical studies, the results provide geographical, income, race and age information on the sources of contribution to the water system. We were able to achieve the overall goal of this Thesis by fulfilling following objectives:

Objective 1: Analyzed the current status of quantifiable pharmaceuticals in Milwaukee County.

Task: Gathered and pre-processed data from studies that quantify API trace levels in Milwaukee County.

Objective 2: Analyzed Milwaukee County's geographic, demographic and socio-economic status to determine and quantify the main population agent attributes to be used in objective 3.

Task: Gathered and pre-processed data on demographics, socio-cultural as well as economic attributes of Milwaukee County residents.

Objective 3: Built an Agent Based Simulation Model, which incorporates county residents as API point source agents whose attributes are listed in objective 2, determining their degree of contribution towards APIs in the waterways.

Chapter 1 explains in detail the problem statement and the importance of this Thesis. The growing ubiquity of pharmaceuticals and personal care products entering the water system are explored along with their growing hazardous effects on the environment. The literature review covered in Chapter 2 examines the impact and prevalence of API's in the water system as well as assessing their prevalence as a representation of the population. Secondly, the application and structure of agent based models are considered and their applicability to analyzing point source identification of water system pollutants. No studies were found that utilize agent based modeling to examine drug concentrations in the water systems. No studies were found that attempt to identify point sources of pharmaceuticals entering the water system from a geospatial and individual detail level.

Chapter 3 covers the data preprocessing and model building procedure followed by the results and analysis of the model in Chapter 4. The results were verified and validated using extant empirical studies, to assess the effectiveness of the model. The results of the model confirm the prevalence of the drug metformin entering the water system while identifying a zip code level detail of individual contributors. In this study, the results for the total number of diabetics in Milwaukee County was determined to be within an acceptable margin of error specified in the model. The model results indicate approximately 91,353 type 2 diabetics in Milwaukee County which is corroborated by Wisconsin's department of health reports indicating 93,020 hence the results are within 2% margin of error. The adjusted contributors that account for the measured concentration of metformin at the SSWTF were determined to be within the range of concentrations measured in the influent stream – Minimum: 3,200ng/L, Median 55,000ng/L, Maximum 100,000ng/L. The model results indicate that 76,899.3 $\pm$ 3,844.97 ng/L concentration present from the contributors which is within range of the actual measured concentration of metformin at the SSWTF influent stream.

This exploratory test bed example shows that agent based modeling can be a valuable tool for industrial engineers and operation research when dealing with geospatial problems that exhibit high variability through agency. Though this research considers Milwaukee and particularly Milwaukee Metropolitan Sewage District, further research should be done to study the effect of variability in climatic and topographic conditions across the nation on the prevalence of APIs to make the model generalizable.

5.2 Future Work

This thesis details a systems approach to point source analysis of metformin (the go to medication for diabetes type 2) concentrations in Milwaukee County. No studies were found during the literature review that present a model that incorporates agency in identifying the source of contaminants. The discussion presented represents an exploration of utilizing industrial engineering modeling and problem solving to identify the source of drug introduction into the water system where the source is individuals in the community. Point source identification can be useful in resolving a solution as well as improving the efficiency of efforts to mitigate the impact of PPCPs in the water ways. With an enhanced understanding of the profile of the sources of data, detailed features of the autonomous objects or agents can be incorporated into the model. These include gender, weight, diet, literacy levels, ethnicity and time since diagnosis, all of which affect either adherence or drug dosage. These added agent attributes will produce a detailed analysis of the point source, which will aid in better directed measures to mitigate the prevalence of PPCPs.

Human beings are known to not always make rational decisions when it comes to implementing potential mitigating measures. Thus, ABMs may be limited in its ability to capture such irrational aspects of human decision making processes. However, so far, ABMs might be the best simulation tool that can be used to incorporate these behaviors and mimic human systems.

This study considered the prevalence of metformin, a drug used to control and treat type 2 diabetes which is non-communicable. The use of ABMS to analyze prevalence of PPCPs used to treat communicable diseases will have to include seasonal effects and susceptibility to infection, thus adding complexity to the simulation model. An example would be antihistamines as they can be in higher use at different times of the year. Another would be for STD outbreaks and concentrations along with its prescribed treatment finding the way into the water system.

