1-1-2012

A multi-agent intelligent system for detecting unknown adverse drug reactions through communication and collaboration

Ayman Mohammad Mansour
Wayne State University,

A MULTI-AGENT INTELLIGENT SYSTEM FOR DETECTING UNKNOWN ADVERSE DRUG REACTIONS THROUGH COMMUNICATION AND COLLABORATION

by

AYMAN MANSOUR

DISSERTATION

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

2012

MAJOR: ELECTRICAL ENGINEERING

Approved by:

_____

Advisor **Date**

_____

_____

_____

DEDICATION

To my parents, Mohammad Mansour and Nahil Mohammad, who scarified the most for me to secure me a happy life.

To my wife Asma, my children Nahil, Mohammad, Lara and Lana, and my sisters for their love, patience, and support this work is dedicated.

ACKNOWLEDGEMENTS

I would like to thank all those who have helped to make this dissertation success. First, I would like to thank God for giving me the opportunity to start my Ph.D. study and leading me to finish it. *Praise be to God, the Cherisher and Sustainer of the worlds.* I would like to take this opportunity to express my profound gratitude and thanks to my advisor Prof. Hao Ying for his unlimited guidance, enormous support and patience from the very early stages of this research. I consider myself privileged to have come in contact with him in my life. Prof. Hao didn't hesitate to offer any kind of help. Thanks a lot Prof. Hao Ying.

Deepest gratitude is also given to my committee members Prof. Syed M. Mahmud and Prof. Feng Lin in the Department of Electrical and Computer Engineering at Wayne State University, and Dr. Yanqing Ji in the Department of Electrical and Computer Engineering at Gonzaga University who monitored my work and took effort in reading and providing valuable comments and guidance on this dissertation.

I would like to also extend my gratitude to Dr. Peter Dews in the Department of Internal Medicine at St John Health Providence Hospital and R. Michael Massanari in the Critical Junctures Institute at Washington for their participation in the evaluation parts of the experiments and for their great help in providing me with the medical aspects of the research knowledge. I should mention here that the evaluation took them long time and they skipped a lot of their families' activities to help me in this research.

I would like to give my special thanks to Prof. Hossein N. Yarandi in the Center for Health Research at Wayne State University for providing me with the statistical analysis of the results.

I would like to thank Ellison Floyd for retrieving the de-identified patient information from Detroit Veterans Affairs Medical Center's databases.

My warm thanks also extend to all the faculty members who taught me in the Electrical and Computer Engineering department at Wayne State University, for providing me a motivating and enthusiastic environment for study and research these past four years.

I am particularly thankful to my friends here at Wayne State University for giving me lots of help. I single out my friends Mohammad Obeidat, Hesham Alsalem, Massoud Alatrash and Fayez Khazalah.

I would also like to express my love, gratitude and sincere thanks to my family members. Without their love and support this would never have been possible.

Finally, the financial support of The Hashemite Kingdom of Jordan Government, Tafial Technical University is gratefully acknowledged. I would not be able to start the PhD program without their support.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1
INTRODUCTION AND PROBLEM STATEMENT

1.1 Motivation and Problem Statement

ADR was defined in [1] as "An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product". ADRs are a major public health problem in the United States [1]. In the year 2010, for instance, Adverse Events Reporting System which is managed by the U.S. Food and Drug Administration (FDA) shows that 82,724 deaths were attributed to serious adverse drug reactions and 471,291 serious cases were reported, which included among others hospitalization, life-threatening, and/or disability [2]. Before drugs are marketed, they are extensively tested in animals and in clinical trials in humans. Clinical trials often refer to pre-marketing studies. Clinical trials have been playing a crucial role in evaluating the overall safety and efficacy of new medications before they get into the market. However, due to many reasons [1] the clinical trials are limited in size and duration, and thus are not capable of detecting rare ADRs. Given the limited information available when the drug is marketed, post-marketing surveillance has become increasingly important. Post-marketing surveillance is the process of identifying, reporting, and responding to the issues occurred while taking medication[1]. The responding includes actions that can be taken to improve product safety and protect the public health, such as labeling changes, safety alerts or

product withdrawals [2]. To date, many methods have been adopted in post-marketing surveillance systems, The most common one is spontaneous reporting systems, such as MedWatch™ [3] in FDA. Those systems suffer from low reporting rates, typically less than 10%. Underreporting of ADRs is a common issue in post-marketing surveillance systems which may delay ADR signal detection and cause underestimation of the size of a problem. Paper [4] explained other limitations including difficulties with adverse event recognition, biases and report quality.

Data mining techniques and Bayesian methods have been used to facilitate the evaluation of ADRs [5]. However, because of the complexity of its mathematics, the unknown features of the data, (i.e., the event background incidences) and the lack of consensus about using data mining in medical applications, data mining is not a preferred method and its use is still limited [3].

Detecting ADR signal pairs is technically a complex problem. This is the case if we realistically assume that there does not exist a set of rules that are readily acceptable to all human experts (e.g., physicians, epidemiologists and pharmacists). The parameters used in identifying the signal pairs are really a vague, subjective measure rather than an objective measure. Furthermore, human experts often disagree one another owing to their knowledge and experiences and there is no "ground truth" to indicate which physician is right or wrong. Because of this and other limitations, current surveillance systems are not ideal for rapidly identifying rare unknown ADRs. A more effective system is needed as the electronic patient records become more and more easily accessible in various health organizations such as hospitals, medical centers and insurance companies. These data

provide a new source of information that has great potentials to detect ADR signals much earlier.

In this dissertation I have developed a multi-agent system to identify adverse drug reaction signal pairs (i.e., potential links between drugs and apparent adverse reactions). The eventual aim of the system is to helps health organization systems achieve earlier identification of potential ADR signal pairs. Intelligent agents may be defined as "software programs that act on behalf of users to find and filter information, negotiate for services, automate complex tasks, and collaborate with other agents to solve complex problems"[6]. Intelligent agents share some common characteristics, including autonomy, collaboration, delegation, and communication skills. A set of agents that help one another in solving problems by using cooperation, coordination and negotiation techniques is called a multi-agent system.

The agents are equipped with intelligent decision maker that arms them with the rule-based reasoning capability. The reasoning is based on a fuzzy inference system implemented using the freeware FuzzyJess [7]. Fuzzy logic is used to represent, interpret, and compute vague and/or subjective information which is very common in medicine.

The developed system design enables the agents to effectively interact and share their experiences by setting up an environment for the agents to learn from each other and work in a proactive way to identify ADR signal pairs. The system allows the most important and insightful detection rules produced by the most experienced agent (i.e., the agent that has the largest amount of patients in its patient database) to bubble up for the

benefit of the entire agent community. The rules will be updated over time, leading to improved similarity-finding performance.

1.2 Adverse Drug Reaction Overview

Medications have brought better health and longer life to the human race. Every day, hundreds of millions of people from all over the world are affected by the medicines. However, medicines are not hundred percent risk-free, and are always associated with some unexpected Adverse Drug Reactions (ADRs).

1.2.1 ADR Statistics

ADR appears in 2.4-5.2 per 100 hospitalized adult patients [8]. A study of serious ADRs shows that such serious events are between the fourth and sixth leading cause of death in the U.S., after heart disease, cancer, accidents, and violence [9]. If the adverse event is not serious, such as loss of appetite, allergy or change in mood, it still has an effect to the life of the patients. Another study has to analysis the causes of hospitalization found that approximately 1.5 million patients a year were hospitalized were caused by adverse drug reactions [9]. This means that around 4,000 patients daily suffer from serious adverse drug reactions so they need to enter hospitals. Although a large number of patients are admitted to hospital as a result of adverse events, 57% of these ADRs were not recognized at the time of admission [10]. Each ADR may increase the stay at hospitals by 2.2 days for a patient case and to lead to an increase in bill by $3,244 per hospital stay [11].

The early detection of ADRs will reduce health care costs approximately by $760,000 per year [8]. A study which analyzed a large number of data came from nursing homes concluded that over half of the adverse events are preventable [3]. Here are more statistics from [3] to show the importance of detecting ADRs as soon as possible:

- In 1995 medication –related problems in United States cause 199000 deaths per year.
- In 2001, 140000 deaths in Untied States have been have been estimated in hospitals which would make it the third leading cause of death in that year.
- It has been expected that 0.31 percent of hospitalized patients in the USA die of ADRs in 1991.
- In Olmsted County, 2.9 per cent of patients died in hospitals as result of ADRs in 1994.
- In 2000, a New Jersey hospital the death rate due to ADRs was 3.2 percent.
- In a US hospital during a 2 years monitored period ended at 1994, 109 patients suffered from medical consequences as a result of medication-related issues or ADRs. These clinical consequences cost $1.5 million.

1.2.2 Types of ADR

Adverse reactions are a recognized hazard of drug therapy. Although some ADRs are minor and resolve without consequences, others can cause permanent disability or death.

The risk of ADRs effects ranges from near zero (with, for example, Nystatin and Hydroxocobalamin) to high (with, for example, Immunosuppressive or Antineoplastic drugs). In the literature they are using two terms Adverse Event (AE) and Adverse Drug Reaction (ADR). The term 'Adverse event (AE)' is slightly different from ADRs [12]. AE is referred to an adverse outcome that occurs while a patient is taking a drug or at some time afterwards, but that may or may not be attributable to the drug [1]. All ADRs are AEs, but not all AEs are ADRs.

ADRs are classified as predictable or unpredictable. Predictable ADRs can be related to drug's pharmacology (i.e., drug interactions) while unpredictable ADRs has not to do drug's pharmacology, (*i.e.,* drug allergy) [13].

For example

Predictable ADRs:

- Side effects (usually minor and self-limited events).
- Secondary effects (predictable but not inevitable events).
- Interactions (effects resulted by using another drug simultaneously).
- Toxicity (effects of taking drugs with large doses).

Unpredictable ADRs:

- Intolerance (very severe side effects).
- Allergic (unanticipated severe effects, usually appears in weak/not immunized patients).

Some serious adverse drug reactions are detected after a drug has been on the market for a while [1]. Therefore, when a drug is approved and began to be available in market, huge numbers of patients will be affected by that potential adverse effect until that potential adverse event has been identified. Until now there is no clearly defined process to be followed in order to detect adverse events [1] and [3]. In section 1.2.3 the literature of the existing ADRs Detection techniques and their problems will be reviewed.

1.2.3 Existing Major ADR Detection Methods

A complete understanding of the safe use of drugs is not possible at the time when drug is developed or marketed. At that time, the safety information is only limited on a few thousand people in typical clinical trials. For example, people are not aware of the risk of heart attacks associated with the use of rofecoxib until five years later after it was launched to the market.

In this section, I briefly introduce several methods for detecting Adverse Drug Reactions. Pre- and post market assessments of drugs are important methods used in identifying ADR signals pairs. Premarket reviews address the issues of safety of a particular drug, and post-marketing surveillance systems check for rare adverse reactions, effects that can be identified only with long-term use.

1.2.3.1 Pre-marketing Studies (clinical trial)

Before drugs are marketed, they are extensively tested in the beginning in animals then in clinical trials in humans. Clinical trials often called pre-marketing studies. Clinical

trials have been playing a crucial role in evaluating the overall safety and efficacy of new medications before they get into the market. However, due to many reasons [1, 3, 14, 15], some rare or serious ADRs are likely to remain unnoticed during the clinical trial program. The First reason that clinical trials cannot catch all the ADR is small sample size (up to 1000 patients). This small size reduces the chance of finding rare adverse effects. The second reason is limited patient diversity (Homogeneous populations). Most trials use healthy patients with only one disease and normally exclude specific groups such as pregnant women, children, and elderly people. The only way to make the clinical trials helpful in term of detecting and identifying adverse drug reaction is to make the medication widely use in a general population and this is impossible because the medication is still not certified. The third reason is insufficient periods of follow-up. Due to this Limited duration, the trials of short duration cannot detect or discover all the ADR specially the long term consequences such as cancer. Once the drug is released and starts to be available in the markets, a huge diversity of patients uses the medication. This will increase the possibility of previously undetected problems to arise and be identified. For example phocomelia which is due to thalidomide took several years to be identified [14]. Additionally, adverse reactions occur at low frequencies that make it difficult to be identified in the small numbers of patients as the one in clinical trials.

The clinical trials cannot predict real life problem that can be resulted from the interaction of medications that a patient is taking simultaneously [1] and [3]. This is beside the difficulty of predicting how the medications will be used by both physicians and patients [16].

1.2.3.2 Post-marketing Surveillance

Given the limited information available when the drug is marketed, postmarketing study has become increasingly important. Post-marketing surveillance is the process of identifying, reporting, and responding to the issues occurred while taking medication [1, 3, 14, 17]. This method is the principal method used for monitoring the safety of marketed drugs nowadays. The responding includes actions that can be taken to improve product safety and protect the public health, such as labeling changes, safety alerts or product withdrawals [12] and [3]. Even if the report does suggest labeling changes, the information provided will be kept for further investigated especially when more information became available. Once the reports are studied and evaluated, the data generated can help to identifying ADR with certain medications and investigate these ADRs to provide clear indicators that can be used to identify other ADR resulted from other medications. To date, many methods have been adopted into postmarketing studies, including ADR case review, comparative observational study, ADRs Spontaneous Reporting, and Data Mining Algorithms.

ADR Cases Review

Case review is one of the most often used methods in the initial recognition of some possible ADRs signals. Many drug safety concerns were initially initiated by case review. For example, A case report in the April 2007 *Journal of Laryngology & Otology* [18] of sudden hearing loss in a man taking sildenafil made the U.S. Food and Drug Administration (FDA) search its Adverse Events Reporting System for other similar cases.

It found 29 similar cases of sudden hearing loss were reported after the medication had been approved and marketed. Those cases trigger an investigation that make the U.S. Food and Drug Administration (FDA) change the label of such mentioning that such medication can lead to sudden hearing loss. This will guide patients on what to do if they experience such hearing problems with taking that medication. As mentioned in the previous example, an initial case report lead to a series of further investigation that can identify an adverse event.

However, with the dramatically increased values of drug safety reports, case review will be extremely unacceptable because such manual searching and reviewing process of unknown signal pairs is time consuming and easily with that amount of huge data a signal pairs can be missed.

Comparative Observational Studies

Traditional comparative epidemiologic methods, sometime called case-control study and cohort study, have been widely used in characterizing the risk and benefit profile of medicines. However, they face similar challenges as clinical trials in terms of insufficient sample size and the difficulty of detecting rare events that need long time to be identified.

ADRs Spontaneous Reporting

In the United States, most ADRs are reported to the Food and Drug Administration by drug manufacturers in early stages. Hospitals and clinics are also required to monitor

suspicious adverse drug events and to report them to FDA. Many large ADRs spontaneous reporting systems (SRS) have been developed worldwide, which make early detection of ADRs signal. To date, the major ADRs SRS available for the public access include the Adverse Event Reporting System (AERS) of the U.S. [19], the Yellow Card of the U.K. [20], the Canadian Adverse Drug Reaction Monitoring Programme (CADRMP) of Canada [21] and Central Drugs Standard Control Organization of India (CDSCO) [22] and [23]. In those systems, Physicians pharmacists and nurses are encouraged to report any reactions that can be associated with drug use. This association is based mainly on their beliefs. Normally the attention is focused more on new medications and serious ADRs rather than old drugs and non-serious or unhurt ADRs. The role for SRS is to continuously monitor all drugs used in a variety of conditions and quantities, generate signals of potential drug problems, and to identify rare ADRs.

ADRs spontaneous reporting System Example: FDA MedWatch Program

The most important source of adverse event information to the FDA in U.S. is the MedWatch program [4, 24, 25]. In this program, healthcare providers and patients can submit an adverse event report via several mechanisms including an online report form, phone, fax and mail. The reports are stored in a database, the Adverse Event Reporting System (AERS) [12]. Besides those reports AERS database contains adverse events reported by the drug manufacturers. The largest source of information about drug safety is the drug companies themselves. The AERS database is made publicly available on the Internet to clinical reviewers and researchers in order to monitor for drug safety and detect

adverse events [12] and [26]. AERS contains approximately around 2.5 million adverse event reports [12]. The FDA searches these reports for serious events that can lead to death, hospitalization or disability. The study of those reports and the statistical analysis of the data available can save patients' lives and lower hospital admission cases. The reports will be used to for signal pairs link generation not testing [17] and [3].

MedWatch has been successful at identifying adverse event of medications but it is still slow and is characterized by other major limitations [3, 4]. For example the system took an average of 5.9 years to detect the toxicity of fifteen medications removed later from the market between 1997 and 2005. The Medwatch system do well in identifying adverse events in the early stages after administration of medications but it was unable to find events that occurred later, during chronic administration, as reported by [17].Since Medwatch is using database for report collections and no unique standards for collection of data, the database can contain incomplete information that will affect the derived results from these information. Detection of signals in Medwatch is limited due to the low percentage of adverse events which are rare event (less than 10 percent). The quality of the reports and the accuracy of the information written in the reports can also affect the detection performance of the adverse events. Some time, for instant, the health providers don't appreciate clinical finding or adverse events until the occurrence became wider in patient population. Also we need to remember that MedWatch reporting is voluntary job and many suspected adverse events are not reported based on the physicians point of view [26] , [12] and [27].

Other Spontaneous reporting systems, such as Yellow Card of the U.K, suffer from low reporting rates, typically less than 10%. Underreporting of ADRs is a common problem in spontaneous surveillance programs which can delay adverse event detection and underestimate a problem size. Knowing the factors that may confirm an adverse event will assist heath providers and physicians in establishing ways to correct underreporting. [28] and [29] provides different reasons that needs to be analyzed in order to improve the quality of reporting. There are huge number of reports that are available in the databases that make it difficult for physicians who to analyze the reports of adverse reactions since they have little time especially most of the reported events have a low likelihood of a causal relation.

Paper [30] explained other limitations that affects the spontaneous report systems . One of these limitations is biases. Different biases can affect the reporting since the spontaneously reported information is uncontrolled and depend heavily on the person who files the report. These biases include the report writing environment, quality of available data at the time of writing the reports, quality of information submitted in the reports and the length of time the medication has been on the market. The adverse event report should include the following: Drug name; demographic data; clinical description of adverse event, including laboratory test results; confounding factors such as concurrent diseases or other medications; temporal information, including date of taking the medications and the date of appearance of the symptoms, start and stop dates of the medication; dose of medication; dechallenge/rechallenge information (if available); and outcome. Have a high quality report is a time consuming process that make physicians or health providers avoid

reporting events. A collaborative approach for detecting and reporting adverse events is needed in order to catch all suspicious cases [28].

Data Mining Algorithms

Pharmacovigilance concern is mainly with the time need to discovery of adverse events taking in to the account the clinical nature of the event, and/or the appearance frequency of event. With this ever-increasing amount of reporting data there is interest in using computer- algorithms to identify the signal pairs. Such techniques are also known as data mining algorithms. Data mining algorithms are used to search extremely large spontaneous reporting system databases for statistical dependencies between drugs and events. Data mining algorithms are relatively new that can provide a fast and efficient way of detecting possible ADRs signal. If data mining algorithms identified a causal relationship between taking the medication and appearance of the event due to sufficient correlation between the statistical dependencies, the data mining algorithms could improve signal pairs detection performance.

Several data mining algorithms have been well described in literature, some are based on simple analysis, e.g., the reporting odds ratios [31] and the proportional reporting ratios [32].

The reporting odds ratios was first established in the Netherlands Pharmacovigilance Centre Lareb [31]. Compared to other data mining algorithms, reporting odds ratios is easy to calculate. Like the traditional odds ratio in epidemiology, reporting odds ratios is an estimate of incidence rate ratio, calculating the odds of the

exposure of suspected medication in those who had adverse events divided by the odds of the exposure of suspected medication in those without adverse events.

The proportional reporting ratios, as another early attempt of quantitative analysis of ADRs reports, was first used by Evans and colleagues in 2000 to demonstrate the risk of uveitis associated with the use of rifabutin [32]. The proportional reporting ratios measures the strength of causal relationship between the suspected drugs and suspected ADRs. The proportional reporting ratios behaves in a similar way to the relative risk. The higher the value of the proportional reporting ratios is, the stronger the strength of the signal appears to be. Screening the ADRs reports based on the values of the estimated PRRs could save time and prevent some unnecessary efforts.

Other DMAs techniques are available, e.g. Bayesian Confidance Propagation Neural Network [33] and Multi-Item Gamma-Poisson Shrinker [34].

Data Mining Algorithm Example: Bayesian methods

Bayesian uses the concept of probability as the degree to which a person believes a proposition, which is completely opposite to the view of 'frequency probability'. 'Classical' frequents always assume that the size of a population is unknown but it is fixed. The population parameter size can be estimated by selecting a random sample out of the population. For example, if we repeat an experiment (e.g., tossing coin) and observe the phenomenon (e.g., head or tail) with enough times, it would become clear what the future probability of reoccurrence will be (e.g., the probability of getting head or tail will close to 0.5). However, it is impossible to keep the event generating conditions exactly the same

especially when this method is used to obtain a large number of outcomes. For example, in tossing coin example, we cannot guarantee that each time the way of tossing the coin is exactly same. Another fundamentally different is that a Bayesian method starts the inference with pre-existing subjective personal estimation of the unknown parameter and the probability distribution (called prior distribution). The subjective assessment can come from the previous experience of the person, who run the experiment, or from experts' knowledge, or from some initial assumptions depending on the circumstances of the experiment. By providing more information, the 'degree of belief' can be updated. Basically, the updating of the information in Bayesian approach is based on using the Bayes Theorem.

Data mining algorithms are being used to explore spontaneous reporting databases for adverse reaction signal pairs. Paper [5] compares the finding of data mining algorithms with those came from classical reporting methods. Most adverse events identified by both methods were highlighted in product labeling. Classical reporting methods identified four potentially unexpected serious adverse events which may lead to label changing and close monitoring. The other finding of that paper that none of these adverse events has been identified using the data mining algorithms. This make the data mining algorithms based on that paper is not helpful since it could not detect or enhance the classical reporting methods surveillance in this particular setting. Data mining algorithms performance may be enhanced by selecting the most appropriate pharmacovigilance tools that are designed specifically for each situation [35]. Also in [36] five data mining algorithms are used for identifying possible adverse drug reactions from spontaneous reports information. The

study concludes that the detected drug–ADR signal pairs vary between different methodologies and this make the data mining algorithms unreliable.

The availability of huge amount of reported events, including false-positive signals as a result of the existence of confounding will produce unhelpful hypotheses. This may affect the capability of data mining algorithms to detect true positive signals of real causal associations which will lead to serious consequences that delay the detection of the signal pairs.

Data mining algorithms had not been generally accepted by health providers, Physicians or pharmacists. This is due three main reasons based on [3]:

1. The apparent complexity of its mathematics and the hidden strategy of detecting the signal pairs deters those unfamiliar with statistics.
2. Even with increasing availability of epidemiological and pharmacoepidemiological databases, background information for calculating prior probabilities is still either unclear or unavailable.
3. The pre-marketing data from clinical trials is usually not available for the public in order to be used for estimating the prior probability because it has been kept confidential between the drug companies and regulatory authorities. Even when they are available, they may not be in a format that is suitable for Bayesian methods.

Since no consensus exists regarding the use of data mining algorithms, the use of such methods in pharmacovigilance is still limited and not embraced by health providers even those methods may draw attention to more “surprising” drug–event signal pairs. In

fact, the unknown features of the data (i.e., the event background incidences) and the underreporting problem of the events from health providers to the regulatory authorities will have direct effect the outcome of data mining algorithms [37].

1.3 Multi-Agent System Technology Overview

"An agent is the fundamental actor in a domain. It combines one or more service capabilities into a unified and integrated execution model which can include access to external software, human users and communication facilities" [38].

1.3.1 Introduction To Multi-Agent Systems

Multi-agent system has been a hot topic in recent years. And it's still be researched and developed because it will have an important effect once it comes to our life. Multi-agent system methodology offers an implementation that fits the design needs. The agent is a special software working for its human client/clients to perform certain tasks that imitate human agents or systems and it has the ability to be autonomous in its action. From that definition we can conclude that an agent is autonomous because it has control over its actions and it pursuit them without direct involvement of its human agent or others. The agent is also social because it can cooperates and communicate with other agents and hence their humans in order to complete the required task. An agent is reactive since it is conscious about the updating of available data and changes in circumstances and responds based on in that in a timely manner. This entire make the agent rational in achieving its goals.

Although the agent can be based on a single agent working just with its human and is trying to perform his task, it is normally found in an environment that consists of multiple agents that not necessarily sharing the same interest. Agents work with each other in a cooperative way to complete certain task that cannot be done with single agent. The agent can interact with each other directly through communication (benefit sharing) or indirectly by providing certain information either to its users or clients which will require immediate actions from other agents in the same environment. Agents decide to work with each other either to complete its own task (or interest) or for mutual benefits to serve the entire environment (or complete a common goal). A set of agents that help one another in solving problems by using cooperation, coordination and negotiation techniques is called a multi-agent system.[39].

Multi-Agent system is also called Distributed Artificial Intelligence since the agents are normally distributed across different locations and collaborate through different network hosts. The system is considered distributed if several units (not necessary agents) are engaged in carrying out a task and it is opposite to the centralized system where a single unit in certain location is carrying out all the parts of a task and no need to interact with other units.

The multi-agent system is a complex system in both its structure and its collaborative functionality. Agents must be supported with interaction strategies that make them capable to select the appropriate activity at the appropriate time [40]. Agent learning focuses on learning how to communicate with other agent, learning how to coordinate different activities, learning how to manage a given task until completion, and learning

from other agents. If the agent is learning from other agent available in its environment, the learning is considered cooperative leaning while if the agent is learning only from its self through expertise and observations, the leaning is considered individual learning.

Multi-agent systems have been widely adopted in many application domains because of its offered advantages [41]. Some of the benefits of using multi-agent system technology in large systems are:

1. The complex task may be divided to different part and each part can be handled concurrently by specific agent. Different tasks or services can be distributed among the agents based on their complexity so each agent will deal with certain number of task rather than dealing with all tasks.
2. The speed of performing a task will be increased due to parallel computation and asynchronous operation.
3. The multi-agent system is more reliable than the centralized system because the multi-agent system is a distributed system than doesn't rely on a single unit in doing a required task. If a failure takes place in a unit in a multi-agent system, the rest of the agents continue doing the task.
4. The multi agent system is a scalable system since agents can be dynamically join or leave a team according to their availability and based on the need required to complete a task.
5. The Computational and communication costs associated with multi agent system are much less than centralized systems. Dividing agents in different team will reduce the communication traffic and hence the cost.

Agent talk with each other using special communication language called agent communication language (ACL). This language relies on speech act theory [39]. An ACL support the agents with a variety of resources needed for exchanging information and knowledge.

The Knowledge Query and Manipulation Language (KQML) was the first agent communication language. Nowadays FIPA–ACL (Foundation for Intelligent Physical Agents - Agent Communication Language) is the most usable agent communication language and it uses almost all the aspect of KQML [42]. FIPA_ACL incorporates a lot of predefined interaction protocols that manage conversations between agents. The primary feature of FIPA-ACL is its compatibility since it allows the use of different content languages. The FIPA model provides an open architecture that allows the agents to be added or removed easily from a team not like other agent communication languages models that have closed architectures where the iterations are fixed.

FIPA-ACL has 22 performative (or communicative acts) that specify the excepted flow of messages (either sent or received) from agents, and type of messages (inform, request, propose, failure, confirm, disconfirm, agree, accept, propose, cancel, refuse, query, etc.). FIPA-ACL makes sure that the sent message will be understood in the same way the sender needs [38] .

1.3.2 Applications of Multi Agent Systems

Multi agent systems (MAS) have received considerable attention from researcher from different fields in recent years. The Research of multi agent system involves applying this technology in different files, investigating the best way to make the agents interact with each other and the focus is mainly on information retrieval and management, developing the existing agent tools and software to make the simulation better, and analyzing the autonomous behavior of agent. In this next two sub section, I will mention some MAS applications.

1.3.2.1 Applications in Healthcare

Multi agent system has been used in heath care domain to solve different kinds of problems. In this section I will motion a set of examples where this technology has been applied.

- *Patient scheduling*: In [43], the researcher proposed a multi-agent system to schedule different medical activities (tasks required by physicians) that is required to be done from a patient in a hospital.

- *Organ transplant management*: coordinating the management of organ and tissue transplants among different medical centers is another application of multi agent system in health care domain [44] , [45] and [46]. In [44] the paper proposed a Multi-Agent architecture to coordinate the Spanish activity in organ transplants. The proposed architecture maintains the current Spanish health organizational structures

and then employs different agents that keep up to date the history of the transplant and the procedures followed. The proposed architecture has two agents. The first one is Emergency coordinator Agent which holds information about patients who need an organ and their clinical condition are severe. The other agent is Historical Agent which has all the history of organ transplant in Spain. Such data can be used for future studies and analyses. The architecture presented in this paper focuses on the organ transplant coordination task. The basic ideal of the proposed system is that one agent gathers the information of patients who are waiting for organ so when the matching organ becomes available the agent will provide the detail and locations of the organ. The researcher found that the proposed architecture accelerate accelerates of the organ transplant process in Spain.

- *Community care*: Multi-agent system has been used in coordinating all the activities that have to be performed in order to provide an efficient health care to the citizens of a community (especially older or disabled person, [47]). Paper [48] presented an architecture that uses multi- agent system technology to assist health care providers at rural areas especially when a specialist is not available, for example, a nurse is trying to diagnose a case in the absence of a specialist. The proposed system has an agent that contains some knowledge about certain diseases including symptoms and the required procedure to be followed. According to the authors of the paper this system will provide the health providers in rural areas with expert opinions (already stored in the system from specialist doctors).

- *Information access*: Multi-agent system is used to gather information from the agents distributed in different location, i.e. agents monitor patients and the system may deploy that gathered information to the corresponding units or person (example physicians) in order to follow up medical care of the cases. Multi agent system has been used to provide the user (patients) with a variety of information about available medical clinics/centers, physicians, and other medical facilities like laboratory centers or medical imagining centers in a particular town [49]. Such services will help patients and save their time.

- *Decision aid systems*: Multi-agent has been used to monitor the clinical condition of patients in hospital and at the same time help in diagnosing the disease [50]. Multi agent system has also been used in reduce unnecessarily visits to general practitioners especially those who suffer from lifelong diseases (for example diabetes and high blood pressure) and they need continues monitoring. For example paper [51] Shows a multi-agent system that has a doctor agent that will monitor the status of a diabetic person. Each time a sugar test is taken, the result will be analyzed by a physician agent using fuzzy inference system that has access to patients' information and history. If the result is abnormal, then the multi agent system will notify the general practitioner of the patient. This may lead to a clinic visit to make sure everything is going fine with the patients. In this paper they are dealing with fixed well known rules for diabetes. No agent learning was presented in this paper.

- *Internal hospital tasks*: Multi-agent system is used for continuously monitoring medical protocols in hospitals [52]. In the proposed system, the agents understand the medical protocols in hospitals and then supervise the usage of them. The agents will warn the practitioners about forbidden procedure and unlawful decisions. Multi-agent system is also used for controlling and mentoring the usage of restricted antibiotics that can affect patients life [53].

- *Tutoring System for Nurse Education:* Paper [54] describes a system that can be used for nurse education. The system provides intelligent tutoring agent called "Ines" that trains the nurses through asking questions and examples (pre defined in the system) and guides the nurse students step by step to understand a topic. The authors claimed that this system provides the nurses with more practical experience and exercises due to lack of facilities, materials and time (given to nurses by instructors or trainers) during their study at school. Such system provide a teaching environment that support nurse education.

1.3.3.2 Other Fields of Applications

Intelligent agents have already been proposed to deal with many different kinds of problems other than health care problems. Here is a short list of examples that shows some fields in which multi agent systems have been applied.

Paper [55] proposed a collaborative multi agent architecture for e- commerce application. This paper specifically focuses on travel industry. In that system travel agencies provide Individual customers with the flight, hotel and car reservation based on three agents: flight agent, hotel agent and car agent.

Paper [56] proposed a system that consists of travel agent that helps in reserving flights in travel industry. All flights data is stored in a single database. When the customer wants to make a reservation for a trip at certain time, the trip information will be passed to a flight agent. The flight agent will use the stored flight data to check if the flight is available or not. If it is available a reservation will be made otherwise the customer will be notified with impossible to fulfill the reservation in the selected dates.

Paper [57] was an attempt to solve the problems of personalized information search through web [58] in a simple way. They proposed one agent, Personalized Search Agent (PSA), that allows the user to specify a specific domain in order to perform the search in, and then browse the retrieved information in that interested domain. The personalized Search Agent is supported with learning mechanism that allows the agent to learn some user profile parameters that will enhance the retrieved results in future search. The learning mechanism is based on user feedbacks. This adaptive tool makes PSA more powerful and effective with use.

In [59], the implementation of multi-agent based Radio frequency identification (RFID) middleware for asset management application was described. Each assist in universities, hospitals or government departments has a bar code that can be scanned to record the status of the assets (especially valuable assists). This is done usually with a bar

code reader which requires line of sight (the reader is facing the asset directly) with the assets in order to be scanned. Otherwise the scan process will fail. In this paper they proposed to use RFID technology to monitor valuable assets. This technology doesn't required line of sight with assets. It just requires the item to be in the area of scanner. This will allows automatic scanning in the absence of human user. Each item will have a unique number placed in a tag that is readable by REIF reader. In this paper they proposed RFID middleware which is the tool that helps to make sense of the RFID tag data. It translates the simple read data into useful information that can be forwarded later to the interested person or unit. The proposed multi agent system consists of three agents. The first agent is Client Application Agent which is just responsible for taking the order of checking the assets from the human user through graphical user interface. It passes the request to the second agent, the Event Generator Event, which will check if the requesting assist is available and it is known by the system. If the name is not registered and not known, it will notify the Client Application Agent otherwise it will contact the third agent; the Reader Agent. The reader agent has a direct contact with the physical reader who is responsible for scanning the items and provides the required details back to the Event Generator Agent which will forward it again to Client Application Agent and hence his user.

Paper [60] discusses using multi-agent system technology for an intelligent environment application. They propose to use multi agent system to remote monitoring an environment through different sensors distributed at different locations. The proposed MAS consists of four intelligent components namely accumulative personal preferences

learning, intelligent resources allocation, reactive controls and context-aware proactive controls.

Paper [61] explored the problems that are facing mobile companies and the used technologies. They expected that multi agent system can enhance services provided to the users and provide real time fraud detection in mobile phone networks. They claimed that the multi agent system can customize the services provided to clients. They propose a multi agent system that consists of Personal Communication Agents, Mobility Network Agents, and of Fraud Breaking Agents.

Papers [62] and [63] show another application of multi agent system which is the application of E- learning and E- teaching. Paper [62] proposed an agent-based Intelligent Tutoring System for e-learning/e-teaching. The proposed system consists of four agents Preferences Agent, Accounting Agent, Exercises Agent and Tests Agent. The multi-agent system provides an environment that enhances the educational system by providing the students with different exercise, materials, and exams. At the same time the performance of the students will be monitored and based on their progress new tasks can be provided. The teachers have access to the system to consult the students. Teachers can change the level of exercises or provide additional materials to support the learning progress and to improve student motivation. The system can provide the teachers with different statistics that will enhance the educational system.

Multi agent system has been used in power Engineering applications such as [64] and [65]. Paper [65] presents possible benefits that can be gained by using multi-agent technology in power engineering industry. The paper included different concepts of agent

system that are appropriate to power engineering field. It also presented a review of important power applications that will be enhanced by multi-agent systems.

1.4 Original Contributions

My contributions are as follows:

- I developed a multi Agent system for identifying adverse drug reaction signal pairs as early as possible [66, 67]. The developed multi-agents system provides Physician Assistant Agents that are capable of collaborating with one another, sharing patients' information and exchanging knowledge. This collaborative system will accelerate the process of detecting ADR signal pairs comparing to the existing system which relay on spontaneous report which suffer from underreporting and other limitations as explained in section 1.2. The developed system can also be used in the early stages of medication testing, i.e. clinical trials, because any case presented to any agent or any decision rule added to the agent brain can be shared with other PAA not as in existing system where a physician or a drug manufacturing company wait until there are sufficient suspicious cases in order to report the potential adverse event. This is very important issue in identifying ADR signal pairs because the adverse event appears normally in a population at very low percentages. Each agent in the developed system is equipped with a decision engine, which enables it to find the causal relationship between a drug and a potential ADR (i.e., a signal pair).The used reasoning is based on fuzzy logic involving fuzzy rules and fuzzy reasoning

implemented using the freeware FuzzyJess [7]. Integrating a decision mechanism into agents make them more proactive and encourage closer agent-human collaboration [39] and [68] . The developed system allows the agents to use different databases available in health organizations systems in the process of identifying the adverse drug reaction signal pairs. Such databases weren't used before in the literature to identify signals pairs. All the existing methods are depending mainly on spontaneous reports reported by physician.

- I developed a methodology that allows the agents in the developed multi-agent system to find similar patients [69]. The developed methodology enables the agents to interact effectively with each other by setting up an environment that allows learning and working in a proactive way. This methodology can also be generally used to address other similarity problems in different field of multi-agent systems. To the best of our knowledge, no work has been reported in the literature to address these issues. Finding similar patients in a multi-agent environment is a complicated problem. This is the case if we realistically assume that there does not exist a set of similarity-finding rules that are readily acceptable to all the users of the agents (i.e., physicians) because "similar" is really a vague, subjective measure rather than an objective measure. Furthermore, the specifications of the similarity-finding rules vary among the agents because agents formulate their similarity rules according to their human users' experience. This will make it difficult among the agents to decide which physician id right or wrong. It should be obvious that these dynamic issues

will pose challenges when the agents work collectively to help one another to reach a common goal (e.g., ADR detection). Patient similarity is characterized by a number of factors related to physician's experience. I developed similarity rules that are used by PAAs to find similar patients. The developed rules is based on temporal association of a medication of interest, abnormality of a laboratory test, age, medications, and Symptoms and morbidities(chronic and acute). There are a total of 38 similarity rules.

- I equipped the agents in the developed system with a fuzzy inference engine in order to be able to find causal relationship between a drug and an adverse reaction. The parameters used in identifying the signal pairs are really a vague, subjective measure rather than an objective measure. Up to our knowledge, no set of rules was clearly mentioned in the literature that took advantage of this vagueness. Furthermore, physicians often disagree one another owing to their knowledge and experience levels and usually there is no “ground truth” to indicate which physician is right or wrong. The developed fuzzy inference engine also uses the distributed databases available for the agents in the multi- agent system. Such databases have not been used before in the literature for such purposes. Databases in current systems are mainly used a for knowing the medical history of patients by only their physicians, improving the quality of provided services and reducing the costs of medical errors. These databases provides valuable information about patients including age, sex, medication took by the patients, symptoms appears on patients, Laboratory tests results, and procedure

followed by the physician at the visit time. The proposed ADR signal pairs detection methodology is based on five cues: temporal association, rechallenge, dechallenge, abnormality in laboratory tests and other explanation. The cues represent the higher-level information that is obtained from the patients' elementary data. The detection rules that use the above cues were acquired through the joint efforts of the engineering and medical team members. There are a total of 52 fuzzy detection rules.

- I have developed a new learning mechanism that allows PAAs in the multi-agent system to effectively learn from each other through exchanging detection and similarity rules. The problem of learning in multi-agent system is an essential problem. All the existence methods deal with multi-agent system in certain aspect where a task will be divided among different agents who have different roles. Then, each agent will complete his part of the task based on the pre-defined rules. Finally, different parts of the job will be collected and the task will be considered done. Other studies uses different agent with same role (like players in a game) to perform a task (win the game) and if a decision need to be made it will be based on majority vote.

  Usually, agents formulate their rules according to their human users' experience. For an individual agent, if these experience-dependent rules are incomplete, it could cause inaccurate determination of required task especially in new issues where the rules still not clears and finalized. In addition, we assume realistically that we do not know which rules are right or wrong. Furthermore, the numbers of patients seen by different physicians (and hence their agents) are different. This will affect physicians'

experience levels as well as the numbers of rules their agents should have. More and better rules should be used as the physician sees more and more patients. This fact should be reflected in the agent system behavior. This make me developed learning mechanize that is based on confidence level approach. This learning mechanism can be used in other applications of multi agent system. Each detection or similarity rule has been assigned a confidence level. The confidence level reflects the experience of the agent in that rule. In other words, the confidence level tells how certain the PAA is about the rule. The rules that have been used have higher confidence levels than those that have not been used. Having confidence levels for the rules allows agents to benefit from each other in a cooperative way. This allows the most important and insightful detection rules to be found and used for the benefit of the entire agent system. The new updated rules will lead to improve the agents' decision performance.

1.5 Organization of the Dissertation

The rest of this dissertation is organized as follows. Chapter 2 presents the design and architecture of a multi agent intelligent system for detecting adverse drug reactions. Chapter 3 describes the methodology used for Finding Similar Patients in Multi Agent Environment. It includes the details of the experiment used to validate the used methodology. Chapter 4 illustrates the approach of identifying Adverse Drug Reaction Signal Pairs by a Multi-Agent Intelligent System. Chapter 4 also includes the experiment used to validate the used multi-agent approach for identifying the signal pairs. Finally, Chapter 5 concludes this dissertation and provides the future directions.

CHAPTER 2

DESIGN AND ARCHITECTURE OF A MULTI-AGENT INTELLIGENT SYSTEM FOR DETECTING ADVERSE DRUG REACTIONS

2.1 Collaborative Multi-Agent System Architecture

Figure 1 depicts the general organization of my multi-agent system for ADR detection that previously proposed [67, 70]. The FDA is at the top of this structure since it is the drug administration authority in the United States. Many health organizations are connected to the FDA. Experts in the FDA and physicians in the local health organizations have their own intelligent agents. The National Regulatory Authority Agent has the highest authority and carries out necessary management and information collection tasks. The Safety Evaluator Assistant Agents help the safety evaluators in the regulatory authority (e.g., FDA) make decisions. The Pharmacist Assistant Agents and the Epidemiologist Assistant Agents utilize the expertise of pharmacists and epidemiologists respectively and collaborate with the Safety Evaluator Assistant Agents in supporting safety evaluator's decision making. The Health Organization Agent is a broker and controller for each health organization. Within each health organization, there would be a unique Health Organization Agent and many PAAs. Physician Assistant Agent (PAA) helps a physician acquire useful information and make decisions. PAA can communicate with other PAAs in the same or different health organizations. The physician Assistant agents' skill levels are not the same. The solution of a problem involves the coordination of the effort of different

agents with different skills and functions. PAAs will react to changes in their environment in a proactive, autonomous and intelligent manner. Each PAA will perform tasks that may be beneficial for the physician.

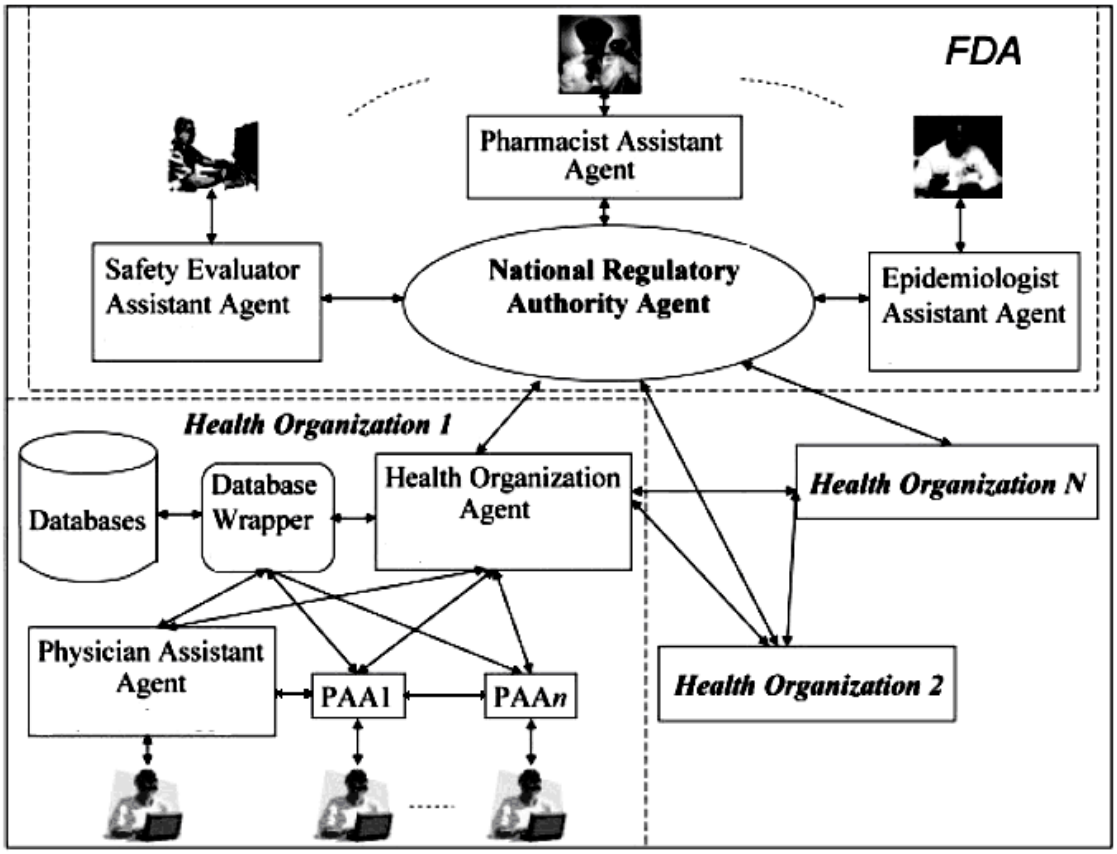


Figure 1. The multi-agent system architecture for ADR detection.

To illustrate the ADR signal-pair detection process, I will focus on PAA only in this study. The PAAs are in the forefront to assist physicians. This is because physicians play an important role in the detection of adverse drug reaction since they are the ones

who deal with patients who suffer from an adverse event. There are many PAAs located in the same or different health organizations.

A PAA would help the physician request the details of a particular suspected patient case and/or similar patient cases from other agents in the same or different health organizations. The PAA will perform according its knowledge. The PAA could also ask other agents about the rules they are using in evaluating certain ADR cases so that the agent can updates rules. The agent can collect similar cases distributed across all the healthcare systems. The PAA could also track the further development of the suspected patient cases under the help of other PAAs in the system. For example, the PAA may be interested in what happens if the suspected drug is discontinued. With more information, the PAA could more easily determine the causal relationship between a new ADR and a specific drug. Once a physician finds potential adverse effects on his/her patient, he/she can, with the help of his/her agent, search more information or simply file a report to the safety officer or safety evaluator, which will trigger the surveillance process for the particular drug.

The PAA will keep all the cases seen by its physician in his records and update them when new information is being available. Next time if any other physician receives such similar case, the agent can automatically inform him/her with that similar case. Finally, the PAA can decide to take any of the following actions depending on the decision reached, i.e.:

- To order some extra clinical tests.
- To continue the same medical treatment or to modify it.

- To schedule another visit for the future.
- To transfer the patient, for example, hospitalize him if his health has deteriorated too much. Patients can also be transferred from one of the health centers to another according to the patient needs.

In the context of this research, a PAA would help the physician retrieve the details of a particular patient case and request similar patient cases. The PAA will provide its physician with the similarity score for each similar patient. The PAAs will also work with each other in order to detect potential ADR signal pairs (i.e., potential links between drugs and apparent adverse reactions).

The detection process starts when an agent sends its request to the rest of the agents to help in a certain suspect case. As a first step the agents will collaboratively work together in a way that the more experienced agents will help the less experienced agents. The agents will start collaboration by providing their detection rules to the other agents. This will allow the most important and insightful detection rules produced by the most experienced agent (defined in this study as the agent that has the largest amount of patients in its patient database) to bubble up for the benefit of the entire agent community. The updated rules will lead to improved detection performance. After finishing the learning process, the agents will retrieve patient cases one by one from their databases in order to evaluate their own cases using the new learned/updated rules. Having ample similar cases will provide the requesting agent with more evidences about the suspect case and thus helps in decision making. The other agents will forward the similar cases along with their

signal *pair strength* to the requesting agent. The agents will keep all the cases seen by their physicians in their records and update the decision when new information becomes available. The proposed multi-agents system would assist physicians in hospitals and clinics, accelerating the process of identifying ADR signal pairs by assuring that the relevant information and knowledge distributed across different locations can be utilized more expediently.

2.2 Design of PAA-Based Multi-Agent System

Figure 2 shows PAA-based multi-agent system that I developed for detecting ADR signal pairs. (n PAAs are shown). Each PAA has its own patient database that contains the records of the patients already seen by its physician. Each PAA is equipped with a certain number of detection and similarity rules. . The rules used in the experimental part were acquired from the physicians on the team through the joint efforts of the engineering and medical team members after a careful analysis of the relevant literature. White Board provides the ability for a PAA to communicate with other PAAs without prior knowledge about them. It contains information about agent service type, agent name, communication languages and ontologies. This information allows White Board to connect different agents located at different health organizations. An agent can use White Board to search for other agents that can provide services to aid it in fulfilling its particular goals. To do that, White Board will provide requesting agent with the name of other agents based on the nature of the request. White Board collects similarity rules and confidence levels from PAAs in order for them to be used in the rule updating process described later.