While pharmaceutical ingredients in the water system get easier to isolate (identify) as general health data becomes more readily available, it would be more difficult to identify sources of over the counter or common chemicals found in the water such as caffeine. It was noted however that the most persistent drugs were those prescribed to treat illness in Milwaukee County (Blair 2013). Of the 54 pharmaceuticals measured in the water system in Milwaukee, several others stand out that could be candidates for further exploration. These include Pyrimidine antibiotic, Carbamazepine, Codeine, Naproxen and Gemfibrozil. These drugs were seen to persist at traceable concentration through the water treatment process into the effluent stream. Overall, ABMS provides a viable tool to analyze sociological systems at both aggregate and constituent unit levels, especially when the geospatial and temporal dynamics are of importance. By incorporating climatic and topographic conditions across the nation on APIs, variability will be incorporated into the model to enhance and enable replication of such a study in different regions of the country.

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Appendix

Table 13: data and results - 53206

Zip Code	**53206**				
Mean Income	$20,260				
Population:	**28,210**				
American Indian	0.3%				
Asian	0.4%				
Black	95.1%				
White	1.6%				
Latino	2.6%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	130	639	2092	1387
	White	0	2	16	10
	Latino	2	18	44	32
	Asian	0	2	4	1
	American Indian	4	4	3	12
Total contributors	**2960**				
Total undiagnosed T2DM and Non-adhere					**1442**

Table 14: data and results - 53233

Zip Code	**53233**				
Mean Income	$20,908				
Population:	**16,453**				
American Indian	0.5%				
Asian	5.4%				
Black	33.3%				
White	56.5%				
Latino	4.3%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	17	137	397	300
	White	8	61	327	177
	Latino	2	12	40	24
	Asian	2	19	52	30
	American Indian	6	9	2	10
Total contributors	**1091**				
Total undiagnosed T2DM and Non-adhere					**541**

Table 15: data and results - 53204

Zip Code	**53204**				
Mean Income	$24,446				
Demographics:	**42,355**				
American Indian	1.6%				
Asian	1.9%				
Black	11.9%				
White	46.5%				
Latino	38.1%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	19	132	406	265
	White	21	136	719	400
	Latino	29	302	876	606
	Asian	4	12	58	27
	American Indian	62	58	33	73
Total contributors	**2867**				
Total undiagnosed T2DM and Non-adhere					**1371**

Table 16: data and results - 53205

Zip Code	**53205**				
Mean Income	$24,601				
Demographics:	**10050**				
American Indian	0.3%				
Asian	5.6%				
Black	85.2%				
White	4.5%				
Latino	4.4%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	43	218	677	465
	White	0	3	16	4
	Latino	3	7	25	20
	Asian	2	16	39	14
	American Indian	3	1	0	5
Total contributors	**1053**				
Total undiagnosed T2DM Non-adhere					**508**

Table 17: data and results - 53218

Zip Code	**53218**				
Mean Income	$29,915				
Demographics:	**40,625**				
American Indian	0.4%				
Asian	9.2%				
Black	70.5%				
White	15.7%				
Latino	4.2%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	126	688	2206	1462
	White	4	34	230	145
	Latino	5	40	99	57
	Asian	12	62	210	132
	American Indian	8	13	6	21
Total contributors	**3743**				
Total undiagnosed T2DM and Non-adhere					**1817**

Table 18: data and results - 53212

Zip Code	**53212**				
Mean Income	$31,077				
Demographics:	**30,416**				
American Indian	0.6%				
Asian	0.9%				
Black	55.5%				
White	35.9%				
Latino	7.1%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	70	411	1270	890
	White	7	72	400	230
	Latino	8	44	116	81
	Asian	1	5	15	10
	American Indian	11	16	6	25
Total contributors	**2452**				
Total undiagnosed T2DM and Non-adhere					**1236**

Table 19: data and results - 53215

Zip Code	**53215**				
Mean Income	$31,207				
Demographics:	**60,953**				
American Indian	1.8%				
Asian	2.7%				
Black	6.5%				
White	53.5%				
Latino	35.5%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	12	100	353	188
	White	31	222	1148	685
	Latino	40	394	1182	807
	Asian	6	35	106	67
	American Indian	94	91	65	123
Total contributors	**3879**				
Total undiagnosed T2DM and Non-adhere					**1870**