White Board contains Shared Data and Notification Unit which is responsible for storing important data about certain cases that matches some special criteria and the location of these cases. The Shared Data and Notification Unit will notify the unavailable agents of the appearance of such information when it becomes available or/and if a modification was made to certain decision. This will assure the reception of information in all circumstances.

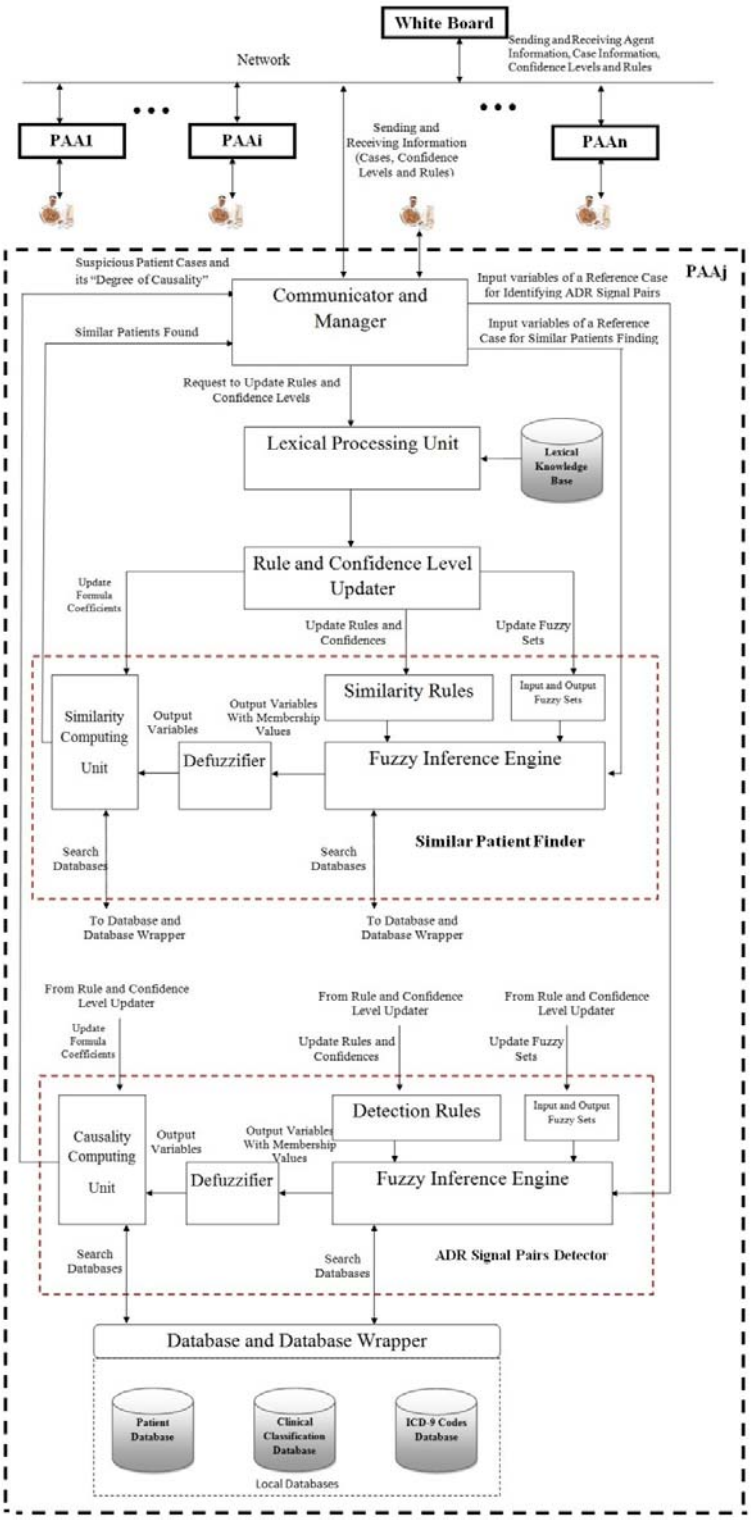


Figure 2. Architecture of the PAA showing the four components.

Below is a scenario illustrating how three PAAs work together to find similar patients using White Board. The same strategy can be applied for identifying signal pairs. PAA1 needs to find patients similar to a particular patient case. It will send a request to the White Board asking for other PAAs available in the system that can help in finding similar patients. The White Board then turns to its agents. The White Board will make a list of agents that are capable of helping PAA1. The White Board knows them from their services type (skills). If the list is empty, the White Board will reply with the message "impossible to do" to indicate it cannot find any agent in the system to help. Otherwise, it iteratively sends "acknowledgment of acceptance" to PAA1. Suppose that the White Board replies to PAA1 and indicates that PAA2 and PAA3 are available. The White Board will also provide PAA1 with the addresses of PAA2 and PAA3 so that the three agents can directly communicate one another.

Then, PAA1 sends separate requests to PAA2 and PAA3, asking to communicate with them. PAA2 and PAA3 will response to PAA1 and inform it either "agree to do" or "reject to do," depending on whether they are busy or not with other agents. Let's assume that just PAA2 is not busy and agree to work with PAA1 and PAA3 is busy and is not available to help. PAA1 will send another request to PAA2 and PAA3, providing them with the patient information. PAA2 and PAA3 will search their patient databases and evaluate their patients and assign a similarity score. Figure 3 shows White Board interaction methodology applied to the previous example.

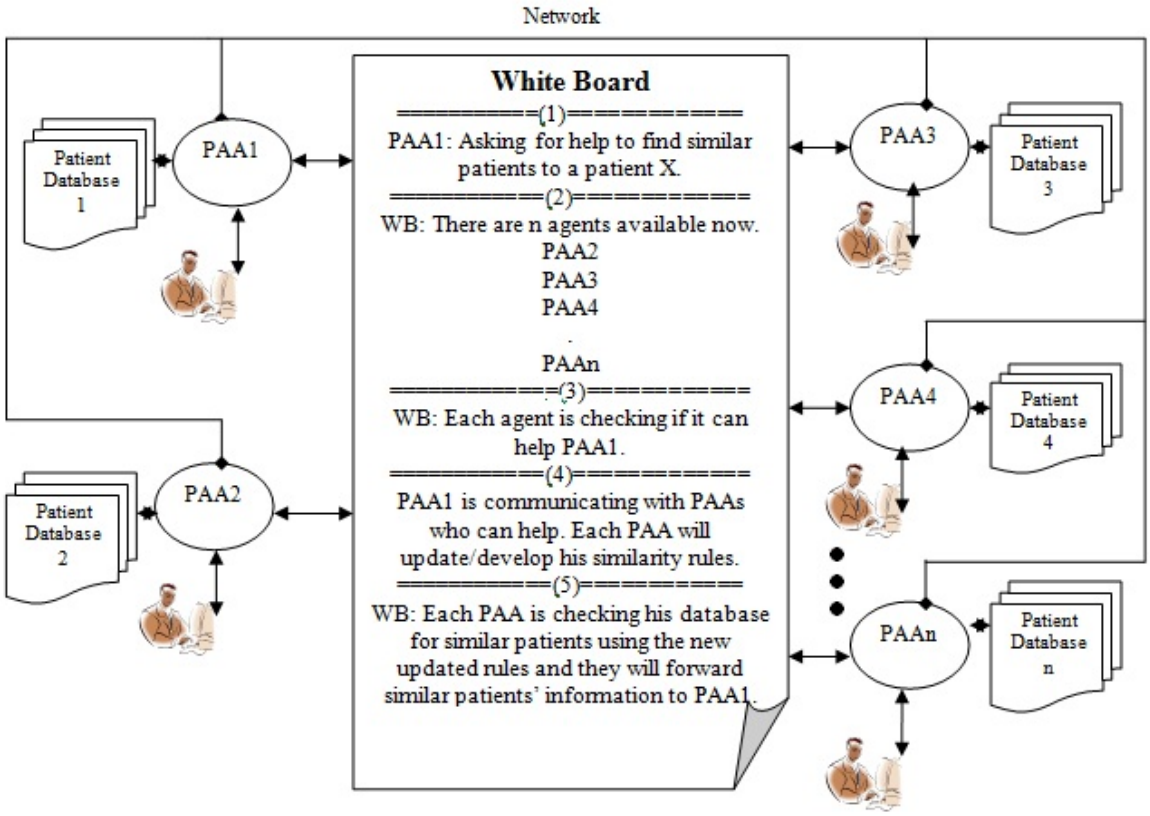


Figure 3. White Board interaction methodology.

Functionally speaking, the PAA's architecture consists of five components - Communicator and Manager, Similar Patient Finder, ADR Signal Pairs Detector, Rule and Confidence Level Updater, and Databases and Database Wrapper.

2.2.1 Communicator and Manager

Communicator and Manager deals with inter-agent communication and manages all incoming and outgoing message. It is responsible for sending requests to Similar Patient Finder to start the process of finding similar patients to a reference patient. When Similar Patient Finder Finishes the similarity finding process, Communicator and Manager

receives similar patients and sends them out to other PAAs. Communicator and Manager is also responsible for sending requests to ADR Signal Pairs Detector to start the process of Identifying Adverse Drug Reaction Signal Pairs (i.e., potential links between drugs and apparent adverse reactions). When ADR Signal Pairs Detector Finishes the identifying process, Communicator and Manager receives suspicious cases and strength of potential link in order to be shared with other PAA and/or its physician. The last task of Communicator and Manager is sending requests to Rule and Confidence Level Updater to update knowledge of Similar Patient Finder and ADR Signal Pairs Detector.

To find similar patients to a reference patient case which is either received from another agent needing similar patients or presented to the PAA by its physician, Communicator and Manager will send the received reference case to Fuzzy Inference Engine in Similar Patient Finder. Fuzzy sets and fuzzy logic are used to handle vague and subjective information in the patient data and physician's knowledge and experience. Fuzzy Inference Engine uses Similarity Rules and fuzzy sets to find output variables that will be used to find similarity factors between the reference case and a local patient being compared with. The retrieved similar patients and their similarity scores are forwarded to Communicator and Manager in order to be sent out to the requesting agent and/or its physician. Having similar cases will provide the requesting agent with more evidences about the suspect case and thus helps in decision making. When a suspect case is identified, the PAA will check whether it is completely unknown or similar to an already known case. If it is unknown and no similar case was found, a solution must be generated

from scratch. If there is some similarity to a previously seen case, the previous decision can be used as a starting point for solving the new one or even to make a decision

To start the process of Identifying Adverse Drug Reaction Signal Pairs, Communicator and Manager sends a request to ADR Signal Pairs Detector. The request is either received from another agent needs to identify a signal pair or from the PAA by its physician, Communicator and Manager will send the suspect pair to Fuzzy Inference Engine in ADR Signal Pairs Detector. Fuzzy Inference Engine uses detection Rules and fuzzy sets to find output variables that will be used to find ADR cues. Local patient cases will be evaluated and the likelihood that a drug causes a suspect ADR will be determined. The strength of this assessment is called Degree of Causality. When ADR Signal Pairs Detector Finishes the identifying process, Communicator and Manager receives suspicious cases and their "Degree of Causality" scores in order to be sent out to the requesting agent and/or its physician.

The other task of Communicator and Manager is sending requests to Rule and Confidence Level Updater to update knowledge of Similar Patient Finder. The updating occurs at programmed times. In this project I let the updating to be done once a day at 12:00 am. In this updating process each PAA will contribute by providing its similarity rules or /and Detection rules, and the corresponding fuzzy sets and parameters of formulas to White Board. Rule and Confidence Level Updater will use the collected rules in White Board to update its own rules and modify the rules confidence levels. This is done by selecting the rules that have the highest confidence level. The confidence level present how much the agent is sure about a rule. This will allow the most important and insightful rules

produced by the most experienced agent (defined in this study as the agent that has the largest amount of patients in its patient database) to bubble up for the benefit of the entire agent community. Rule and Confidence Level Updater will also update the associated fuzzy sets, and parameters of the similarity formulas in Computing Unit. The updated rules will lead to improved decision performance.

2.2.2 Databases and Database Wrapper

Databases and Database Wrapper contains a Patient Database, an ICD-9 Codes Database, and a Clinical Classification Database. Database Wrapper provides two important functions: a) it provides frequently-used methods for database connectivity. It provides a simple layer that can deal with standard database language (e.g., SQL). Java Database Connectivity (JDBC) wrapper library was used in my dissertation, and b) it offers a wrapper that maps the human description of a case to different medical codes (ICD-9, Clinical Classification, etc.) that are commonly used in U.S and it also provides the opposite mapping. Such codes describe the medical conditions of patients, symptoms phenomenon and the procedures followed by physician in order to diagnose a case.

2.2.3 Lexical Processing Unit

The agents are supported with ability of mapping free text terms to unique concepts. This was done by this unit. It uses the Lexical Variants Generator (LVG) program provided by the National Library of Medicine [71]. LVG is the most powerful solution for lexical variations at the individual word level. This unit will allows the agents

to deal with inflectional variants, spelling variants, acronyms and abbreviations, expansions, derivational variants, synonyms as well as combinations of these. For example the agent will deal the following spelling variant words lab, laboratory, labs, laboratory (with spilling mistake) as laboratory term.

2.2.4 Lexical Knowledge Base

This Lexical knowledge base consists of linguistic knowledge, such as synonyms of medical words, grammatical patterns in which they can appear, possible abbreviation of the medical words and complex medical terminology.

2.2.5 Similar Patient Finder

2.2.5.1 Input and Output Variables and Fuzzy Sets

Patient similarity is characterized by a number of factors related to physician's experience. Finding the similarity between a reference patient and compared patients in the local databases is based on temporal association of a medication of interest, abnormality of a laboratory test, age, medications, and morbidities. Temporal association describes the relationship between taking a drug and appearance of symptom.

Abnormality of a laboratory test shows the degree of elevation of a laboratory test result. The abnormality will be calculated for Transaminases (AST, ALT), Creatine Kinase (CK), Potassium, and Creatinine, which are common tests .Age is another important factor

in finding the similarity. The side effect risk of a medication in a healthy adult is not that danger as in elderly patients.

Medication factor shows the overall view of medications took by the patients including medication name, class and quantity. The morbidities factor present all the symptoms appear on a patient and have been verified by his physician. The symptoms are recorded at the time of physician visit as ICD-9 codes.

For Each factor input and output variables will be defined in order to be used by the Fuzzy Inference Engine, and each variable is fuzzified by input fuzzy sets.

The fuzzy sets used in fuzzifying the Input and Output variables are shown in

Table **1**. Triangular and bell fuzzy sets are specified by three parameters a, b and c while the gaussian fuzzy set is specified by two parameters a and b.

Table 1.Definitions of Fuzzy Sets

Fuzzy Set Type	Fuzzy Set Definition
Triangular	$\mu_T(x) = \begin{cases} -\frac{1}{a-b}(a-x), & a \le x \le b \\ \frac{1}{c-b}(c-x), & b \le x \le c \\ 0, & otherwise \end{cases}$
Bell	$\mu_B(x) = \frac{1}{1+\left\lvert\frac{a-x}{b}\right\rvert^{2c}}, \quad c > 0$
Gaussian	$\mu_G(x) = \mathrm{e}^{-\frac{(a-x)^2}{2b^2}}$

2.2.5.2 Fuzzy Similarity Rules

Similar Patient Finder is equipped with the similarity rules that link the input variables to the output variables using If-Then rules with a condition and a conclusion. The initial similarity rules and formulas are provided to the PAA by its physician based on his/her experience. Different experience will lead to different similarity finding rules. In this research, the similarity rules are provided by the physicians on the team. There are a total of 38 rules developed by the physicians and is used by the four PAAs implanted in this project. The rules are distributed among the PAAs to imitate real life problem where each physician has his own rules based on his experience. As a result, each PAA will have part of the rules to emulate different levels of experiences of the physician users of the agents.

The first step in allowing the agents to benefit from each other is to find a strategy to represent the experience of the agents for each rule. In this dissertation, I proposed assigning a confidence level, a value in [0, 1], to each rule based on the experience of the agent in that rule. The confidence level tells how much the PAAs are sure about its rules. In general, to assign a confidence level for a given patient record set to the rule, the confidence level is defined as the fraction of the patient records in the set that will fire the rule. In other words, how many times the PAA has used that rule. Sometimes the PAA has not used all the rules in its Similar Patient Finder. The rules that have been used have higher confidence levels than those that have not been used. Each time a new case is presented to a PAA in order to be evaluated, Rule and Confidence Level Updater updates the confidence levels of the used rules and if the physician input a new rule, it will be

added to its PAA rules. PAA will get new rules or/and update rules confidence levels through communicating with other PAA. The confidence levels affect the contribution of the rules which consequently affects the calculation of the total similarity between a reference patient and the compared patients. The inferred output of each rule is scaled by the confidence level value via algebraic product before aggregating the output of individual rules.

2.2.5.3 Fuzzy Inference Engine and Defuzzifier

A reference patient case is evaluated by Fuzzy Inference Engine using the similarity rules to find similar patient cases stored in the local Patient Database. Fuzzy Inference Engine evaluates the rules using the min-max fuzzy inference operations. Fuzzy Inference System follows Mamdani fuzzy model. The resulting aggregated fuzzy set is converted to numerical values for the output variables by Defuzzifier that uses the center of gravity scheme.

2.2.5.4 Similarity Computing Unit

Similarity Computing Unit contains formulas that are used in Similar Patient Finder to get the total similarity score between a reference patient and compared patients. It contains Similarity Formulas of the resulted defuzzified output resulted from Fuzzy Inference System, Morbidities Similarity Formula, Medication Similarity Formulas and Total Similarity Formula. The retrieved similar patients and their similarity scores are

forwarded to Communicator and Manager in order to be sent out to the requesting agent and/or its physician.

2.2.6 ADR Signal Pairs Detector

2.2.6.1 Input and Output Variables and Fuzzy Sets

ADR signal pairs detection methodology is based on five cues: temporal association, rechallenge, dechallenge, abnormality in laboratory tests and other explanation. The cues represent the higher-level information that is obtained from the patients' elementary data. For example, Temporal Association is the cue that describes the time duration between taking the drug and the appearance of a possible adverse event. What happens after the drug is stopped (Dechallenge) or re-initiated (Rechallenge) also provides important cues. Temporal association, rechallenge and dechallenge are all time-related. The Abnormality in Laboratory Tests is a variable that is also extracted from patient's laboratory test results. It describes the degree of the abnormality of a laboratory test. Other Explanations denotes alternative explanations by concurrent diseases or other drugs. The symptoms of an underlying disease or the one caused by another drug which is taken concurrently with the drug of interest cannot be differentiated from those of a potential ADR and thus the obtained cues (e.g., temporal association) values do not necessarily imply any degree of causality.

For Each cue input and output variables will be defined in order to be used by the Fuzzy Inference Engine, and each variable is fuzzified by input fuzzy sets. For a particular pair, the cue values are extracted from a specific patient case using fuzzy sets and rules.

2.2.6.2 Fuzzy Detection Rules

Similar Patient Finder is equipped with the detection rules that link the input variables to the output variables using If-Then rules with a condition and a conclusion. The initial detection rules and formulas are provided to the PAA by its physician based on his/her experience. Different experience will lead to different detection rules. There are a total of 52 fuzzy detection rules. These rules will be distributed among the PAAs. This will be explained later in the experimental part. The rules are distributed among the PAAs to imitate real life problem where each physician has his own rules based on his experience. As a result, each PAA will have part of the rules to emulate different levels of experiences of the physician users of the agents. In the real life each physician will provide his PAA with the preliminary detection rules based on his experience through Graphical User Interface. Each rule will be assigned a confidence level, a value in [0, 1]. The confidence level tells how much the PAAs are sure about its rules.

2.2.6.3 Fuzzy Inference Engine and Defuzzifier

Fuzzy Inference System follows Mamdani fuzzy model. Each detection rule will be evaluated and the results of the individual rules will be combined to obtain fuzzy sets of the cue. The evaluations of the rules and the combination of the results of the individual

rules are performed using Min-Max fuzzy sets operations. The cues will be extracted from the resulted fuzzy sets by Defuzzifier.

2.2.6.4 Causality Computing Unit

Causality Computing Unit contains the formulas that are used to find the causal relationship between a drug and a potential ADR (i.e., a signal pair). This causality assessment is called Degree of Causality. When ADR Signal Pairs Detector finishes the identifying process, Communicator and Manager receives suspicious cases and their "Degree of Causality" scores in order to be sent out to the requesting agent and/or its physician.

2.3 Rule and Confidence Level Updater

Each agent in the developed system has only part of the rules representing the experience level of its human user. This is the case if we realistically assume that there does not exist a set of rules that are readily acceptable to all the users of the agents (i.e., physicians). The specifications of the rules vary among the agents. There are some key rules all the agents will have. The key rules help PAAs to make a basic signal pair decision (i.e., Potassium Temporal Association rules) or basic similarity finding (i.e., the rules involving calculating Total Laboratory Similarity and Total Similarity). Agents formulate their rules according to their human users' experience. For an individual agent, these experience-dependent rules are incomplete, which could cause inaccurate identification of signal pairs. In addition, we assume realistically that we do not know which rules are right

or wrong. Furthermore, the numbers of patients seen by different physicians (and hence their agents) are different. This will affect physicians' experience levels as well as the numbers of rules their agents will have. More and better rules will become available as the physician sees more and more patients. This fact should be reflected in the agent system behavior

The first step in allowing the agents to benefit from each other is to find a strategy to represent the experience of the agents for each rule. I developed a strategy where each rule will be assigned a confidence level, a value in [0, 1]. A rule will have a confidence level based on the experience of the agent having the rule. In general, to assign a confidence level for a given patient record set to the rule, the confidence level is defined as the fraction of the patient records in the set that will fire the rule. The confidence level tells how much the PAAs are sure about its rules. The confidence level is calculated using the number of patients applicable to the rule. In other words, it represents how many times the PAA has used that rule. Sometimes the PAA has not used all the rules in its Knowledge Base. The rules that have been used should have higher confidence levels than those that have not been. The confidence level will be used in the process of updating and exchanging rules between the agents. When PAAs start collaborating with each other, each PAA will provide its own rules to the others.

The agent will randomly contact one or more PAAs to be evolved in rules and confidence levels update. The updating occurs at programmed times. Each PAA of the randomly contacted agents will provide its own rules to White Board to let other PAA benefit from it. Rule and Confidence Level Updater uses these rules and confidence levels

to construct a new similarity rules and detection rules that take advantage of the experience of the other PAAs. The agents will start the similarity learning process by comparing its own similarity factors with other agents' similarity factors. It will add the factors that are not in its Similar Patient Finder. In order to do that the PAA will compare the confidence levels of the available rules of the missing factors and add the ones that have the highest confidence levels to its Similar Patient Finder. At the same time Rule and Confidence Level Updater updates the corresponding inputs and outputs fuzzy sets of the new rules. After that, Rule and Confidence Level Updater will update the other factors already exist in its finder. It compares the confidence level of each of its rules with the confidence level of the related rules in other PAAs. Then Rule and Confidence Level Updater adapts the rules that have the highest confidence levels. Then the corresponding inputs and outputs fuzzy sets are updated. The gained rules through the interaction will improve the similarity task performance.

Similar procedure will be followed to update the detection rules of the ADR Signal Pairs Detector. Rule and Confidence Level Updater will add the cues that are not in its Detector from other PAAs that have the highest confidence levels. After that, the agent will use the same comparison methodology to update other cues that already available in its detector. The agent will compare the confidence level of each of its rules with the confidence level of the same rules in other PAAs. Then the PAA will adapt the rules with the highest confidence levels. Then the corresponding inputs and outputs fuzzy sets are updated. The gained rules through the interaction will improve the detection task performance.

Figure 4 shows an example to illustrate this methodology where PAA1 and PAA2 are updating their rules. PAA1 has ADR detection rules involving Temporal Association and Dechallenge while PAA2 has ADR rules involving Laboratory Tests and Dechallenge. PAA1 will add PAA2's Laboratory Tests rules to its knowledge base because it doesn't have such rules. For the Dechallenge rules, PAA1 will compare its rules' confidence levels with those of PAA2's. If a PAA2's rule's confidence level is higher, PAA1 will adopt PAA2's Dechallenge rule by overriding its own Dechallenge rules. At the same time, PAA2 follows the same procedure in updating its rules involving Laboratory Test and Dechallenge rules.

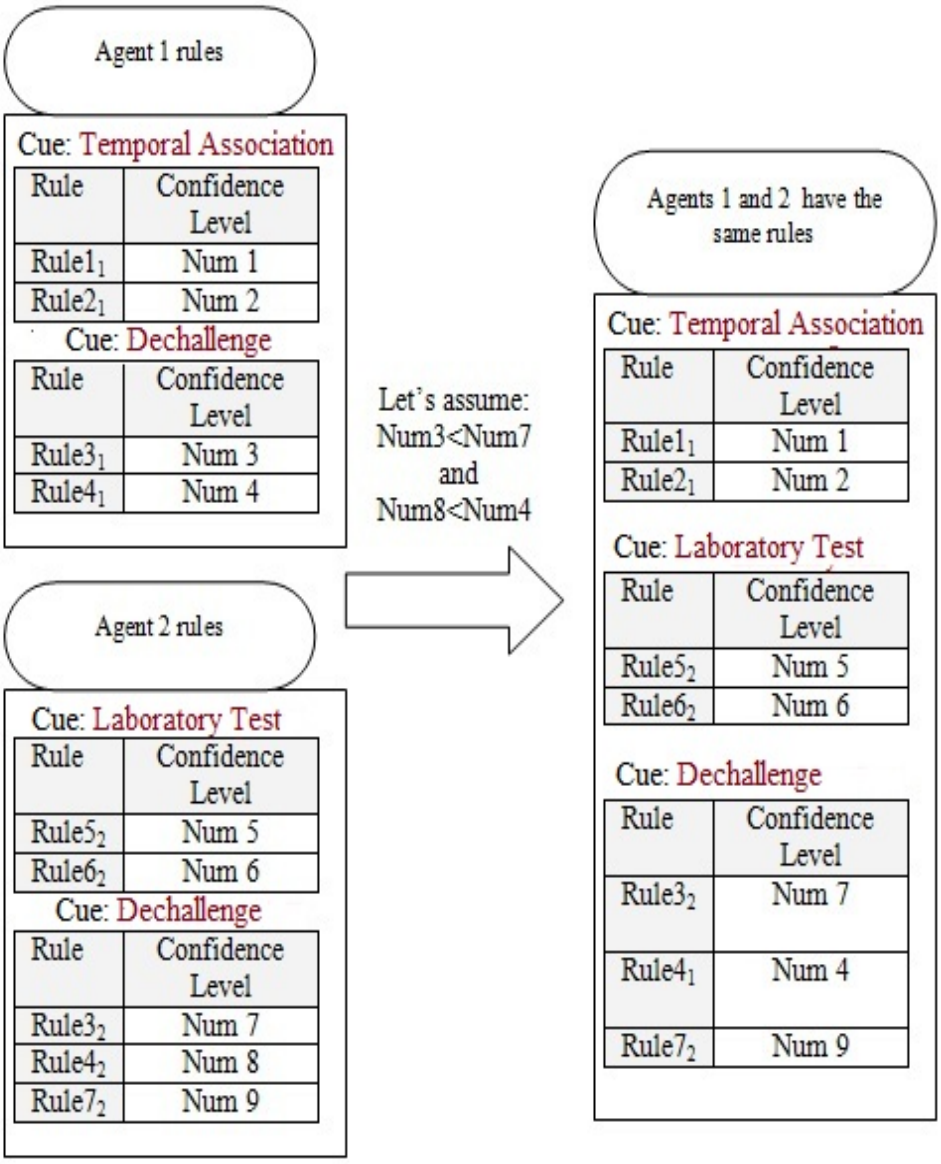


Figure 4. Updating ADR signal pair detection rules in two PAAs.

The confidence level of a rule will be updated each time a rule has been used either for evaluating a new or old case. The physician can input new rules to the system at any time through sending a request to Communicator and Manager which then forward the

request to Rule and Confidence Level Updater. Rules and Confidence Level Updater add the new input rules from the agent's physician to the agent similarity or detection rules.

The confidence level will affect the contribution of the rule. For instance, if the system assigns a confidence level of 0.4 for a rule "If Potassium Laboratory Test Value is Low, then Abnormality in Potassium Laboratory Test is Low" it means there is a 40% confidence on that rule. This will affect the output of that rule which consequently affect the calculation of the Total Potassium Temporal Association.

For example if there a scene that contains PAA_1 and PAA_2. For the meantime let's assume that the only factor used by PAAs in the scene is the age factor and it is just contains one Age rule in its decision. Let's say that the total number of cases used Age rules before for PAA1 =22 and the total number of patients in the PAA_1 Database is 30 patients. Suppose that PAA_1 is evaluating a new case. Then PAA_1 will do the following:

Step 1: PAA Confidence Level Update

In this step the PAA will update its rules based on the new patient case. Let's assume that PAA1 used in that evaluating his Age rule. This will increase the total number of cases used age rule by one. Besides, the total number of patients will be increased also to 31. The confidence level will be updated using the following rule:

Confidence Levels of Age rules = Total number of cases used Age rules / Total number of patients in the PAA_1 Database.

So the confidence level will be updated from 22/30= 0.73 to 23/31= 0.74. In case the new Confidence level is lower than the new confidence level, the new confidence will stay the same as the old one.

Step 2: Confidence Level Update using Other Agents' Rules

In this step, the PAA will communicate with other agents in the scene. PAA_1 will look at other agents' confidence level for the age rule. If the agent finds another agent with higher confidence level, not necessarily the highest, PAA_1 will update its age rule and adapt the other agent rule with the new confidence level. PAA_1 confidence level is 0.74 for the Age rule as described in step 1. Let's assume PAA_2 confidence level is 0.85. Then PAA_1 will adopt PAA_2 Age rule and will use PAA_2 confidence level's value in future evaluation because by adapting these rules PAA_1 will benefit from the experience of the PAA_2 which is shown here as a rule. The new confidence level for PAA_1 will be 0.85. This step is summarized in Table 2 for this sense.

Table 2. Steps to update confidence levels for the example PAA1 and PAA2.

Step \ Agent	**PAA_1**	**PAA_2**
1	Number of times the age rule has been used is 22.	Number of times the age rules has been used is 79.
	Total Number of Patients used in updating the confidence Level is 30.	Total Number of Patients used in updating the confidence Level is 88.
	Calculate the confidence level for the age rules using the following formula $Age\_CL_{PAA1} = 22/30 = 0.733$.	Calculate the confidence level for the age rules using the following formula $Age\_CL_{A2} = 79/88 = 0.897$
2	New patient needs to be evaluated.	N/A
3	The new confidence level will be 0.74.	No change to the confidence level.
4	PAA_1 asks PAA_2 for help.	PAA_2 received the request and accept providing the help.
5	Communication is provided between the two PAA to talk with each other and help each other.	
6	Comparing the confidence level for the age rule to see which agent has more experience in Age than the other. Here let's assume that PAA1 Confidence level is lower that PAA2 Confidence level.	
7	Agent 1 Adopt Agent 2 age rules.	
8	If another new case needs to be evaluated by PAA_1 The new confidence level will be equal to 0.897.	If another new case needs to be evaluated by PAA_2 The confidence level will be equal to 0.897.

2.4 Agent Communication Behaviors and Agnet Team Construction

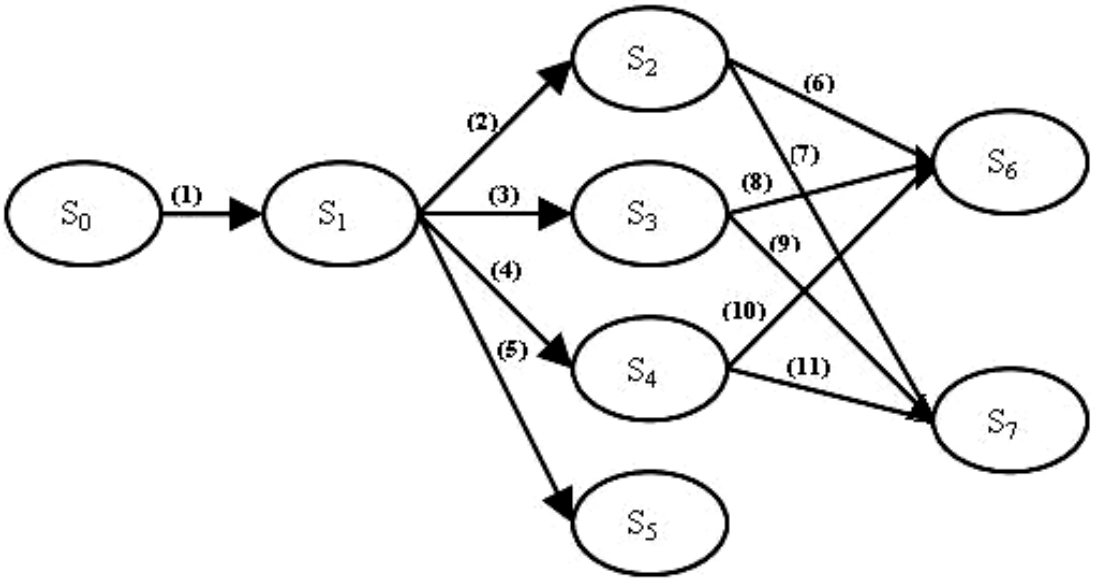
Agents can have different roles and abilities with different (for instance, hospital, physician). Agents are communicating between each other using certain communication protocols. The main components of any multi-agent system implementation are: the agents and their roles, the dialogic framework, the scenes, the performative structure, and the normative rules [40, 41]. In a health organization system, agents play the roles of physicians, pharmacists, epidemiologists, and so on [72, 73]**.** The agent playing a given role must follows the pattern of behaviors and scenarios initially provided by system designer and later by his human user.

The communication protocols used between agents have to be fixed. Agents interact through speech acts language. For example query, inform, request, offer, accept, withdraw, and reject speech acts has been used in the developed system .Interaction between agents occurs within a scene. The developed system composed several scenes which are basically group meeting composed of a set of agents playing different roles and communicating with a well-defined communication protocol. To specify a scene, the first step is to identify which are the agents that will participate in the scene. Agents with different roles can enter and exit a scene to go to another one. The second step is to define the communication protocol [72, 73].

A scene can be described as a graph, which can be regarded as a state diagram. The nodes represent different states of a conversation and the arcs are labeled with expressions of the communication language making the conversation passes from one state to another.

The graph has a single initial state and a set of final states representing different endings of the conversation.

Figure 5 shows the state diagram of a scene how three agents, PAA1, PAA2 and PAA3, have a conversation. A communication protocol will be used in the communication request of PAA1 to PAA2 and PAA3 in order talk about an ADR signal pair. Initially, the conversation is in state S_0. Then PAA1 initiates the conversation and the system enters the next state S_1. Several possibilities then open up. PAA2 and PAA3 may accept or reject the request. Depending on their answers, the next state will be S_2 if both agents accept, S_3 if only PAA2 accepts, S_4 if only PAA3 accepts or S_5 if both reject. If the task has been successfully completed, state S_6 will be reached. Otherwise state S_7 will be reached.



(1) PAA1 sends a request to PAA2 and PAA3.
(2) Both PAA2 and PAA3 accept the request.
(3) Only PAA2 accepts the request.
(4) Only PAA3 accepts the request.
(5) Both PAA2 and PAA3 reject the request.
(6) One or both agents succeed in doing the request
(7) Both PAA2 and PAA3 fail in doing the task.
(8) PAA2 succeeds in doing the task.
(9) PAA2 fails in doing the task.
(10) PAA3 succeeds in doing the task.
(11) PAA3 fails in doing the task.

Figure 5. The state diagram of a scene involving three PAAs.

To describe what is happening during a conversation between two PAA agents, Petri nets can be used (Figure 6 shows an example). Petri nets have a number of advantages when used to analyze conversations in multi-agent systems [40]. A Petri net is defined as an oriented graph comprising two sorts of nodes: *places and transitions* [40]. This graph is constituted in such a way that the arcs can only link places to transitions or transitions to places. Places are graphically represented by circles and transitions by bars. The places correspond to the state of the agent during a conversation stage. The transitions correspond either to synchronization due to the receipt of messages or to conditions of actions. Places IA and IB describe the initial states where the PAAs find themselves before the beginning of the conversation. Places FA1, FA2, FB1 and FB2 represent the end of conversation states. Starting from state IA, PAA1 sends a request "to do (T)" to PAA2 and moves in to state WA1, which represents waiting for a response. If PAA2 can't do the task, it sends a refusal to PAA1, which then goes into state FA1, which indicates that PAA1 must look elsewhere to have its task carried out. If PAA2 can do the task, it sends an acceptance message to PAA1, which places PAA1 into wait for a response state WA2. During this time, PAA2 is in state WB, while trying to carry out the task. Once finishing the task, it sends a notification of end of accomplishment to PAA1, which places PAA1 in state FA2 and places PAA2 in state FB2. If not, PAA2 indicates that it cannot do the task, which places PAA1 in state FA1 and places PAA2 in state FB1.

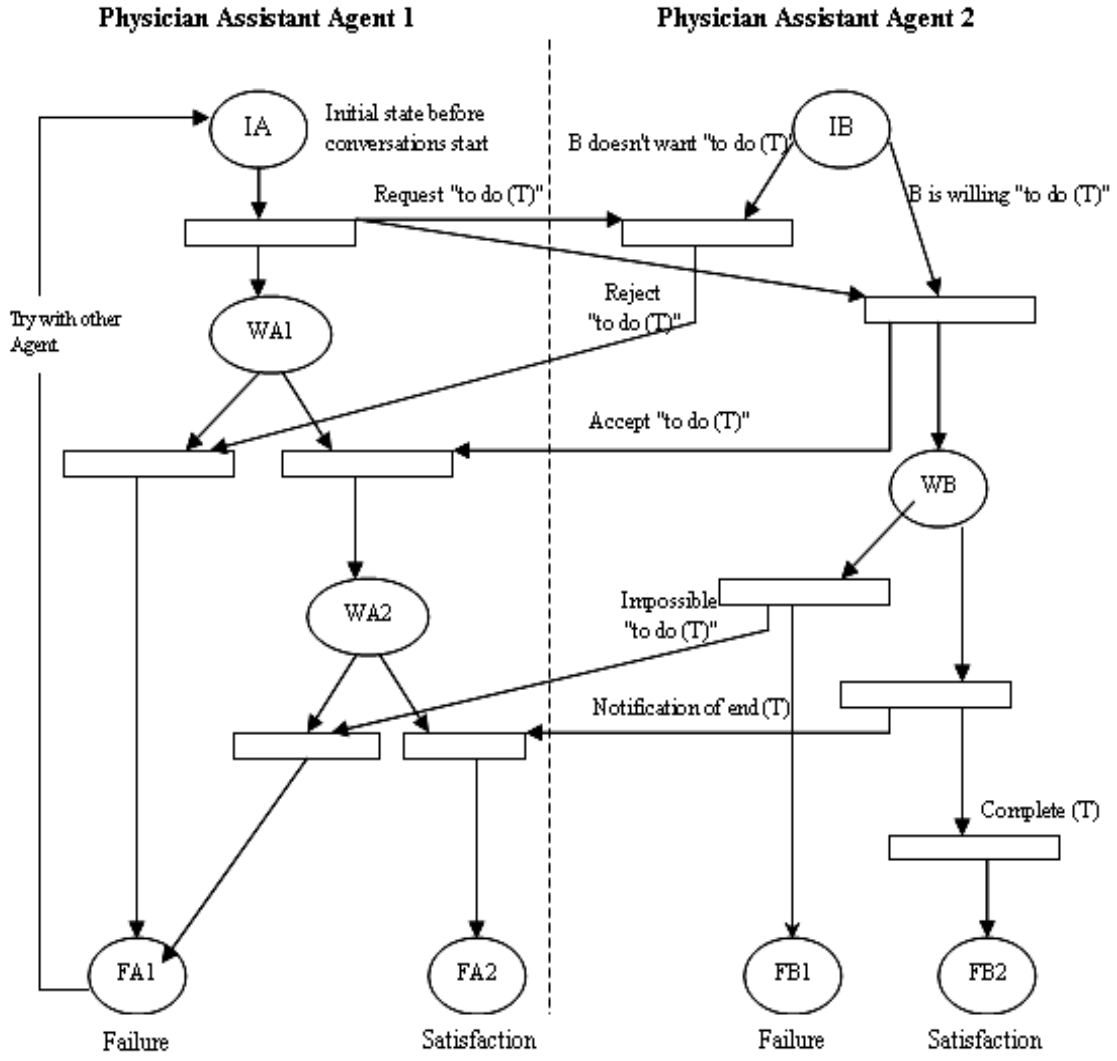


Figure 6. Conversational model of an ADR task between two PAAs using the Petri nets approach.

In real life problem we have a lot of physicians in the same or different health organization. It's reasonable to find a way to divide the PAAs into different teams and each team can focus on a certain ADR. This will faster the process of signal pair identification and reduces communication overhead. Also I need to take in my account that a new PAA can join a team at any time and it need to join the correct team.

The agent in the developed system can be added to a team according to the name of medication (and its class) and the potential adverse event. To do that, a strategy of classifying medications is needed and required to be included the identification system. The National Drug Code System [74] was chosen as a therapeutic or pharmacological classification technique . The National Drug Code provides each medication by a unique 10-digit number which is composed of 3-segment. Each segment provides certain information. The first segment provides 4 or 5 digits to describe the medication labeler. A labeler is any firm that manufactures, repacks or distributes a medication. The second segment provides 3 or 4 digits to the actual contents of a medication product including doses and formulation. The third segment provides 1 or 2 digits that description of the trade package such as forms of the medication (for example tablets or liquid) and sizes (or number of tablets).

Table 3 shows example for those codes for drug LISNOPRIL. In some exceptional cases, the second and third segments may contain characters besides digits.

Table 3. Examples of National Drug Codes for Drug Lisinopril.

Drug	Dose	Package	FDA NDC Number
LISINOPRIL	2.5 mg/1	30 TABLET in 1 BOTTLE, PLASTIC	0143-1265-30
LISINOPRIL	5 mg/1	100 TABLET in 1 BOTTLE, PLASTIC	0143-1266-01

The drug name will be extracted from the query sent by the agent. Then the drug name will be converted using National Drug Code Directory to 10 digits. For example if

the agent are interested in Lisinopril drug regardless the dose then the first segment, i.e. 0143, will be used. After that, the white board agent checks whether a team for this drug class already existed. If not, a new team would be created and registered to the main container based on the NDC number.

2.5 System Implementation

For system construction and execution, JADE 3.7 agent platform (Java Agent DEvelopment Framework) is adopted [60]. JADE is an open-source software framework. JADE is a widely used package in multi agent system implantation [75]. JADE is following the specifications laid by The Foundation for Intelligent Physical Agents (FIPA) for multi agent system implementations [42]. It provides a set of Java classes that makes it easy to implement the systems. JADE can run on a variety of operating systems including Windows and Linux.

2.5.1 JAVA Agent Development Framework

The JADE platform includes most of agent's specifications. Each agent is implemented in JADE as a single thread. JADE provide a multi thread environment that allows the agents to execute parallel tasks. Different cooperative behaviors can effectively schedules in JADE. JADE incorporates some ready to use behaviors that commonly used by agents during performing certain task. Among the others, JADE offers a behavior that allows full integration with JESS which is a rule based engine that performs all the

necessary reasoning. JADE provides follows FIPA standers. JADE consists of the following three parts

1. A runtime environment where agents can perform the requires task,
2. A library of classes which are used in the design of multi-agent system,
3. Graphical User Interfaces that can be used for debugging the designed system and monitor the actions of certain agents.

In brief, JADE runtime environment consists of two essential built-in agents namely Agent Management Service (AMS) and Directory Facilitator (DF).The multi agent system cannot operate without the Agent management service agent while it can without the directory facilitator (DF) agent. The AMS is responsible for managing the interactions of the agents in the system. To that AMS agent is responsible for registering and naming any agent join the system or being created. It keeps all the agent names beside some description about the location of agents**.** The Directory Facilitator agent maintains a description of the services that the agents are ready to provide to the others. Any registered agent can use the DF agent to search for specific services or help that can be handled by other agents. At the same time any agent can use the DF agent to announce for its own services that are available to other. Since agent are normally distributed at different location. Each location will have a runtime environment that hosts the agents, which is called a “Container”. Each container has AMS and DF agents. The containers will communicate with each other using a pre defined protocols. Agents live in the containers. All the dissections and interactions between agents take place in JADE containers[75].

One container needs to be assign as main container which represents the bootstrap point of a platform. It is the first container to be launched and all the other containers must join it by registering with it. For my system, the main container hosts four PAAs (I choose four because it is representative enough while computing time is still reasonable).

Agents will be assigned a unique identifier and an address that will be used to register the agent in its container. This agent life-cycle management allows effective communication between agents. JADE also provides tools that manage both locally and remotely agent life cycles including create, suspend, resume, freeze, thaw, migrate, clone and kill.

JADE provides flexible communication architecture to be used by the agents. JADE provides messaging system that follows FIPA_ACL standers. The messaging system manages message traffics and monitors the resulted queues provided to agents. JADE provides the agents with different modes to access their. The full FIPA communication model has been implemented in JADE and all its components have been integrated including the interaction protocols. Agent ontology management has been also implemented besides allowing the user to implement user-defined ontologies that allow agents to communicate easily and effectively. JADE allows the use of Web which will provide the multi-agents system with several services that can enhance the job of the agents.

2.5.2 Java Classes

During the development of the system with JADE, the following types of Java code classes are created and implemented:

Agent classes, which is used for describing the agent types. In this category I have utilized (1) class HOAs that implements Health Organization Agents, (1) class PAA that implements PAAs, and (2) class DBWA that implements Database Wrapper Agents. An agent is implemented in JADE by extending the provided Agent class and overriding the default implementation of the methods that are automatically invoked by the platform during the agent lifecycle, including setup() and takedown(). In the implementation stage all agent classes extend the *Agent* base class. The Agent Activity classes will be called in Agent classes.

Agent Activity classes, also called behaviors, which are used for describing the activities performed by the agents in the system. Agent actions are normally specified through behavior classes. It describes and gives specifications of possible dialogues and scenarios the participating agents could face. A behavior is implemented in JADE by extending the provided Behavior Base class. In the implementation I have used Java classes for defining behaviors that describe the agent's responses to FIPA messages, like INFORM and SUBSCRIBE. The agents communicate only using FIPA defined language. A behavior is implemented in JADE by extending the provided *Behavior* abstract base

class. The class *Behavior* is the root of a class hierarchy abstracting various agent behavior types.

Reasoning classes, which are used for the implementation of the various reasoning models and Fuzzy Inference Engine employed by PAAs, for example, the Fuzzy Similar Patients Finder employed by PAAs. Here I use FuzzyJess Toolkit from the National Research Council of Canada's Institute for Information Technology. It is a set of Java classes that provide the capability for handling fuzzy concepts and reasoning [7]. It is compatible with JADE. It allows the user to use Java language to define membership functions, set antecedent and consequent of a fuzzy rule, and makes a fuzzy inference. FuzzyJess uses Jess (Java Expert System Shell). Jess provides the basic elements of an expert system, including fact-list, knowledge base that contains all the rules, and an inference engine which controls overall execution of the rules. Jess includes a special class called Rete, which is used to embed Jess in JADE.

Ontology classes, which are necessary for implementing the agent communication semantics using concepts and relations. Ontology classes are implemented using a set of Java classes. An Ontology class is implemented by extending the provided Ontology Abstract Base class.

Graphical User Interface (GUI) classes, which provide the user with a graphical interface to the multi-agent system, initiate a search, and show the results of a query to the user. Figure 7 shows the GUI of the developed system.