Table 20: data and results - 53210

Zip Code	**53210**				
Mean Income	$31,485				
Demographics:	**28,126**				
American Indian	0.5%				
Asian	1.6%				
Black	75%				
White	18.8%				
Latino	4.1%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	92	492	1635	1088
	White	2	38	198	101
	Latino	6	20	64	40
	Asian	2	8	31	18
	American Indian	8	15	5	15
Total contributors	**2616**				
Total undiagnosed T2DM and Non-adhere					**1262**

Table 21: data and results - 53216

Zip Code	**53216**				
Mean Income	$33,418				
Demographics:	**32,264**				
American Indian	0.3%				
Asian	1.4%				
Black	81.6%				
White	13%				
Latino	3.7%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	126	621	2074	1373
	White	3	26	153	80
	Latino	6	23	64	43
	Asian	3	8	29	14
	American Indian	5	4	4	15
Total contributors	**3149**				
Total undiagnosed T2DM and Non-adhere					**1525**

Table 22: data and results - 53209

Zip Code	**53209**				
Mean Income	$36,433				
Demographics:	**46,917**				
American Indian	0.4%				
Asian	1.2%				
Black	69.7%				
White	25.2%				
Latino	3.5%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	143	771	2527	1636
	White	7	73	414	256
	Latino	5	31	87	58
	Asian	3	11	35	16
	American Indian	8	14	5	22
Total contributors	**4134**				
Total undiagnosed T2DM and Non-adhere					**1988**

Table 23: data and results - 53208

Zip Code	**53208**				
Mean Income	$36,624				
Population:	**31,133**				
American Indian	0.7%				
Asian	9.4%				
Black	51.6%				
White	31.8%				
Latino	6.5%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	68	385	1198	844
	White	4	75	350	224
	Latino	3	49	104	67
	Asian	12	54	175	102
	American Indian	14	18	3	28
Total contributors	**2960**				
Total undiagnosed T2DM and Non-adhere					**1442**

Table 24: data and results - 53225

Zip Code	**53225**				
Mean Income	$37,443				
Population:	**25,706**				
American Indian	0.5%				
Asian	4.7%				
Black	52.7%				
White	36.5%				
Latino	5.6%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	57	334	1012	701
	White	5	66	352	199
	Latino	6	28	69	54
	Asian	6	23	77	46
	American Indian	7	17	1	16
Total contributors	**2060**				
Total undiagnosed T2DM and Non-adhere					**316**

Table 25: data and results - 53214

Zip Code	**53214**				
Mean Income	$44,953				
Population:	**34,725**				
American Indian	1.2%				
Asian	1.8%				
Black	5.0%				
White	83.4%				
Latino	8.6%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	9	44	153	80
	White	23	187	1016	593
	Latino	6	47	172	111
	Asian	4	8	39	25
	American Indian	34	35	27	57
Total contributors	**1804**				
Total undiagnosed T2DM and Non-adhere					**866**

Table 26: data and results - 53224

Zip Code	**53224**				
Mean Income	$47,824				
Population:	**21,284**				
American Indian	0.5%				
Asian	4.6%				
Black	56.4%				
White	31.3%				
Latino	7.2%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	46	303	930	605
	White	3	38	257	133
	Latino	5	29	77	61
	Asian	4	18	50	37
	American Indian	8	14	3	14
Total contributors	**1785**				
Total undiagnosed T2DM and Non-adhere					**850**

Table 27: data and results - 53110

Zip Code	**53110**				
Mean Income	$51,175				
Population:	**18,320**				
American Indian	0.9%				
Asian	1.4%				
Black	2.7%				
White	88.7%				
Latino	6.3%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	1	13	45	17
	White	15	113	559	329
	Latino	2	18	62	45
	Asian	1	1	19	9
	American Indian	13	19	8	20
Total contributors	**889**				
Total undiagnosed T2DM and Non-adhere					**420**

Table 28: data and results - 53221

Zip Code	**53221**				
Mean Income	$52,821				
Population:	**37,701**				
American Indian	1.0%				
Asian	5.3%				
Black	3.8%				
White	79.7%				
Latino	10.2%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	9	38	130	54
	White	23	206	1043	618
	Latino	4	76	218	133
	Asian	7	33	123	80
	American Indian	31	33	24	46
Total contributors	**1998**				
Total undiagnosed T2DM and Non-adhere					**931**