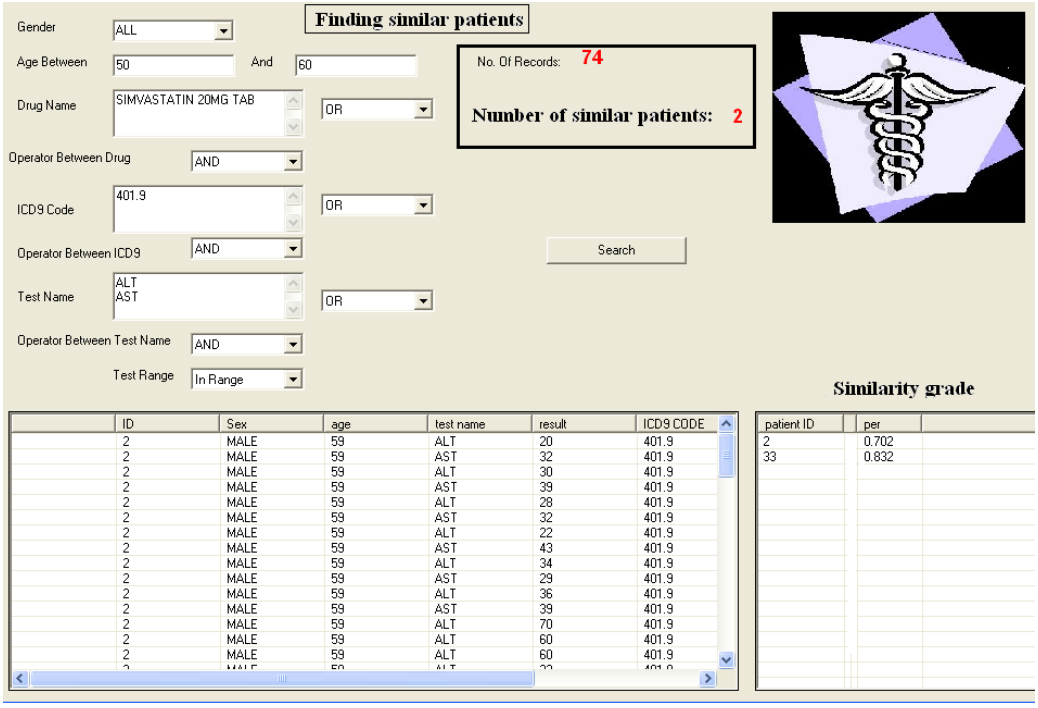


Figure 7. The GUI of the developed system.

White Board classes, JADE provides the classes used to help an agent publish and search for services through method calls. These classes help agents use the White Board.

Inter-agent Protocols implantation classes, protocols are implemented in JADE using special kind of behaviors which are responsible for proper ordering of the message sequences for protocol they implement.

CHAPTER 3

FINDING SIMILAR PATIENTS IN THE MULTI AGENT ENVIRONMENT

Early detection of unknown ADRs could save patient lives and prevent unnecessary hospitalizations. In this dissertation, I developed a multi-agent system for ADR detection. In the developed system, an agent is assigned to a physician to play an assist role. Through the study, I encounter the interesting problem of how the agents should collaborate to find patients in their patient databases that are similar to any given patient provided by one of the agents as a prototype. Actually, finding similar patients is one of the important steps toward ADR detection in a multi-agent setting. This would also be a necessary step in many other medical applications of multi-agent systems.

At the same time it is complicated to find similar patients in a multi-agent environment especially if I realistically assume that there does not exist a set of similarity-finding rules that are readily acceptable to all the users of the agents (i.e., physicians). This is because no two patients are identical and "similar" is really a vague, subjective measure rather than an objective measure. Furthermore, physicians often disagree one another owing to their knowledge and experiences. The specifications of the similarity-finding rules vary among the agents. Agents formulate their similarity rules according to their human users' experience. For an individual agent, if these experience-dependent rules are incomplete, it could cause inaccurate determination of similar patients. In addition, we assume realistically that we do not know which rules are right or wrong. Furthermore, the numbers of patients seen by different physicians (and hence their agents) are different. This will affect physicians' experience levels as well as the numbers of rules their agents should

have. More and better rules should be used as the physician sees more and more patients. This fact should be reflected in the agent system behavior. It should be obvious that these dynamic issues will pose challenges when the agents work collectively to help one another to reach a common goal (e.g., ADR detection).

In this dissertation, I developed a new methodology for finding similar patient in the multi agent system[69]. In that system, a similar patient search starts when an agent sends a request along with the patient of interest to the rest of the agents in the system to help in finding similar patients. The agents will start collaboratively one another in a way that the more experienced agents will help the less experienced agents in updating the similarity rules. Each agent will provide its similarity rules to the other agents. Then, the agents will retrieve patient cases one by one from their databases in order to evaluate their own cases using the new, updated similarity rules. The other agents will forward the similar cases along with their similarity scores to the requesting agent who may present the result to its user - physician. Having similar cases will provide the requesting agent with more evidence about the interested case and thus helps in decision making by the agent or by its physician.

3.1 Design of the Similar Patient Finder

Patient similarity is characterized by a number of factors related to physician's experience. In this dissertation finding the similarity between a reference patient and compared patients in the local databases is based on temporal association of a medication of interest, abnormality of a laboratory test, Symptoms and morbidities(chronic and acute), age, and medications.

The similarity rules used in the experimental part were acquired from the physicians on the team through the joint efforts of the engineering and medical team members after a careful analysis of the relevant literature. There are a total of 38 fuzzy rules.

3.1.1 Temporal Association of Medication Similarity

Temporal association gives the relationship between the time of taking a drug and the time of symptom occurrence. This time duration is called Symptom Appearance Duration. It should be noted that in the case of a potential ADR, exposure to a drug should always precede the effect (symptom). This distinction is important because the effect might result from entirely different causes (e.g., underlying diseases or reception of another medication).

For example if we assume Enalapril is the interested drug and we have the situation which is shown in Figure 8. In this case, since the ICD-9 code 729.1 (myalgia) occurs before all the start dates of Enalapril, it cannot be considered as an adverse event caused by

that drug. The ICD-9 code 786.2 (cough) occurs after the first start date of Enalapril in 24 days. Thus it can be caused by the drug.

DRUG NAME	START DATE
ENALAPRIL MALEATE 5MG TAB	5/19/2006
LOVASTATIN 10MG TAB	5/23/2007
ENALAPRIL MALEATE 5MG TAB	10/2/2008
SIMVASTATIN 20MG TAB	10/28/2008

ICD9 CODE	DIAG DATE
729.1	8/23/2004
786.2	6/12/2006

Figure 8. Example of possible ADR event.

Based on the experience of the physicians on the team, we define the following fuzzy rules to link cause (drug) to effect (ADR):

- If Symptom Appearance Duration is Short Then Temporal Association is Likely.
- If Symptom Appearance Duration is Medium Then Temporal Association is Possible.
- If Symptom Appearance Duration is Long Then Temporal Association is Unlikely.

Both Symptom Appearance Duration and Temporal Association are variables characterized by triangular fuzzy sets. Figure 9 and Figure 10 show the fuzzy sets for Symptom Appearance Duration and Temporal Association, respectively.

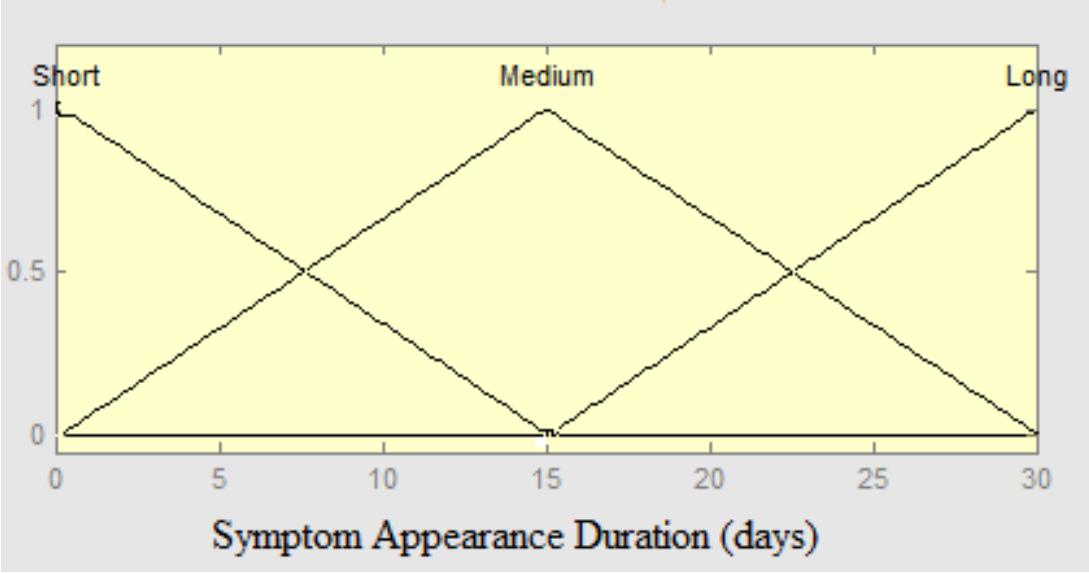


Figure 9. Fuzzy sets for Symptom Appearance Duration.

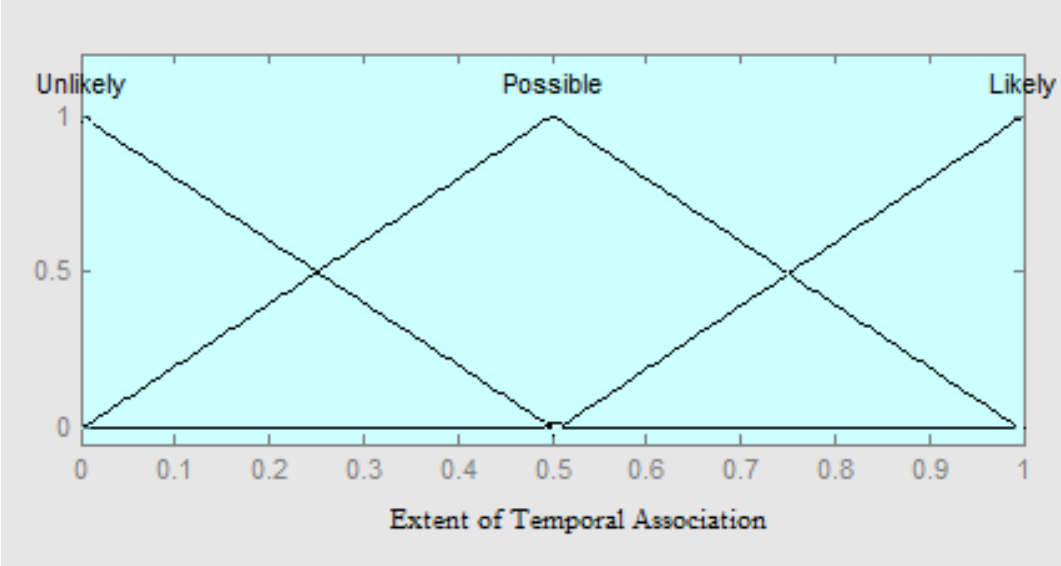


Figure 10. Fuzzy sets for Temporal Association.

Temporal Association Distance is the distance between the Temporal Association of the reference patient and a patient being compared with. It is defined as follows:

Temporal Distance = | Temporal Association of reference patient - Temporal Association of a patient being compared |

The similarity between a reference patient and a compared patient of a factor resulted from Fuzzy Inference Engine is given by:

$$Similarity \quad (x, y) = 1 - | x - y |$$

Since x and y are values between 0 and one then Similarity will be the same. Roughly speaking, the distance which is given by | x - y| is comparing "how far the similarity factors are," so its negation will point out "how similar they are." This equation is called local similarity measure.

Based on that, the Temporal Similarity between the reference patient and the compared patient is calculated using:

Temporal Similarity = 1- Temporal Distance

The resulted similarity value will be between 0 and 1.

3.1.2 Laboratory Test Similarity

This section discusses the rules used to determine similarity based on Laboratory Tests, which include Creatine phosphokinase (CPK) Laboratory Test (also known as Creatine Kinase (CK)), Transaminases Laboratory Test (either ALT or AST), Creatinine Laboratory Test and Potassium Laboratory Test. These laboratory tests are mainly used in

ADRs detection study. Most people with adverse event in the early stages feel well and have no clear symptoms that would lead a health care provider. This place a large emphasis on laboratory tests to diagnose, predict or evaluate a medical problem since they are indicative of extensive problems in the patient. The liver for example is one of the organs that can be affected from medications. The liver has several functions and it is usually called the body's manufacturing and filtering unit. The Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) laboratory test are typically used to evaluate liver functions or liver injury. Elevation of these tests is reflects a damage to the liver cell. Another example is the CK test. The elevation of CK laboratory result rise when muscle or heart cells are injured. Abnormality of a laboratory test shows the degree of elevation of a laboratory test result.

For each laboratory test, the laboratory result will be converted to its abnormality value. The interpretation of abnormality value of laboratory test results is very important to understand the situation of the patients. The abnormality value will be zero for the laboratory results in normal ranges. For other ranges, The Abnormality value will be calculated using fuzzy Inference system. The laboratory results will be the input to the system and the Abnormality value will be the output. Both the input and the output are fuzzy variables.

First, the Abnormalities of laboratory tests will be calculated for both the reference patient and the compared patient. Then the distance measure between these two values will be founded. Finally the similarity value between the reference patient and the compared patient is calculated. The resulted similarity value will be in the range of 0 and 1. The

similarity between two exact patients the similarity is one. If two patients are totally different the similarity is one. The abnormalities ranges used in defining the fuzzy rules and the membership functions of the fuzzy variables differ according to the characteristics of the laboratory test.

For example for the laboratory test AST, there are five fuzzy sets for the variable Laboratory Test Value as input- *Very Low, Low, Medium, High and Very High* (Figure 11), and five fuzzy sets as output to define the variable Abnormality in Laboratory Test: *Very Low, Low, Medium, High and Very High* (Figure 12).

The rules used to determine Abnormality in AST Laboratory Test are as follows,

- If AST Laboratory Test Value is *Very Low*, then Abnormality in AST Laboratory Test is *Very Low.*
- If AST Laboratory Test Value is *Low*, then Abnormality in AST Laboratory Test is *Low.*
- If AST Laboratory Test Value is *Medium*, then Abnormality in AST Laboratory Test is *Medium*.
- If AST Laboratory Test Value is *High*, then Abnormality in AST Laboratory Test is *High.*
- If AST Laboratory Test Value is *Very High*, then Abnormality in AST Laboratory Test is *Very High.*

These fuzzy rules are extracted from the knowledge provided by the physicians in our team.

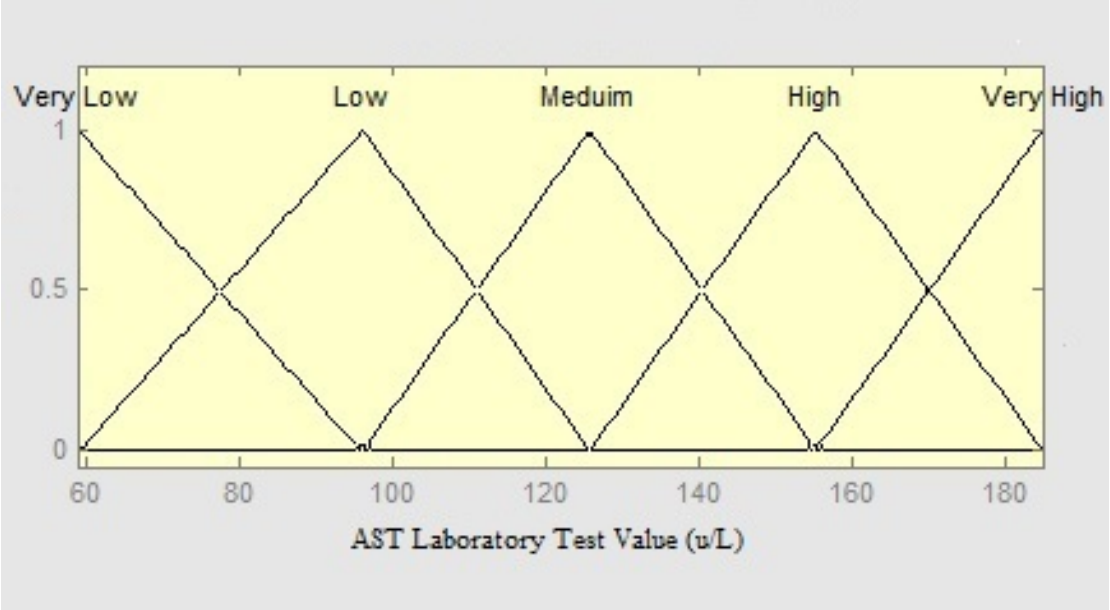


Figure 11. Fuzzy sets for AST Laboratory Test Value.

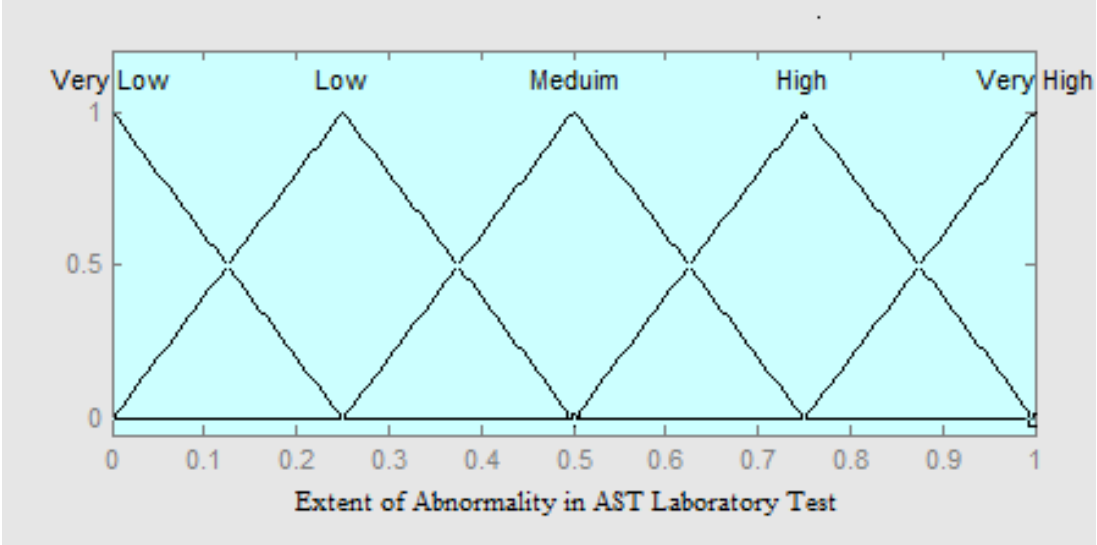


Figure 12. Fuzzy sets for Abnormality in AST Laboratory Test.

Then AST Laboratory Abnormality Distance, which is the distance between the Abnormality in AST Laboratory Test of the reference patient and that of a patient being compared with, is calculated using the following definition:

AST Laboratory Abnormality Distance = | Abnormality in AST Laboratory Test of reference patient – Abnormality in AST Laboratory Test of patient being compared |

AST Laboratory Similarity will be found based on the Laboratory Abnormality using the following rules,

AST Abnormality Similarity = 1- AST Laboratory Abnormality Distance

The same procedure will be followed for other laboratory tests. Here are the rules and the fuzzy sets for ALT, CK, Potassium and Creatinine laboratory tests.

The rules used to determine Abnormality in ALT Laboratory Test are as follows,

- If ALT Laboratory Test Value is *Very Low*, then Abnormality in ALT Laboratory Test is *Very Low.*
- If ALT Laboratory Test Value is *Low*, then Abnormality in ALT Laboratory Test is *Low.*
- If ALT Laboratory Test Value is *Medium*, then Abnormality in ALT Laboratory Test is *Medium*.

- If ALT Laboratory Test Value is *High*, then Abnormality in ALT Laboratory Test is *High.*
- If ALT Laboratory Test Value is *Very High*, then Abnormality in ALT Laboratory Test is *Very High.*

The fuzzy sets used to determine ALT Laboratory Test Value are shown in Figure 13. The Abnormality in ALT Laboratory is a fuzzy variable whose fuzzy sets are shown in Figure 14.

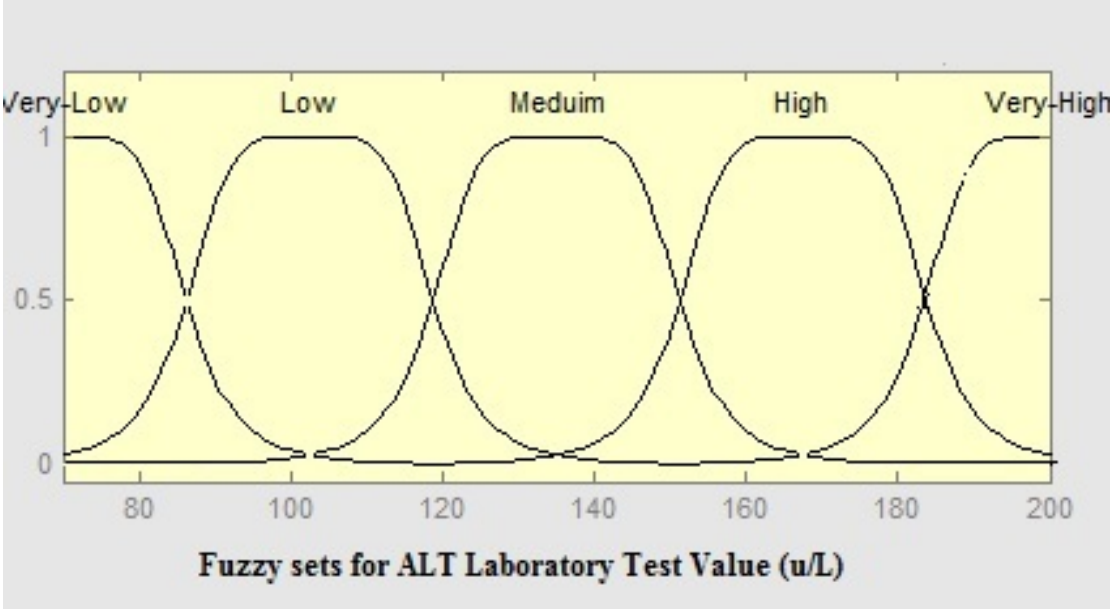


Figure 13. Fuzzy sets for ALT Laboratory Test Value.

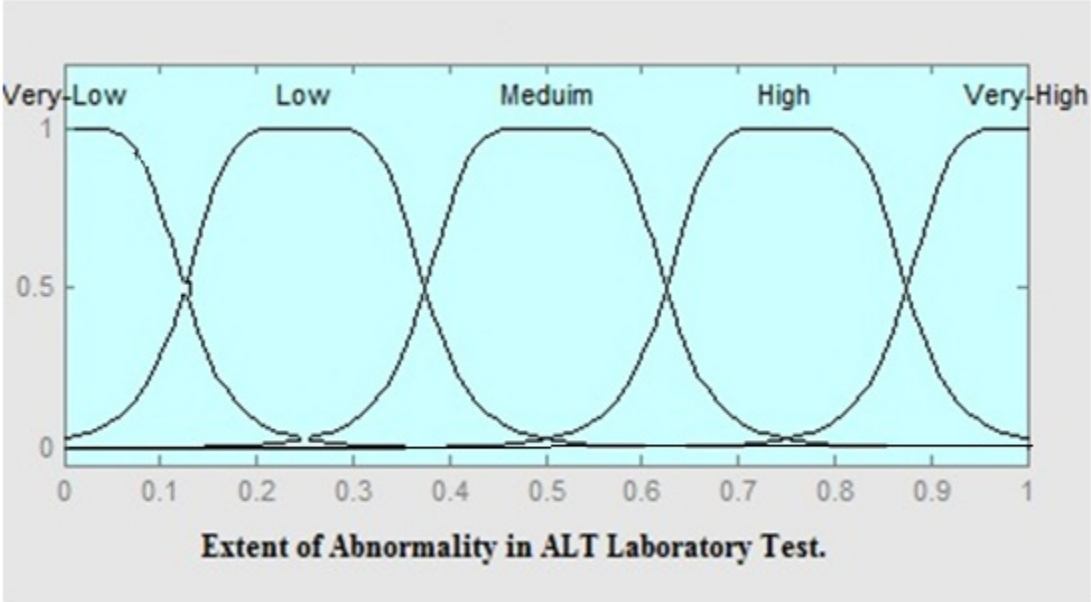


Figure 14. Fuzzy sets for Abnormality in ALT Laboratory Test.

Then ALT Laboratory Abnormality Distance, which is the distance between the Abnormality in ALT Laboratory Test of the reference patient and that of a patient being compared with, is calculated using the following definition:

ALT Laboratory Abnormality Distance = | Abnormality in ALT Laboratory Test of reference patient – Abnormality in ALT Laboratory Test of patient being compared |

ALT Laboratory Similarity will be found based on the Laboratory Abnormality using the following rules,

ALT Abnormality Similarity = 1- ALT Laboratory Abnormality Distance

The rules used to determine Abnormality in CK Laboratory Test are as follows,

- If CK Laboratory Test Value is *Very Low*, then Abnormality in CK Laboratory Test is *Very Low.*
- If CK Laboratory Test Value is *Low*, then Abnormality in CK Laboratory Test is *Low.*
- If CK Laboratory Test Value is *High*, then Abnormality in CK Laboratory Test is *High.*
- If CK Laboratory Test Value is *Very High*, then Abnormality in CK Laboratory Test is *Very High.*

Both CK Laboratory Test and Abnormality in Ck Laboratory are fuzzy variables and their fuzzy values are represented by bell shaped membership functions. Figure 15 shows the CK Laboratory Test. The Abnormality in Ck Laboratory is shown in Figure 16).

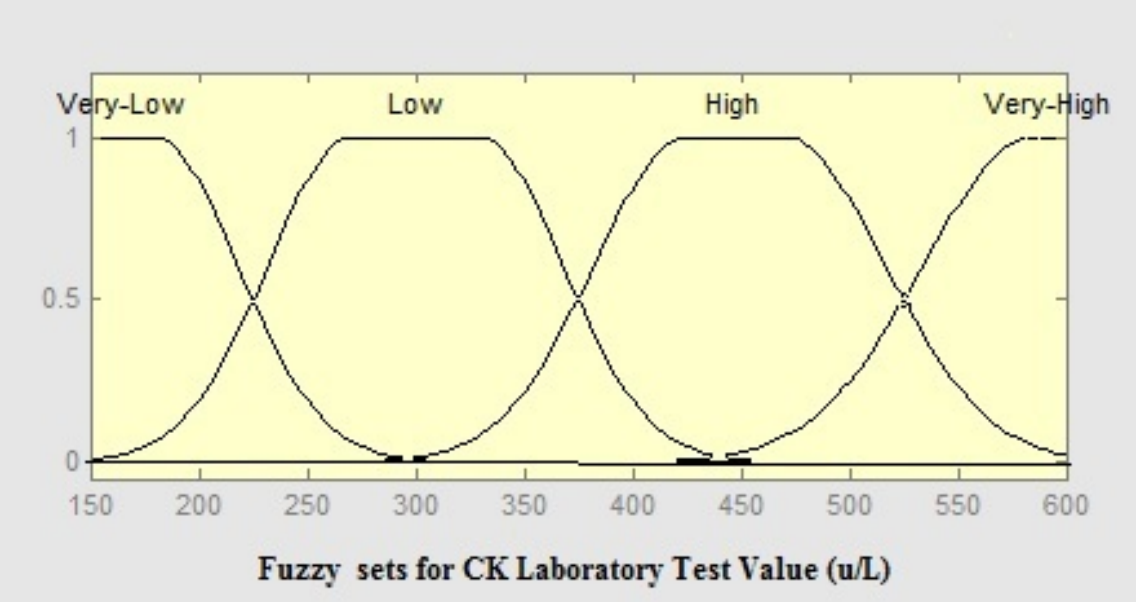


Figure 15. Fuzzy sets for CK Laboratory Test Value.

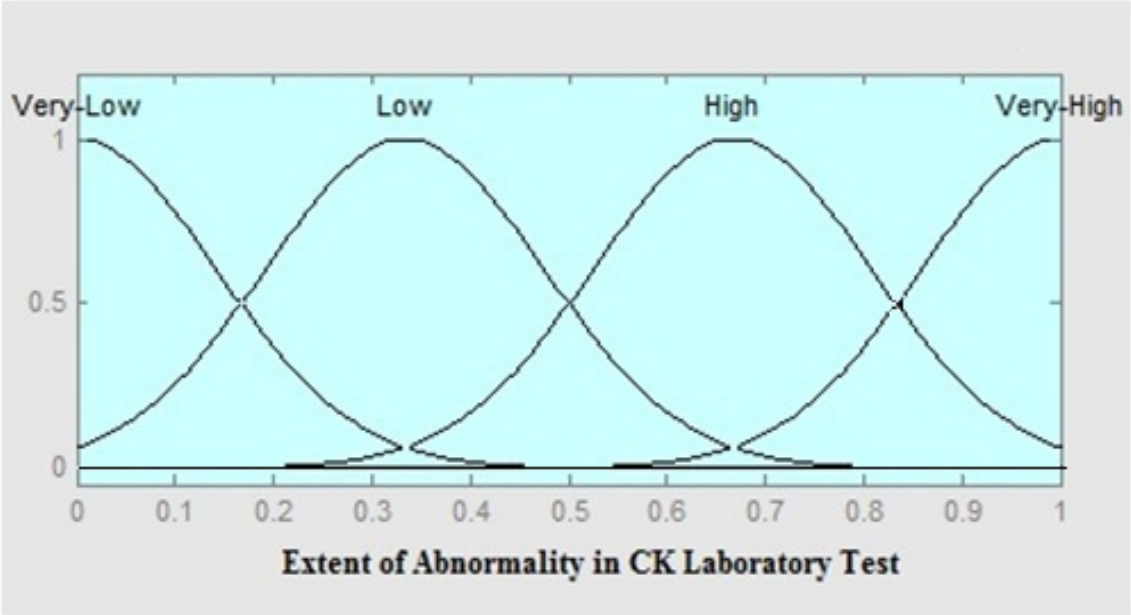


Figure 16. Fuzzy sets for Abnormality in CK Laboratory Test.

Then CK Laboratory Abnormality Distance, which is the distance between the Abnormality in CK Laboratory Test of the reference patient and that of a patient being compared with, is calculated using the following definition:

CK Laboratory Abnormality Distance = | Abnormality in CK Laboratory Test of reference patient – Abnormality in CK Laboratory Test of patient being compared |

CK Laboratory Similarity will be found based on the Laboratory Abnormality using the following rules,

CK Abnormality Similarity = 1- CK Laboratory Abnormality Distance

The rules used to determine Abnormality in Potassium Laboratory Test are as follows,

- If Potassium Laboratory Test Value is *Low*, then Abnormality in Potassium Laboratory Test is *Low.*
- If Potassium Laboratory Test Value is *Medium*, then Abnormality in Potassium Laboratory Test is *Medium*.
- If Potassium Laboratory Test Value is *High*, then Abnormality in Potassium Laboratory Test is *High.*

Potassium Laboratory Test Value is a fuzzy variable and its fuzzy values are shown in Figure 17. The fuzzy sets used to determine Abnormality in Potassium Laboratory Test is shown in Figure 18.

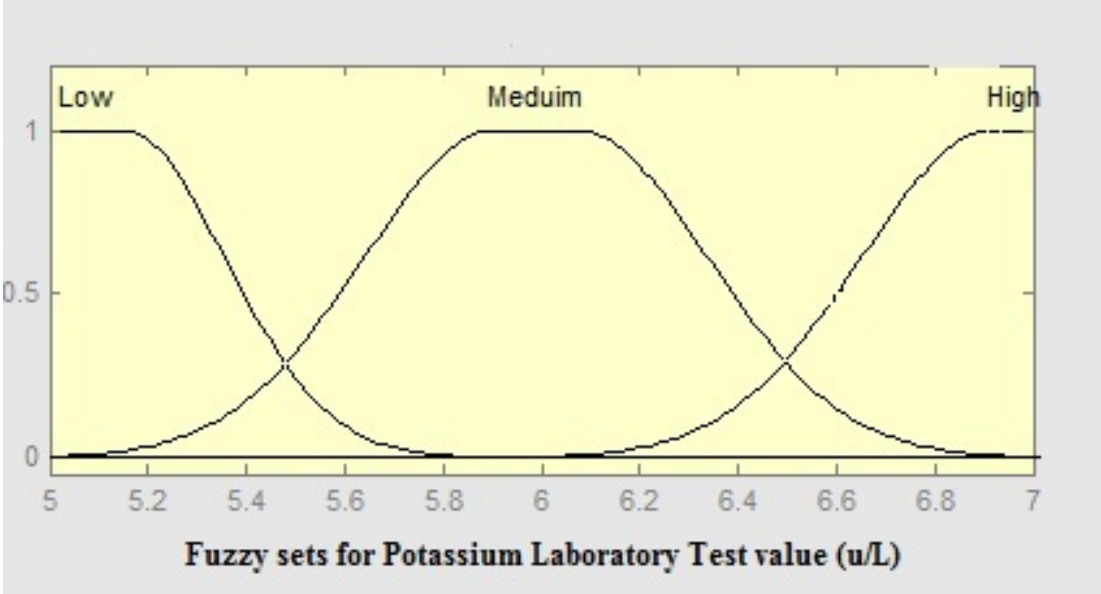


Figure 17. Fuzzy sets for Potassium Laboratory Test Value.

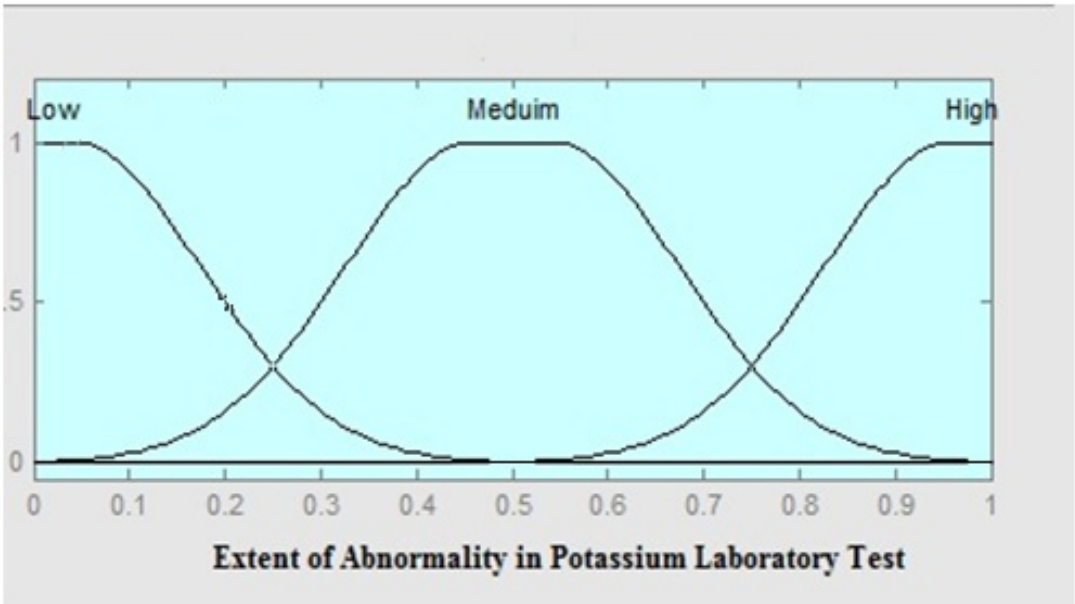


Figure 18. Fuzzy sets for Abnormality in Potassium Laboratory Test.

Then Potassium Laboratory Abnormality Distance, which is the distance between the Abnormality in Potassium Laboratory Test of the reference patient and that of a patient being compared with, is calculated using the following definition:

Potassium Laboratory Abnormality Distance = | Abnormality in Potassium Laboratory Test of reference patient – Abnormality in Potassium Laboratory Test of patient being compared |

AST Laboratory Similarity will be found based on the Laboratory Abnormality using the following rules,

Potassium Abnormality Similarity = 1- Potassium Laboratory Abnormality Distance

The rules used to determine Abnormality in Creatinine Laboratory Test are as follows,

- If Creatinine Laboratory Test Value is *Low*, then Abnormality in Creatinine Laboratory Test is *Low.*
- If Creatinine Laboratory Test Value is *High*, then Abnormality in Creatinine Laboratory Test is *High.*

The Creatinine Laboratory Test Value that is used to determine Abnormality in Creatinine Laboratory Test. Both variables are characterized by bell fuzzy sets (Figure 19 and Figure 20)

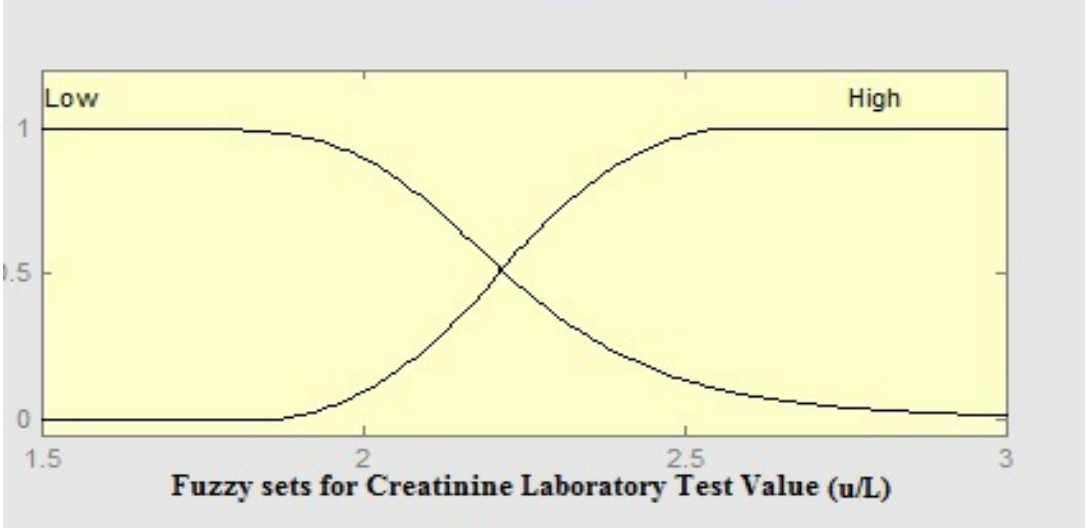


Figure 19. Fuzzy sets for Creatinine Laboratory Test Value.

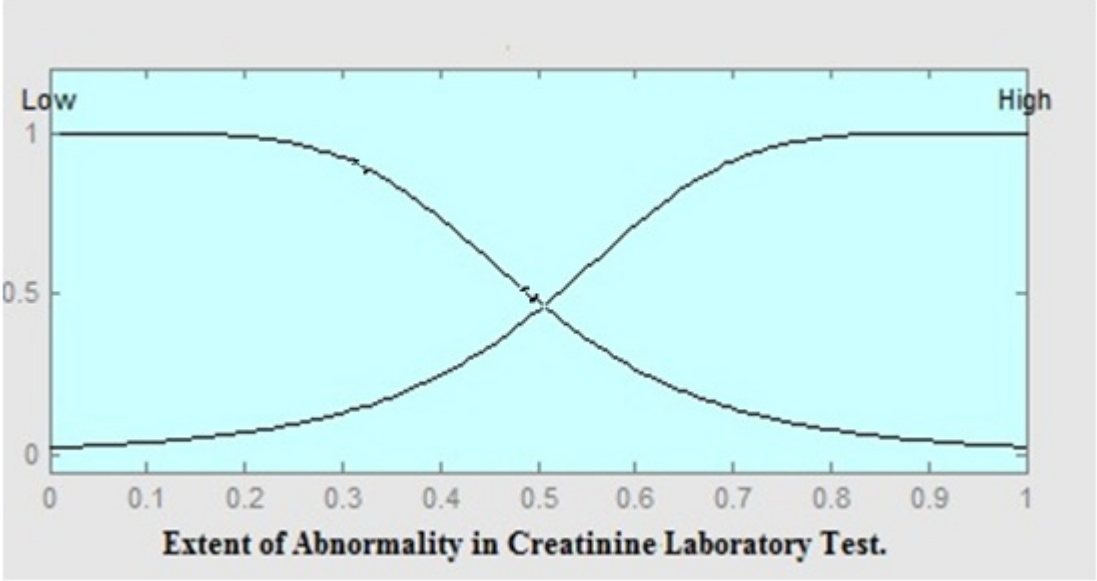


Figure 20. Fuzzy sets for Abnormality in Creatinine Laboratory Test.

Then Creatinine Laboratory Abnormality Distance, which is the distance between the Abnormality in Creatinine Laboratory Test of the reference patient and that of a patient being compared with, is calculated using the following definition:

Creatinine Laboratory Abnormality Distance = | Abnormality in Creatinine Laboratory Test of reference patient – Abnormality in Creatinine Laboratory Test of patient being compared |.

Creatinine Laboratory Similarity will be found based on the Laboratory Abnormality using the following rules,

Creatinine Abnormality Similarity = 1- Creatinine Laboratory Abnormality Distance.

The aggregated laboratory abnormality similarity between the referenced patient and the compared patient is calculated as a linear combination of the corresponding sub abnormality similarities. The aggregated Laboratory Abnormality Similarity is computed as the following:

Laboratory Abnormality Similarity = w_1 x AST Abnormality Similarity + w_2 x ALT Abnormality Similarity + w_3 x CK Abnormality Similarity + w_4 x Potassium Abnormality Similarity + w_5 x Creatinine Abnormality Similarity. where $w_1 + w_2 + w_3 + w_4 + w_5 = 1$

The weights control the importance of the sub similarities. In ADR problem some laboratory abnormalities are more important that the other based on the studied medication. This makes some weights greater than the others. For example in case of Statin drugs, the importance of laboratory tests AST, ALT, and CK is higher than the importance of Potassium and Creatinine laboratory tests. The opposite is valid in the case of Inhibitor Drugs. In this study I deal with these sub similarities in equal amount of importance. In case of equally importance

3.1.3 Symptom and Morbidity Similarities

To find the similarity based on morbidities the *International Classification of Diseases, 9th Revision, and Clinical Modification* (ICD-9-CM) code will be used. The ICD-9 code provides codes to classify diseases and a wide variety of signs, symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or disease. Every health condition is assigned a unique category and given a unique code. For example, if a patient is diagnosed with Hepatitis C, he/she will be given the ICD-9 code "070.51". If the diagnosis is for something acute, something that goes away with treatment like a rash or the flu, then the ICD-9 code will be less important because the illness or condition will go away. However, if the patient is diagnosed with a chronic or lifelong problem, like heart disease or diabetes, the ICD-9 code will be more important and will affect his future medical care.

Since different ICD-9 codes may represent the same (or similar) diagnoses, I clustered the ICD-9 codes into a manageable number of categories based on the clinical

classifications system (CCS) for the ICD-9-CM fact sheet Developed at the Agency for Healthcare Research and Quality [76], the CCS groups over 13,600 ICD-9 codes into 285 mutually exclusive and clinically meaningful categories. The clinical classifications system makes it easy for physicians and hence their agents to understand patient cases and analyze them for similarity task.

In order to find the similarity based on ICD-9s, the ICD-9 codes of the reference patient and the compared patients will be converted to the corresponding CCS categories. Some of the CCS categories are of importance that will be used in finding similar patients while the other will be discarded.

To find ICD-9 similarity between the reference patient and the compared patients, the ICD-9 of the reference patient and the compared patient is converted to their corresponding CCS Categories. Then the duplicated CCS categories resulted from converting different ICD-9 codes that belong to the same CCS category will be removed. Finally, the similarity between the two resulted CCS Categories is calculated using Jacard Coefficients as shown in the following steps

Step 1:

Convert the ICD-9 of the reference patient to their CCS Categories.

Step 2:

Convert the ICD-9 of the compared patients to their CCS Categories.

Step 3:

Remove the duplicated categories resulted from the conversion of different ICD-9 codes belonging to the same CCS category.

Step 4:

The two new CCS vectors will be compared to find how many categories are in common.

$$Symptoms\ and\ Morbidities\ Similarities = \frac{MS_{11}}{MS_{01} + MS_{10} + MS_{11}}$$

where Jacard coefficients are defined as follows,

MS_{01} is the number of CCS categories where reference patient has them and compared patient doesn't.

MS_{10} is the number of CCS categories where reference patient doesn't have them and compared patient has them.

MS_{11} is the number of CCS categories where both reference patient and compared patient have them.

Example:

Reference patient has 5 CCS categories= {93,105,125,200,242} and the compared patient has 6 CCS categories = { 93,106,107,126,200,242}.

The CCS Categories set is the union of both CCS categories sets founded in the reference patient and the compared patient. In this example the CCS Categories set is { 93,105,106,107,125,126,200,242}

CCS Categories	**93**	**105**	**106**	**107**	**125**	**126**	**200**	**242**
Reference patient	Yes	Yes	No	No	Yes	No	Yes	Yes
Compared patient	Yes	No	Yes	Yes	No	Yes	Yes	Yes

Then the Jacards coefficients are calculated as shown:

MS_{01} =2

MS_{10} = 3

MS_{11}=3

Then the Symptoms and Morbidities Similarities = (3)/ (2+3+3) =3/8.

3.3.4 Age Similarity

Age is an important factor in determining the similarity between the patients because some symptoms are potentially will be considered more serious according to age. For example, acute diarrhea in an adult is not that danger as in an elderly patient which could produce dehydration more quickly;

Based on the literature and the physicians on our team, the age of a patient will be classified to one out of four groups. These groups are:

- Group 1: Age is below 35 years.
- Group 2: Age is between 35 and 69 years.
- Group 3: Age is Between 70 and 90 years.
- Group 4: Age is greater than 90 years.

The Age similarity between the age of reference patient and the age of compared patient will be calculated as follows:

Rule 1:

If the two ages belongs to the same Age Group, then the Similarity will be equal to 1.00.

Rule 2:

If Rule 1 not satisfied and the two ages belong to different groups, the similarity will be calculated as follows:

Step 2-1: The difference between the age of the reference patient and the age of the compared patient is calculated using this equation:

Age Distance = | Age of reference patient - Age of compared patient|.

Step 2-2: Use the Age Distance to fire the Age Similarity fuzzy rules which are deduced as shown below:

- If Age Distance is *Very Short*, then Age Similarity is *Very High*.
- If Age Distance is *Short*, then Age Similarity is *High*.
- If Age Distance is *Large*, then Age Similarity is *Low*.
- If Age Distance is *Very Large*, then Age Similarity is *Very Low*.

The input Age Distance is defined by the following membership functions: Very Short, Short, Large, and Very large. The output of the fuzzy logic, the Age similarity, is defined by four membership functions very low (*V L*), low (*L*), High (*H*), and Very High (*VH*). The centroid method is used for defuzzification. Both Age Distance and Age Similarity are represented by triangular membership functions (Figure 21 and Figure 22).

Figure 21. Fuzzy sets for Age Distance.

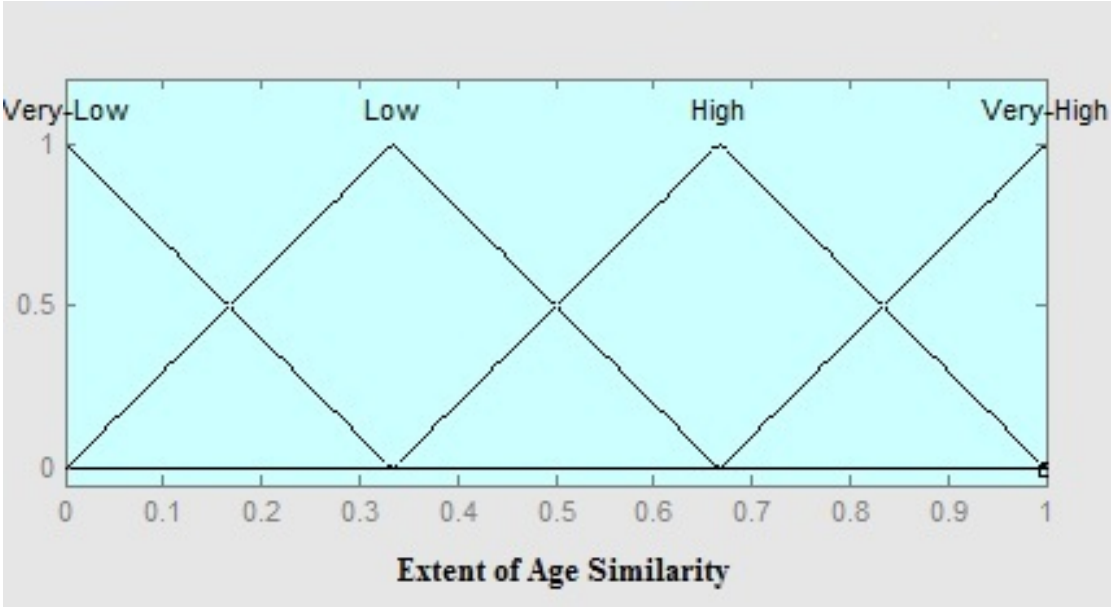


Figure 22. Fuzzy sets for Age Similarity.

3.3.5 Medication Similarity

The Medication Similarity plays a key role in identifying ADR since an adverse event can change by changing the medication. Sometimes the resulted adverse events are pleasant as in the case of some out of counter medications that are used to treat various mild conditions and diseases such as pain relievers and fever reducers. However, sometimes, the resulted adverse events are dangerous and can cause a great harm to human body.

Finding medication similarity is based on three factors which are Medication Name Medication Class and Medication Quantity.

The procedure for finding similarity based on medication is shown in steps A to D:

Step A: Medication Name Similarity

To find similarity based on medication name, all Drugs the reference patient and the compared patient took will be retrieved. Then the duplicated drug names in each of the retrieved lists will be removed. After that the drug doses attached to the drug name will be removed. The two drug lists will be compared to find the similarity using Jacard coefficients as shown below:

Step A.1:

Remove the duplicated drug names from the retrieved list of the reference patient.