Table 29: data and results - 53219

Zip Code	**53219**				
Mean Income	$53,381				
Population:	**33,880**				
American Indian	1.1%				
Asian	1.7%				
Black	3.4%				
White	85.9%				
Latino	7.9%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	6	30	103	47
	White	24	199	1005	589
	Latino	4	42	160	103
	Asian	4	9	38	25
	American Indian	32	30	24	56
Total contributors	**1710**				
Total undiagnosed T2DM and Non-adhere					**824**

Table 30: data and results - 53220

Zip Code	**53220**				
Mean Income	$54,772				
Population:	**26,303**				
American Indian	1.1%				
Asian	3.1%				
Black	2.9%				
White	87.1%				
Latino	5.9%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	3	23	69	29
	White	18	161	804	474
	Latino	4	23	87	68
	Asian	2	9	47	35
	American Indian	21	25	19	35
Total contributors	**1315**				
Total undiagnosed T2DM and Non-adhere					**641**

Table 31: data and results - 53223

Zip Code	**53223**				
Mean Income	$55,175				
Population:	**29,230**				
American Indian	0.4%				
Asian	5.8%				
Black	48.5%				
White	40.7%				
Latino	4.6%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	63	350	1069	758
	White	7	79	432	245
	Latino	3	31	64	46
	Asian	10	30	96	60
	American Indian	6	10	2	17
Total contributors	**2252**				
Total undiagnosed T2DM and Non-adhere					**1126**

Table 32: data and results - 53235

Zip Code	**53235**				
Mean Income	$55,514				
Population:	**9,270**				
American Indian	1.0%				
Asian	2.1%				
Black	2.7%				
White	89%				
Latino	5.2%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	1	6	22	9
	White	9	63	276	179
	Latino	1	11	32	15
	Asian	0	1	18	6
	American Indian	9	14	6	12
Total contributors	**469**				
Total undiagnosed T2DM and Non-adhere					**221**

Table 33: data and results - 53172

Zip Code	**53172**				
Mean Income	$56,451				
Population:	**21,156**				
American Indian	0.8%				
Asian	1.1%				
Black	2%				
White	91.6%				
Latino	4.5%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	0	9	39	13
	White	16	137	688	408
	Latino	3	15	52	37
	Asian	2	4	21	6
	American Indian	16	20	9	23
Total contributors	**1031**				
Total undiagnosed T2DM and Non-adhere					**487**

Table 34: data and results - 53207

Zip Code	**53207**				
Mean Income	$56,653				
Population:	**35,149**				
American Indian	1.2%				
Asian	1.5%				
Black	2.7%				
White	86%				
Latino	8.6%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	6	28	77	37
	White	25	207	1059	624
	Latino	5	48	176	114
	Asian	4	8	34	22
	American Indian	35	37	27	64
Total contributors	**1776**				
Total undiagnosed T2DM and Non-adhere					**861**

Table 35: data and results - 53227

Zip Code	**53227**				
Mean Income	$58,529				
Population:	**23,357**				
American Indian	0.8%				
Asian	3%				
Black	3.4%				
White	88.4%				
Latino	4.4%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	3	17	63	31
	White	16	137	723	421
	Latino	3	15	57	41
	Asian	3	7	45	29
	American Indian	15	18	9	25
Total contributors	**1131**				
Total undiagnosed T2DM and Non-adhere					**547**

Table 36: data and results - 53222

Zip Code	**53222**				
Mean Income	$63,410				
Population:	**25,165**				
American Indian	0.5%				
Asian	3%				
Black	22.1%				
White	70.1%				
Latino	4.3%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	18	141	434	284
	White	11	122	638	364
	Latino	4	20	60	41
	Asian	4	14	51	32
	American Indian	6	12	5	12
Total contributors	**1540**				
Total undiagnosed T2DM and Non-adhere					**733**

Table 37: data and results - 53228

Zip Code	**53228**				
Mean Income	$79,896				
Population:	**14,369**				
American Indian	0.7%				
Asian	2.5%				
Black	1.7%				
White	91.7%				
Latino	3.4%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	0	4	21	9
	White	13	99	443	263
	Latino	1	14	29	17
	Asian	2	4	28	11
	American Indian	9	13	4	11
Total contributors	**684**				
Total undiagnosed T2DM and Non-adhere					**311**

Table 38: data and results - 53154

Zip Code	**53154**				
Mean Income	$80,268				
Population:	**34,451**				
American Indian	0.7%				
Asian	4.5%				
Black	2.8%				
White	87.7%				
Latino	4.3%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	6	31	80	37
	White	25	216	1054	612
	Latino	3	16	81	55
	Asian	7	31	94	63
	American Indian	19	15	8	37
Total contributors	**1686**				
Total undiagnosed T2DM and Non-adhere					**804**

Table 39: data and results - 53130

Zip Code	**53130**				
Mean Income	$84,297				
Population:	**7755**				
American Indian	1%				
Asian	1.7%				
Black	1.0%				
White	94.7%				
Latino	1.6%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	0	2	4	3
	White	6	54	259	151
	Latino	0	3	9	1
	Asian	0	0	12	4
	American Indian	8	13	4	11
Total contributors	**374**				
Total undiagnosed T2DM and Non-adhere					**170**

Table 40: data and results - 53129

Zip Code	**53129**				
Mean Income	$89,129				
Population:	**13,973**				
American Indian	0.4%				
Asian	3.1%				
Black	1.2%				
White	92.8%				
Latino	2.5%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	0	5	10	6
	White	12	98	432	259
	Latino	0	12	18	12
	Asian	2	6	36	14
	American Indian	5	6	1	7
Total contributors	**643**				
Total undiagnosed T2DM and Non-adhere					**298**

Table 41: data and results - 53226

Zip Code	**53226**				
Mean Income	$110,823				
Population:	**18,370**				
American Indian	0.4%				
Asian	3.2%				
Black	3.3%				
White	89.9%				
Latino	3.2%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	2	15	47	25
	White	13	115	565	327
	Latino	2	14	27	23
	Asian	2	8	42	21
	American Indian	7	5	3	8
Total contributors	**867**				
Total undiagnosed T2DM and Non-adhere					**404**

Table 42: data and results - 53132

Zip Code	**53132**				
Mean Income	$113,221				
Population:	**34,863**				
American Indian	0.3%				
Asian	5.3%				
Black	4.9%				
White	87.1%				
Latino	2.4%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	9	44	146	73
	White	22	202	1048	610
	Latino	1	10	49	35
	Asian	12	37	104	74
	American Indian	7	4	4	20
Total contributors	**1699**				
Total undiagnosed T2DM and Non-adhere					**812**

Table 43: data and results - 53213

Zip Code	**53213**				
Mean Income	$118,052				
Population:	**26,020**				
American Indian	0.4%				
Asian	2.3%				
Black	4.1%				
White	90.1%				
Latino	3.1%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	4	25	88	43
	White	16	166	825	487
	Latino	5	18	42	33
	Asian	5	12	33	22
	American Indian	7	7	4	14
Total contributors	**1257**				
Total undiagnosed T2DM and Non-adhere					**599**

Table 44: data and results - 53211

Zip Code	**53211**				
Mean Income	$174,451				
Population:	**35,406**				
American Indian	0.2%				
Asian	4.3%				
Black	2.8%				
White	89.7%				
Latino	3%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	6	30	78	41
	White	24	218	1100	641
	Latino	3	19	59	43
	Asian	8	31	91	57
	American Indian	5	3	2	14
Total contributors	**1677**				
Total undiagnosed T2DM and Non-adhere					**796**

Table 45: data and results - 53202

Zip Code	**53202**				
Mean Income	$185,739				
Population:	**23,386**				
American Indian	0.4%				
Asian	5%				
Black	7.4%				
White	83.9%				
Latino	3.3%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	7	48	145	70
	White	12	116	678	396
	Latino	2	10	43	31
	Asian	5	20	66	47
	American Indian	6	6	3	14
Total contributors	**1167**				
Total undiagnosed T2DM and Non-adhere					**558**

Table 46: data and results - 53217

Zip Code	**53217**				
Mean Income	$253,082				
Population:	**29,192**				
American Indian	0.2%				
Asian	4.1%				
Black	4%				
White	89.3%				
Latino	2.4%				
T2 diabetes		**18-44**	**45-64**	**65+**	**Non-adhere**
	Black	5	30	94	48
	White	17	185	899	532
	Latino	3	14	36	30
	Asian	8	23	70	47
	American Indian	4	3	2	8
Total contributors	**1393**				
Total undiagnosed T2DM and Non-adhere					**665**