Step A.2:

Remove the duplicated drug names from the retrieved list of the compared patient.

Step A.3:

The two new Drug lists will be compared. The Drug Name similarity is calculated using the Jacard Coefficients:

$$Medication\ Name\ Similarity = \frac{MD_{11}}{MD_{01} + MD_{10} + MD_{11}}$$

where,

MD_{01} is the number of Drug Agents that the reference patient has them and compared patient doesn't.

MD_{10} is the number of Drug Agents that the reference patient doesn't have them and compared patient has them.

MD_{11} is the number of Drug Agents where both the reference patient and the compared patient have them.

The resulted Drug Similarity will be between 0 and 1

Example:

Reference patient has 3 Drug Agents={ Rosuvastatin, Simvastatin, Captopril} and the compared patient has 4 Drug Agents ={ Simvastatin, Captopril, Enalapril, Benazepril}.

The Drug Agents set is the union of both Drug Agents founded in Reference patient and compared patient.

In this example the Drug Agents set is {Rosuvastatin, Simvastatin, Captopril, Enalapril, Benazepril}.

Drug Name	Rosuvastatin	Simvastatin	Captopril	Benazepril	Enalapril
Reference patient	Yes	Yes	Yes	No	NO
Compared patient	NO	Yes	Yes	Yes	Yes

Then the Jacards coefficients are calculated as shown:

MD_{01} =1

MD_{10} =2

MD_{11}=2

Then Medication Name Similarity = (2)/ (1+2+2) =2/5.

Step B: Medication Classes Similarity

A drug may be classified by the chemical type of the active ingredient or by the way it is used to treat a particular condition. To achieve this, we need to find a strategy of classifying drugs available in the market and then use it in the developed framework. The medications were catalogued according to the Anatomical Therapeutic Chemical

classification. This system is recommended by the WHO for drug utilization studies. In the Anatomical Therapeutic Chemical classification system, the active substances of a medication are divided into different groups according to the functional system they have effects on besides the chemical properties of the medication. For example, in the Anatomical Therapeutic Chemical system captopril and enalapril which are inhibitors medications are given the code C09AA.

To find the similarity based on medication classes, the drugs taken by both reference and compared patients will be converted to their drug classes. The converted list will have duplicated classes as a result of conversion of different drugs that belongs to the same drug class. Those duplicated classes will be removed from the converted lists. Then, the new two lists will be compared looking for the matches between them. The matched numbers will be used to find similarity using Simple Matching coefficients.

Simple matching coefficient is useful when both positive and negative values carried equal information (symmetry). Here are the steps used in calculating the similarity:

Step B.1:

Convert the drug names of the reference patient to their corresponding drug classes.

Step B.2:

Convert the drug names of the compared patients to their corresponding drug classes.

Step B.3:

Remove the duplicated classes resulted from the conversion of different Drugs that belong to the same Drug classes.

Step B.4:

The two new lists will be compared to find how many categories are in common using the following SMC:

$$Medication\ Class\ Similarity = \frac{MT_{11} + MT_{00}}{MT_{01} + MT_{10} + MT_{11} + MT_{00}}$$

where,

MT_{01} is the number of medication classes where reference patient has them and compared patient doesn't.

MT_{10} is the number of medication classes where reference patient doesn't have them and compared patient has them.

MT_{00} is the number of medication classes where both reference patient and compared patient have them.

MT_{11} is the number of medication classes where both reference patient and compared patient don't have them.

Example:

Reference patient has 1 Drug class = {Statin} and the compared patient has 3 Drug Classes = {Statin, Analgesics (pain relievers), Antipyretics (fever reducers)}.

The Drug Classes set is selected base on interested classes.

In this example let's assume the interested drug classes set is= {Statin, Inhibiters, analgesics}.

Drug Class	**Statin**	**Analgesics**	**Inhibiters**
Reference patient	Yes	No	No
Compared patient	Yes	Yes	No

Then the SMC coefficients are calculated as shown:

MT_{01} =0

MT_{10} = 1

MT_{00} = 1

MT_{11}=1

Then Medication Class Similarity= (1+1)/ (0+1+1+1) =2/3.

Step C: Medication Quantity Similarity

A large medication quantity can increases the possibility of adverse medication reactions and drug-drug interactions. It has also been associated with Toxicity which can be defined as "a consequence of administering a drug in quantities exceeding those capable of being physiologically managed by the host"[77]. Medication Quantity Similarity shows the similarity based on exposure amount of a medication class. In this dissertation, we are interested just in two drug classes which are Statin and Inhibitors. To find similarity based on medication quantity, medications of the reference patient is retrieved one by one and converted to the corresponding drug class using the Anatomical Therapeutic Chemical classification. Then the drug class will be examined whether it is one of the interested classes or not, i.e., Statin or Inhibitor. If yes, the doses of that medication will be extracted and added to the total dose of the class it belongs to (i.e., Statin drugs quantity or Inhibitor drugs quantity). Then the same procedure is done for the compared patient.

The medication similarity will be calculated as shown:

Step C.1: Retrieve a medication of the reference patient.

Step C.2: Remove the drug dose from the drug name of that medication in order to be used.

Step C.3: Convert the drug name to the corresponding Drug Classes using the Anatomical Therapeutic Chemical classification (see Step B of this section).

Step C.4: Examine the drug class if it is belonging to the interested classes, i.e., Statin or Inhibitor. If the drug class belongs to the interested classes, the drug dose of that medication will be used.

Step C.5: Add the extracted drug dose to the total dose of the interested class it belongs to (i.e., Statin drugs quantity or Inhibitor drugs quantity). The total interested class doses are initialized to zero in the beginning.

Step C.6: Repeat step 1 to 5 until processing all medications of the reference patient,

Step C.7: Repeat step 1 to 6 for the compared patient.

Step C.8: The Medication Quantity Similarity is calculated as the following:

The Medication Quantity Similarity = 1 if:

(Statin drugs quantity >90 and Inhibitor drugs quantity >90)

or

(Statin drugs quantity <90 and Inhibitor drugs quantity <90)

The Medication Quantity Similarity = 0 if:

(Statin drugs quantity <90 and Inhibitor drugs quantity >90)

or

(Statin drugs quantity>90 and Inhibitor drugs quantity <90)

Threshold 90 is based on the fact that a drug-ADR pair is recognized if the potential ADR occurs at least once after one of the start dates of the drug within a certain period of time (i.e., 90 days). In that period of time the patient will take around 90 pills of medication.

Step D: Total Medication Similarity

Medication Similarity is calculated using the following tests:

Test D-1: if the compared patient took medication classes that are totally different than the ones the reference patient then Medication Similarity is equal to zero without looking to other medication Similarities.

No need to do Test 2 if Test 1 was satisfied.

Test D-2: If the compared patient took some medication classes that are found in the reference patient medication list then Medication Similarity is calculated as the following:

Medication Similarity= w_1 x Medication Names Similarity + w_3 x Medication Class Similarity + w_2 x Medication Quantity Similarity.

where $w_1+w_2+w_3=1$.

The selection of coefficients for combining sub similarities is experience dependent. Every coefficient depicts the weight of the corresponding sub-similarities. From the experience of the physician on our team the weights are w_1=0.45, w_2=0.25 and w_3 = 0.30.

3.3.6 Overall Similarity

The similarity factors will be summed to give an overall weighted similarity between the referenced patient and the compared patient. The overall similarity is computed as in:

Overall Similarity = w_1 x Temporal Association Similarity + w_2 x Laboratory Tests Similarity + w_3 x Symptoms and Morbidities Similarity + w_4 x Age Similarity + w_5 x Medication Similarity.

where $w_1 + w_2 + w_3 + w_4 + w_5 = 1$.

The similarity scores are between 0 and 1 and a higher score represents a higher similarity. The selection of the coefficients for combining similarities is a crucial issue. Every coefficient depicts the weight of the corresponding sub factor similarity. These weights control the importance of the factors. In case of equally importance the weights will have the value 0.20. The weights can differ according to the physician point of view and depending on his experience. The weights can be adjusted base on the importance of the rule.

In general, if the experience-based similarity model classifies the similarity between *x* and *y* based on *m* parameters then the degree of similarity is defined as:

$$Sim_{Global}(x, y) = \sum_{i=1}^{m} Sim(i) * w_i$$

Where is Sim(i) is local similarity value for the parameter i ,and w_i represent the corresponding weight of parameter i which represents the relative significance of that parameter. Moreover,

$$\sum_{i=1}^{m} w_i = 1 \text{ and } \mathrm{Sim_{Global}(x,y)} \in [0,1]$$

The final similarity score between the reference patient and a patient being compared with, which comes from different factors, is represented by "Degree of Similarity" whose values are labeled as "*Very High*," "*High*," "*Medium*," "*Low*," and "*Very Low*". The similarity scores will be between 0 and 1 and a higher score represents a higher similarity. The similarity levels are shown below:

- Level 1: Similarity score from 0.00 to 0.19 represents Very Low Similarity.
- Level 2: Similarity score from 0.20 to 0.39 represents Low Similarity.
- Level 3: Similarity score from 0.40 to 0.59 represents Moderate Similarity.
- Level 4: Similarity score from 0.60 to 0.79 represents High Similarity.
- Level 5: Similarity score from 0.80 to 1.0 represents Very High Similarity.

Those levels are decided by a bio-statistician and the physicians in our team. The compared patient is said to be matched with the reference patient to degree α, if S (C, C') $\geq\alpha$ where $\alpha \in [0, 1]$ is a similarity threshold chosen by the user.

In the design of the Fuzzy Similar Patients Finder, we use the following settings: the Min-Max fuzzy inference and the centroid defuzzifier. Resulted Patients similarity vary in the strength based on (1) the experience of the agent; (2) the importance of the rules; and (3) presence or absence of some similarity rules;

3.2 Experiments

3.2.1 Experiment Settings

The purpose of the simulation experiment is to examine whether the PAAs work together to find similar patients. To do that, I retrieved the patients who received at least one of the 8 drugs of interest in Veterans Affairs Medical Center in Detroit during the time period from January 1, 2005 to December 31, 2008. These 8 drugs represent the first targets in studying ADRs. These drugs are statin drugs and inhibitor drugs. A statin is a type of drug that helps patients lowers their cholesterol. An inhibitor is a type of drug that treats high blood pressure. The interested drugs include 6 statin drugs (i.e., rosuvastatin, atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) and 2 inhibitors (angiotensin-converting enzyme inhibitor) drugs (i.e., captopril, and enalapril).

The retrieved patient data includes dispensing of drug, office visits, symptoms experienced, and laboratory testing. For each event certain details were obtained. The data for dispensing of drug includes name of the drug, quantity of the drug dispensed, dose of

the drug, drug start date, and the number of refills. The office visits data includes treatment regimens, treatment start dates and stop dates. The symptoms experienced data includes the symptoms appearance date, the symptoms ICD-9 codes and the ICD-9 code description. The laboratory testing data includes the names of the laboratory tests, laboratory test dates, laboratory test normal ranges and laboratory test results. The total number of retrieved patients was 20,000 (19,102 males and 898 females). Their average age was 68.0. This large number of patients was retrieved to be used in developing a detection methodology for ADRs. All the data was stored in a Microsoft Access database. The database had five tables, each of which contained one of the five types of information: (1) demographic data, (2) clinic visit data, (3) diagnostic data, (4) drug data, and (5) laboratory data.

The experiment setting has four steps as shown below:

Step 1: Selection of the patients

The 20,000 patients are clustered into three groups. The 1st group is for the patients who took only Inhibitor drugs and they are 3,414 patients. The 2rd group is for the patients who took both drug classes, Statin and Inhibitor, and it contains 7,711 patients. The 3rd group is for the patients who took only Statin drugs and it contains 8,875 patients. For the similarity evaluation experiments, we have selected randomly 199 patients out of the 20,000 patients. We have selected 1% patients from each group. From the 1st, 2nd, 3rd group we have select 34, 77, and 88 patients respectively. The selection of 1% samples from each group was based on systematic sampling. The Systematic Sampling selects certain number

of members from a large population. To do the selection each member in the population (size N) will be assigned a number (from 1 to N) then a random number will be selected from this large population in order to be as a reference point to the systematic sampling process. Finally the selection of the members will be based on a fixed periodic interval of sampling.

The n^{th}" member is selected by dividing the total number of members in the general population by the desired number of members for the sampled population. For example, for selecting a random group of 88 patients from a population of 8,800 using systematic sampling, you would simply select every 100^{th} person, since 8,800/88 = 100. Systematic sampling can be considered random, as long as the periodic sampling interval is determined beforehand and the sampling starting point is random [78].

Step 2: Distribution of the patients and the similarity rules among the PAAs

I formed the agent system by implementing four PAAs. I divided the 199 patients among the agents as follows: PAA1 to PAA4 had 10 (5%), 29 (15%), 60(30%), and 100 (50%) patients, respectively. By that I had PAAs with different levels of experiences.

The 200 patient was distributed to the 4 agents based on the following:

- 1^{st} PAA will have 10 patients: 2 from 1^{st} group, 4 from 2^{rd} group, and 4 from 3^{rd} group.
- 2^{nd} PAA will have 29 patients: 4 from 1st group, 12 from 2^{rd} group, and 13 from 3^{rd} group.

- 3rd PAA will have 60 patients: 11 from 1st group, 23 from 2rd group, and 26 from 3rd group.
- 4th PAA will have 99 patients: 17 from 1st group, 38 from 2rd group, and 45 from 3rd group.

By that I assure having low to high expert PAAs.

Each PAA had part of the rules. The total number of the rules is 38. Some of these rules are key rules that all the agents will have. The key rules help PAAs to make a basic signal Similarity Finding (i.e., the rules involving calculating the Total Laboratory Similarity and the Global Similarity). The remaining rules, which were randomly distributed, are classified into two classes: unique rules and overlapping rules. The numbers of each class that an agent has depended on the number of patients it had. The numbers of unique rules and overlapping rules shared between the PAAs are shown in Table 4.

Table 4. Numbers of Unique and Overlapping Rules used by PAAs

Agents	Number of Unique Rules	Number of Overlapped Rules	Total Number of Rules
PAA1	1	9	10
PAA2	1	18	19
PAA3	9	16	25
PAA4	7	23	30

Step 3: Select a random index as a reference case.

This index reference patient can be any patient from the 20,000 patients. In this experiment the reference patient has the following characteristics:

1. Age 56.
2. Medications: Simvastatin and any of the ACIH drugs.
3. Has normal kidney function.
4. Has hypertension (ICD-9 401.9).
5. Has high cholesterol (ICD-9 272.0).

Step 4: run the program and getting the result

The process of starting the agents involved their registration with the JADE Main Container, which assigned a unique identifier to each PAA. The reference case was given to PAA1. Then, PAA1 will contact White Board in order to locate other agents available to assist in the case of interest. White Board will inform the PAA about the availability of other PAAs (i.e., PAA2, PAA3 and PAA4). The PAAs will then work with each other in order to update their detection rules. Finally, each PAA will evaluate its own patient's cases and assign a similarity score for each of the cases. The evaluation outcome of each case will be forwarded to PAA1.

3.2.2 Experiement Results

PAA2, PAA3, and PAA4 provided PAA1 with the patient 29, 60 and 100 patients, respectively, with their similarity level. The similarity level belongs to one out of the five

levels, i.e., Level 1 = 'Very Low Similarity,' Level 2 = 'Low Similarity,' Level 3 = 'Moderate Similarity,' Level 4 = 'High Similarity.' and Level 5='Very High Similarity.' At the same time PAA1 evaluated its own patients, i.e., 10 patients. . The similarity levels assigned to each of the patient provided by the four PAAs are shown in Table 5.

Table 5. Results of Similar Patients found by the 4-PAAs System.

Number of patients / Agents	Level 1 "Very Low Similarity"	Level 2 "Low Similarity"	Level 3 "Moderate Similarity"	Level 4 "High Similarity"	Level 5 "Very High Similarity"	Total Number of Patients
PAA1	0	1	2	4	3	10
PAA2	1	3	6	10	9	29
PAA3	0	6	17	23	14	60
PAA4	2	12	21	38	27	100
Total number of patients	3	22	22	75	53	199

The multi-agent system took 6 hours to evaluate the 199 patients. From the software standpoint, the four agents collaboratively worked one another as designed. They updated their detection rules in proactive way and used the updated rules in evaluating the cases.

Two physicians were participated in this study. They were asked to independently review each of the 199 patient cases and assigned a similarity level for the compared patients. In this evaluation, patient cases were retrieved one by one from Databases using a visual basic program done for that purpose. Figure 23 gives a scenario of the user interface. The top frame shows patients' demographic information such as sex and age. For each patient, the other frames present his/her laboratory, pharmacy and diagnosis data.

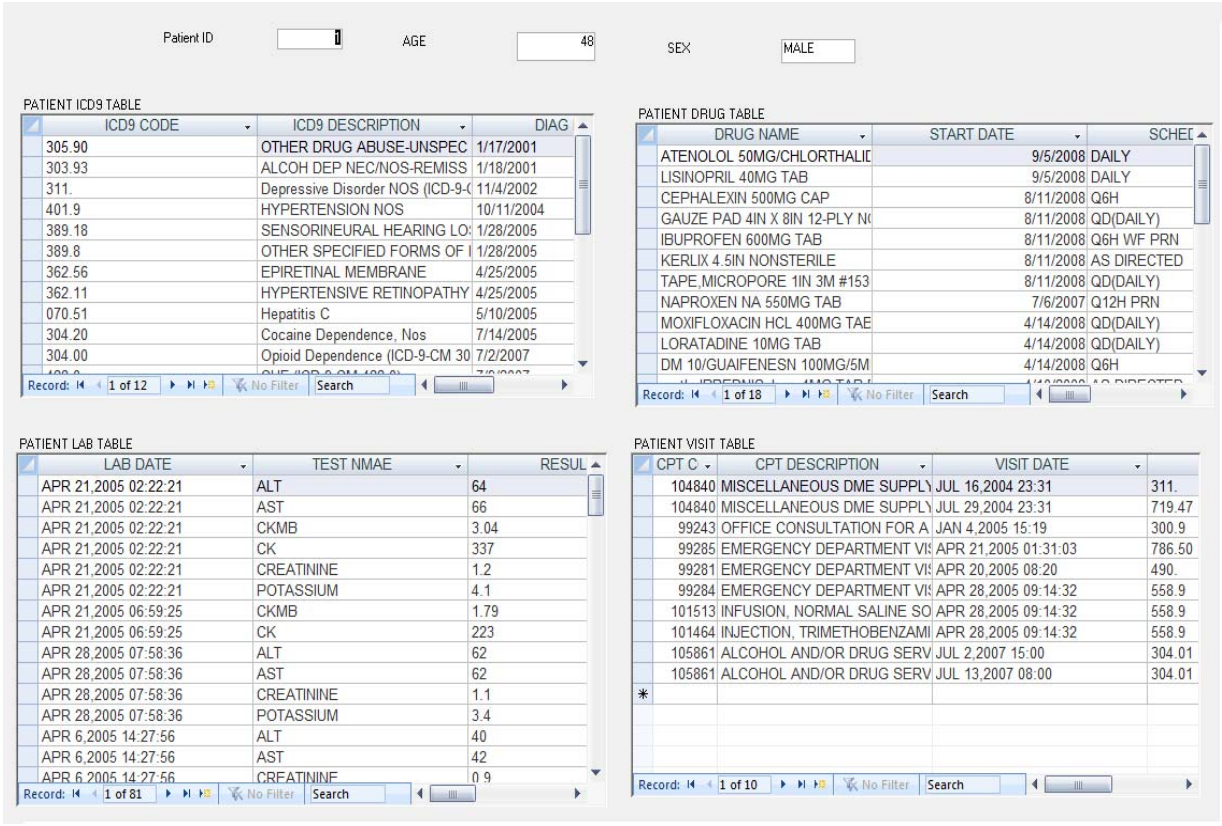


Figure 23. User interface for showing patient data.

The physician checked whether the patient is similar to the index patient or not. Then the physician assigned the similarity in a numerical score between 1 and 5 to show the strength of similarity. Where 1 = 'Very Low Similarity,' 2 = 'Low Similarity,' 3 = 'Moderate Similarity,' 4 = 'High Similarity.' and 5='Very High Similarity.' The similarity results generated by the multi-agent system and the two physicians (Physician 1 and physician 2) are shown in Table 6.

Table 6. Similarity Results Generated by the Multi-Agent System and Two Physicians (Physician 1 and Physician 2)

Patient ID	The System Decision Level	Physician 1 Decision Level	Physician 2 Decision Level	Drug Group	Agent
1	4	4	4	Group 2	PAA 1
2	5	5	5	Group 2	PAA 1
3	3	5	3	Group 1	PAA 1
4	5	5	5	Group 2	PAA 1
5	4	3	4	Group 2	PAA 1
6	4	3	4	Group 1	PAA 1
7	3	2	2	Group 3	PAA 1
8	2	2	2	Group 3	PAA 1
9	5	5	5	Group 3	PAA 1
10	4	5	5	Group 3	PAA 1
11	5	5	5	Group 2	PAA 2
12	4	4	4	Group 2	PAA 2
13	4	4	4	Group 2	PAA 2
14	4	3	3	Group 2	PAA 2
15	4	4	5	Group 2	PAA 2
16	4	4	4	Group 2	PAA 2
17	5	5	5	Group 2	PAA 2
18	4	3	3	Group 1	PAA 2
19	5	5	5	Group 2	PAA 2
20	3	3	3	Group 2	PAA 2
21	1	1	1	Group 1	PAA 2
22	5	5	5	Group 2	PAA 2
23	5	5	5	Group 2	PAA 2
24	2	2	2	Group 1	PAA 2
25	5	5	5	Group 2	PAA 2
26	3	4	3	Group 1	PAA 2
27	3	3	3	Group 3	PAA 2
28	5	5	5	Group 3	PAA 2
29	4	4	4	Group 3	PAA 2
30	3	3	3	Group 3	PAA 2
31	5	5	5	Group 3	PAA 2
32	4	4	4	Group 3	PAA 2
33	4	3	3	Group 3	PAA 2
34	2	2	2	Group 3	PAA 2

35	3	2	3	Group 3	PAA 2
36	4	4	4	Group 3	PAA 2
37	5	5	5	Group 3	PAA 2
38	2	1	1	Group 3	PAA 2
39	3	3	3	Group 3	PAA 2
40	2	2	2	Group 1	PAA 3
41	3	3	3	Group 1	PAA 3
42	3	3	3	Group 3	PAA 3
43	3	4	3	Group 3	PAA 3
44	5	5	5	Group 3	PAA 3
45	3	3	3	Group 3	PAA 3
46	3	3	3	Group 3	PAA 3
47	4	4	4	Group 2	PAA 3
48	5	5	5	Group 3	PAA 3
49	5	5	5	Group 2	PAA 3
50	4	5	4	Group 2	PAA 3
51	2	3	2	Group 1	PAA 3
52	5	5	5	Group 2	PAA 3
53	4	5	5	Group 2	PAA 3
54	2	2	2	Group 1	PAA 3
55	4	4	4	Group 2	PAA 3
56	5	5	5	Group 2	PAA 3
57	4	4	4	Group 1	PAA 3
58	4	4	4	Group 2	PAA 3
59	4	5	4	Group 2	PAA 3
60	4	3	4	Group 1	PAA 3
61	5	5	5	Group 2	PAA 3
62	5	5	5	Group 2	PAA 3
63	4	4	5	Group 1	PAA 3
64	5	5	5	Group 2	PAA 3
65	4	4	4	Group 2	PAA 3
66	3	3	3	Group 1	PAA 3
67	4	5	4	Group 2	PAA 3
68	5	5	5	Group 2	PAA 3
69	4	4	4	Group 3	PAA 3
70	4	4	3	Group 1	PAA 3
71	3	3	3	Group 2	PAA 3
72	4	4	4	Group 3	PAA 3
73	4	4	4	Group 2	PAA 3

74	2	2	2	Group 3	PAA 3
75	3	3	3	Group 1	PAA 3
76	3	3	3	Group 3	PAA 3
77	5	5	5	Group 3	PAA 3
78	2	2	2	Group 3	PAA 3
79	3	3	2	Group 1	PAA 3
80	3	3	3	Group 3	PAA 3
81	3	4	3	Group 3	PAA 3
82	4	4	4	Group 3	PAA 3
83	3	1	3	Group 3	PAA 3
84	4	4	4	Group 2	PAA 3
85	4	5	4	Group 2	PAA 3
86	5	5	4	Group 2	PAA 3
87	5	5	5	Group 2	PAA 3
88	5	5	5	Group 2	PAA 3
89	3	3	3	Group 3	PAA 3
90	2	3	2	Group 2	PAA 3
91	3	3	3	Group 3	PAA 3
92	3	3	3	Group 3	PAA 3
93	5	4	4	Group 3	PAA 3
94	3	3	3	Group 3	PAA 3
95	4	4	4	Group 3	PAA 3
96	4	3	4	Group 3	PAA 3
97	4	4	4	Group 3	PAA 3
98	4	4	4	Group 3	PAA 3
99	4	4	4	Group 3	PAA 3
100	3	3	4	Group 3	PAA 4
101	2	2	2	Group 3	PAA 4
102	4	5	3	Group 3	PAA 4
103	4	4	4	Group 3	PAA 4
104	3	3	3	Group 3	PAA 4
105	3	3	3	Group 3	PAA 4
106	3	3	3	Group 3	PAA 4
107	2	2	2	Group 1	PAA 4
108	4	3	3	Group 3	PAA 4
109	4	4	4	Group 3	PAA 4
110	4	3	4	Group 1	PAA 4
111	1	1	1	Group 3	PAA 4
112	5	5	5	Group 3	PAA 4

113	4	4	4	Group 3	PAA 4
114	4	4	4	Group 3	PAA 4
115	4	4	4	Group 3	PAA 4
116	4	4	4	Group 2	PAA 4
117	4	4	4	Group 1	PAA 4
118	5	5	5	Group 3	PAA 4
119	3	3	3	Group 3	PAA 4
120	5	5	5	Group 3	PAA 4
121	3	4	4	Group 3	PAA 4
122	4	3	4	Group 3	PAA 4
123	4	4	4	Group 3	PAA 4
124	1	1	1	Group 3	PAA 4
125	3	3	3	Group 3	PAA 4
126	5	5	5	Group 3	PAA 4
127	4	4	3	Group 3	PAA 4
128	2	3	2	Group 3	PAA 4
129	3	3	3	Group 3	PAA 4
130	4	5	5	Group 3	PAA 4
131	4	3	4	Group 3	PAA 4
132	4	4	4	Group 2	PAA 4
133	4	4	4	Group 2	PAA 4
134	5	5	5	Group 2	PAA 4
135	4	4	4	Group 2	PAA 4
136	5	3	4	Group 2	PAA 4
137	3	3	2	Group 1	PAA 4
138	3	4	4	Group 2	PAA 4
139	2	2	2	Group 3	PAA 4
140	5	5	5	Group 2	PAA 4
141	3	3	3	Group 3	PAA 4
142	4	5	5	Group 2	PAA 4
143	2	3	2	Group 1	PAA 4
144	3	3	3	Group 3	PAA 4
145	5	5	5	Group 2	PAA 4
146	2	1	2	Group 3	PAA 4
147	3	3	3	Group 3	PAA 4
148	3	3	3	Group 3	PAA 4
149	3	3	3	Group 1	PAA 4
150	4	4	4	Group 3	PAA 4
151	4	5	5	Group 3	PAA 4

152	2	2	2	Group 1	PAA 4
153	3	3	3	Group 3	PAA 4
154	4	4	4	Group 1	PAA 4
155	5	5	5	Group 2	PAA 4
156	5	5	5	Group 2	PAA 4
157	4	4	4	Group 2	PAA 4
158	4	4	4	Group 1	PAA 4
159	2	2	2	Group 2	PAA 4
160	5	5	5	Group 2	PAA 4
161	4	4	4	Group 2	PAA 4
162	2	3	2	Group 1	PAA 4
163	4	4	4	Group 2	PAA 4
164	4	4	4	Group 2	PAA 4
165	5	5	5	Group 3	PAA 4
166	5	5	5	Group 2	PAA 4
167	3	3	3	Group 1	PAA 4
168	5	5	5	Group 3	PAA 4
169	4	4	4	Group 2	PAA 4
170	4	4	4	Group 3	PAA 4
171	4	4	4	Group 2	PAA 4
172	4	5	5	Group 3	PAA 4
173	2	2	2	Group 1	PAA 4
174	5	5	5	Group 2	PAA 4
175	3	3	3	Group 3	PAA 4
176	5	5	5	Group 2	PAA 4
177	3	3	3	Group 3	PAA 4
178	5	5	5	Group 3	PAA 4
179	5	5	5	Group 2	PAA 4
180	2	2	2	Group 1	PAA 4
181	5	5	5	Group 3	PAA 4
182	5	5	5	Group 2	PAA 4
183	4	4	4	Group 1	PAA 4
184	4	4	4	Group 2	PAA 4
185	3	3	3	Group 1	PAA 4
186	5	5	5	Group 2	PAA 4
187	4	4	4	Group 2	PAA 4
188	2	2	2	Group 1	PAA 4
189	5	4	4	Group 2	PAA 4
190	4	5	5	Group 2	PAA 4

191	3	3	3	Group 1	PAA 4
192	4	4	4	Group 2	PAA 4
193	4	4	4	Group 2	PAA 4
194	4	4	4	Group 2	PAA 4
195	5	5	5	Group 2	PAA 4
196	5	5	5	Group 2	PAA 4
197	5	5	5	Group 2	PAA 4
198	5	5	5	Group 2	PAA 4
199	5	5	5	Group 2	PAA 4

3.2.3 Analysis of the Result

This section examines the agreement between the scores generated by the developed algorithm and those by each of the two physicians. In this dissertation we used Kappa statistic to give the agreement between physicians and the system. A Kappa score ranges between 1 which shows full agreement and 0 which shows no agreement. In the literature there is no consensus about the interpretation of Kappa. However [79] which is commonly used suggests that there is excellent agreement if the Kappa coefficient is greater than 0.75, poor agreement for Kappa coefficient less than 0.4, and fair to good agreement for kappa coefficient between 0.40 and 0.75 as shown in Table 7.

Table 7. Interpretation of Kappa.

Kappa	**Agreement**
<0.45	Poor Agreement
0.45-0.75	Fair Agreement
>0.75	Excellent Agreement

Table 8, 9 and 10 summarizes the number of matches between the decision of the system and the two physicians.

Table 8.Confusion Matrix of System by Physician 1

		Physician 1					
MAS System	**Frequency**	**1**	**2**	**3**	**4**	**5**	**Total**
	1	3	0	0	0	0	3
	2	2	15	5	0	0	22
	3	1	2	37	5	1	46
	4	0	0	11	52	12	75
	5	0	0	1	2	50	53
	Total	6	17	54	59	63	199

Table 9. Confusion Matrix of System by Physician 2

		Physician 2					
MAS System	**Frequency**	**1**	**2**	**3**	**4**	**5**	**Total**
	1	3	0	0	0	0	3
	2	1	21	0	0	0	22
	3	0	3	40	3	0	46
	4	0	0	7	59	9	75
	5	0	0	0	4	49	53
	Total	4	24	47	66	58	199

Table 10. Confusion Matrix of Physician 1 by Physician 2

		Physician 2					
Physician 1	**Frequency**	**1**	**2**	**3**	**4**	**5**	**Total**
	1	4	1	1	0	0	6
	2	0	16	1	0	0	17
	3	0	7	38	9	0	54
	4	0	0	5	52	2	59
	5	0	0	2	5	56	63
	Total	4	24	47	66	58	199

The estimate of agreements is as follows: Kappa = 0.8014 for physician 1 and the developed system; Kappa = 0.8802 for physician 2 and the developed system; Kappa = 0.8452 for physician 1 and physician 2. These coefficients suggest excellent agreement between the system and the physicians. The asymptotic standard error (ASE) is also computed, as well as 95% confidence bounds. Those values are computed using Weighted Kappa which considers disagreement close to the diagonals less heavily than disagreement further away from the diagonals. The simple Kappa is also provided. The results of these two methods are shown in Table 11, 12 and 13.

Table 11. Kappa Statistics between Physician 1 vs. MAS System.

Kappa Statistics between Physician 1 vs. MAS System				
Statistic	**Value**	**ASE**	**95% Confidence Limits**	
Simple Kappa	0.7114	0.0393	0.6344	0.7884
Weighted Kappa	**0.8014**	0.0292	0.7441	0.8586

Table 12. Kappa Statistics between Physician 2 vs. MAS System.

Kappa Statistics between Physician 2 vs. MAS System				
Statistic	**Value**	**ASE**	**95% Confidence Limits**	
Simple Kappa	0.8139	0.0335	0.7482	0.8796
Weighted Kappa	**0.8802**	0.0224	0.8363	0.9242

Table 13. Kappa Statistics between Physician 1 vs. Physician 2

Kappa Statistics between Physician 1 vs. Physician 2				
Statistic	**Value**	**ASE**	**95% Confidence Limits**	
Simple Kappa	0.7742	0.0356	0.7043	0.8441
Weighted Kappa	**0.8452**	0.0263	0.7937	0.8967

3.3 Summary

I have developed a methodology that enables agents in a multi-agent environment to find similar patients. I implemented the system using JADE and FuzzyJess software packages and tested the system using four agents. Using real patient data, the results show that the agents effectively worked together to find similar patients. The experimental results indicate that the developed approach has excellent agreement with the decision of two physicians.

CHAPTER 4

IDENTIFYING ADVERSE DRUG REACTION SIGNAL PAIRS BY THE MULTI-AGENT SYSTEM

Detecting ADR signal pairs is technically a complex problem. This is the case if we realistically assume that there does not exist a set of rules that are readily acceptable to all human experts (e.g., physicians, epidemiologists and pharmacists). The parameters used in identifying the signal pairs are really a vague, subjective measure rather than an objective measure. Furthermore, human experts often disagree one another owing to their knowledge and experiences and there is no "ground truth" to indicate which physician is right or wrong. Because of this and other limitations, current surveillance systems are not ideal for rapidly identifying rare unknown ADRs. A more effective system is needed as the electronic patient records become more and more easily accessible in various health organizations such as hospitals, medical centers and insurance companies. These data provide a new source of information that has great potentials to detect ADR signals much earlier.

In this chapter I presented the details a multi-agent system and the detection rules I recently developed [66]. The aim of the system is to help health organization systems achieve earlier identification of potential ADR signal pairs. The PAA is equipped with the rule-based reasoning capability. More specifically, we have designed and developed a fuzzy inference engine for finding the causal relationship between a drug and an adverse reaction. This engine is called *Fuzzy ADR Signal Pairs Detector*. The Detector is a fuzzy rule-based system.

4.1 Cues for Drug Causality Assessment

My ADR signal pairs detection methodology is based on five cues: temporal association, rechallenge, dechallenge, abnormality in laboratory tests and other explanation. The cues represent the higher-level information that is obtained from the patients' elementary data. The cues employed to evaluate the causality are abstracted from the description in [3] and summarized in

Table **14**.

Table 14. Cues for Drug Causality Assessment.

Cue	Cue Type	Cue Values	Abstraction Method
Temporal Association	Fuzzy	Likely, Probable, Possible, Unlikely	Fuzzy Reasoning
Dechallenge	Fuzzy	Likely, Probable, Possible, Unlikely	Fuzzy Reasoning
Rechallenge	Fuzzy	Likely, Possible, Unlikely	Fuzzy Reasoning
Abnormality in laboratory tests	Fuzzy	Low, Medium, High	Fuzzy Reasoning
Other explanations	Nominal	Yes, No	Crisp Reasoning

Temporal Association is the cue that reflects the relationship between taking the drug and the appearance of a possible adverse event. What happens after the drug is stopped (Dechallenge) or re-initiated (Rechallenge) also provides important cues. Temporal association, rechallenge and dechallenge are all time-related. For a particular pair, their values can be extracted from a specific patient case using fuzzy sets and rules.

The Abnormality in Laboratory Tests is a fuzzy variable that is also extracted from patient's laboratory test results. It describes the degree of the abnormality of a laboratory test. Other Explanations denotes alternative explanations by concurrent diseases or other drugs. The symptoms of an underlying disease or the one caused by another drug which is taken concurrently with the drug of interest cannot be differentiated from those of a potential ADR and thus the obtained cues (e.g., temporal association) values do not necessarily imply any degree of causality.

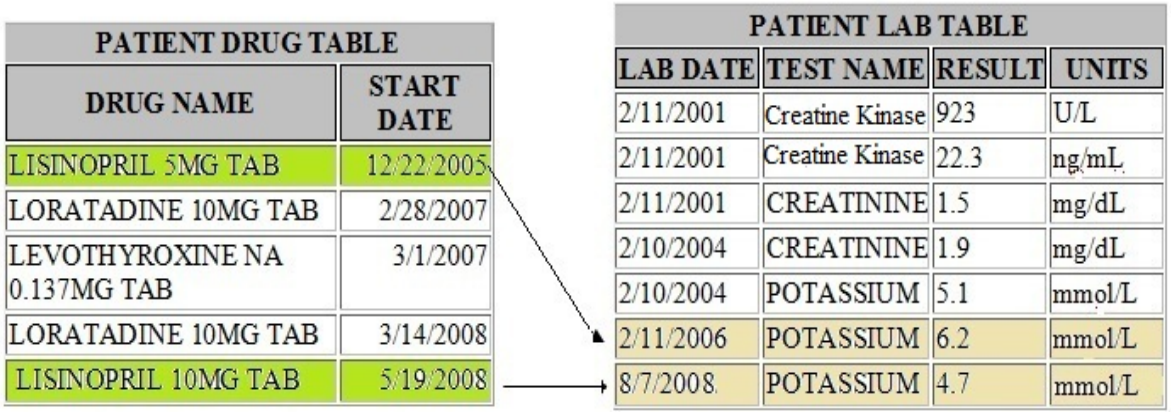
To get some of those cues, we used the ICD-9-CM (International Classification of Diseases, Ninth Edition, Clinical Modification) and CPT codes (Physicians' Current Procedural Terminology), two widely used coding standards in the United States. Using these codes, every clinical condition of the patients, symptoms that appears one patients and any treatment required or done by a health provider has a unique code**.**

The detection rules that use the above cues were acquired through the joint efforts of the engineering and medical team members. There are a total of 52 detection rules. These rules will be distributed among the PAAs. This will be explained later in the experimental part. In the real life each physician will provide his PAA with the preliminary detection rules based on his experience through Graphical User Interface and through the time PAA will learn new rules from other PAAs.

4.1.1 Laboratory Test Abnormality

As a first step the abnormality of laboratory tests are studied and analyzed. The abnormality of the laboratory tests is a very important factor in ADR signal pair detection. Most people with an adverse event in the early stages feel well and have no specific

findings on physical examination that would inform a health care provider. This places a large emphasis on laboratory test results that will be used to help diagnose patients and predict a patient's response to certain medications. A signal pair is recognized if the potential ADR occurs after one of the start dates of the drugs within a certain period of time (i.e., 120 days). Lisinopril was selected as the target drug for this ADR signal generation study. Figure 24 shows that two pairs are found within one case. The laboratory tests occur after the first start date of Lisinopril. Thus a pair is formed between the drug and the closest occurrence of the elevation laboratory test. The potassium laboratory test which occurs before all the start dates of Lisinopril does not form a pair with the drug.



PATIENT DRUG TABLE

DRUG NAME	START DATE
LISINOPRIL 5MG TAB	12/22/2005
LORATADINE 10MG TAB	2/28/2007
LEVOTHYROXINE NA 0.137MG TAB	3/1/2007
LORATADINE 10MG TAB	3/14/2008
LISINOPRIL 10MG TAB	5/19/2008

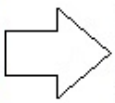
PATIENT LAB TABLE

LAB DATE	TEST NAME	RESULT	UNITS
2/11/2001	Creatine Kinase	923	U/L
2/11/2001	Creatine Kinase	22.3	ng/mL
2/11/2001	CREATININE	1.5	mg/dL
2/10/2004	CREATININE	1.9	mg/dL
2/10/2004	POTASSIUM	5.1	mmol/L
2/11/2006	POTASSIUM	6.2	mmol/L
8/7/2008	POTASSIUM	4.7	mmol/L

Figure 24. Sample signal pairs within a patient case

The patients' database normally contains different refill dates. We can get the drug start date from those refill dates for diagnosing purposes based on the following critical: If the refill date is after 150 days of previous refill date, then this refill date will be considered as a new start date that should be used for signal pairs finding. Otherwise the refill date will not be considered as a new start date and it will not be used in signal pairs finding progress. Figure 25 shows an example of such situation.

PATIENT DRUG TABLE	
DRUG NAME	Fill DATE
LISINOPRIL 40MG TAB	5/26/2007
LISINOPRIL 40MG TAB	2/19/2008
LISINOPRIL 40MG TAB	4/4/2008
LISINOPRIL 40MG TAB	8/24/2009
LISINOPRIL 40MG TAB	1/15/2010



DRUG NAME	START DATE
LISINOPRIL 40MG TAB	5/26/2007
LISINOPRIL 40MG TAB	2/19/2008
LISINOPRIL 40MG TAB	8/24/2009

Figure 25. Sample start dates out of refills dates.

After a signal pair is found, its degree of association is assessed using fuzzy rules. Abnormalities of the laboratory tests are indicator of extensive problems in the patient. The more the elevation, the more the strength of the ADR signal.

In this study, the hyperkalemia is the ADR of interest. Hyperkalemia is an excessive level of potassium in the bloodstream. Potassium laboratory test reflects the functionality of the muscles, heart, and nerves. Potassium laboratory test will give an essential cue about this ADR. To get the degree of the abnormality of the potassium laboratory test, the laboratory result will be converted to its abnormality value. The abnormality value will be zero for a laboratory result in the normal ranges. For other values, the abnormality value will be calculated using fuzzy rules. The laboratory results will be the input to the system and the abnormality value will be the output. Both the input and the output are fuzzy variables. There are three fuzzy sets for the input variable Potassium Laboratory Test Value- Low, Medium, and High (Figure 26), and three fuzzy

sets for the output variable Abnormality in Potassium Laboratory Test- Low, Medium, and High (Figure 27). Here are the rules:

- If Potassium Laboratory Test Value is *Low*, then Abnormality in Potassium Laboratory Test is *Low*.
- If Potassium Laboratory Test Value is *Medium*, then Abnormality in Potassium Laboratory Test is *Medium*.
- If Potassium Laboratory Test Value is *High*, then Abnormality in Potassium Laboratory Test is *High*.

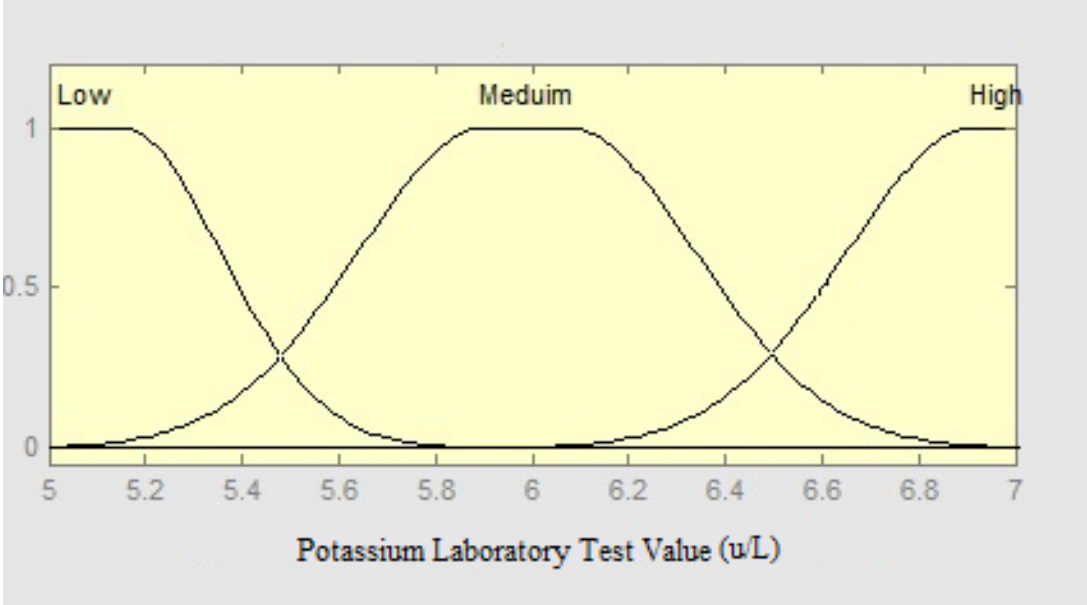


Figure 26. Fuzzy sets for Potassium Laboratory Test Value

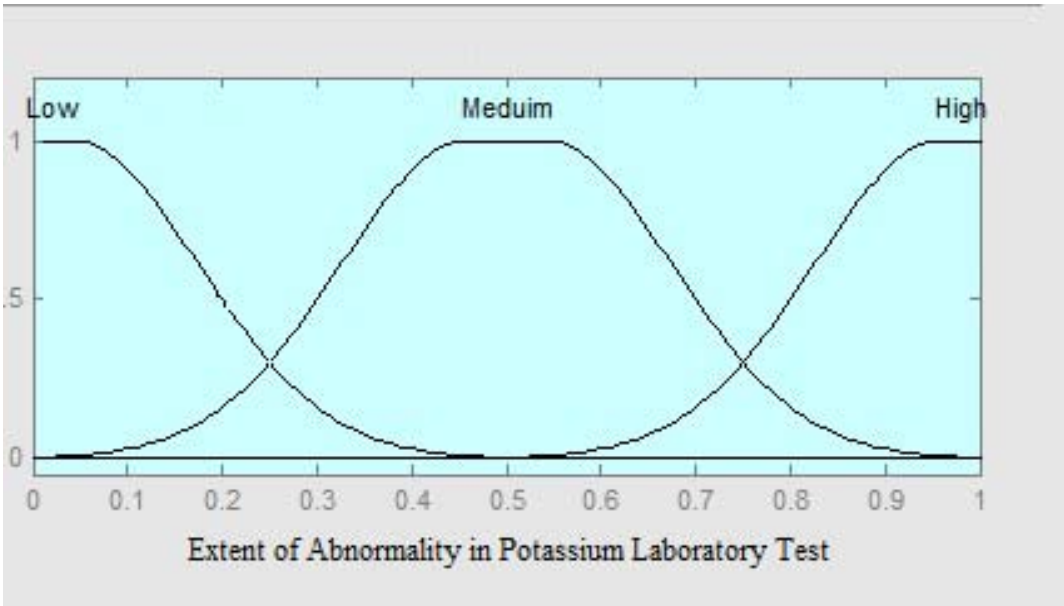


Figure 27. Fuzzy sets for Abnormality in Potassium Laboratory Test

4.1.2 Laboratory Test Temporal Association

Laboratory test temporal association is determined by the length of duration between a drug start date and a Laboratory result elevation occurrence date. Based on the experience of the physicians on the team, I define nine fuzzy rules of the Potassium Laboratory Test Temporal Association. Here are the rules:

- If Time Duration between drug-taking and the appearance of the elevated potassium lab is *Short* and Abnormality in Potassium Laboratory Test is *High,* then Potassium Laboratory Test Temporal Association is *Likely*.
- If Time Duration between drug-taking and the appearance of the elevated potassium lab is *Short* and the Abnormality in Potassium Laboratory Test is *Medium,* then Potassium Laboratory Test Temporal Association is *Possible*.

- If Time Duration between drug-taking and the appearance of the elevated potassium lab is *Short* and Abnormality in Potassium Laboratory Test is *Low*, then Potassium Laboratory Test Temporal Association is *Unlikely*.

- If Time Duration between drug-taking and the appearance of the elevated potassium lab is *Medium* and Abnormality in Potassium Laboratory Test is *High,* then Potassium Laboratory Test Temporal Association is *Likely*.

- If Time Duration between drug-taking and the appearance of the elevated potassium lab is *Medium* and Abnormality in Potassium Laboratory Test is *Medium*, then Potassium Laboratory Test Temporal Association is *Possible*.

- If Time Duration between drug-taking and the appearance of the elevated potassium lab is *Medium* and Abnormality in Potassium Laboratory Test is *Low,* then Potassium Laboratory Test Temporal Association is *Unlikely*.

- If Time Duration between drug-taking and the appearance of the elevated potassium lab is *Long* and Abnormality in Potassium Laboratory Test is *High,* then Potassium Laboratory Test Temporal Association is *Possible*.

- If Time Duration between drug-taking and the appearance of the elevated potassium lab is *Long* and Abnormality in Potassium Laboratory Test is *Medium*, then Potassium Laboratory Test Temporal Association is *Unlikely*.

- If Time Duration between drug-taking and the appearance of the elevated potassium lab is *Long* and Abnormality in Potassium Laboratory Test is *Low*, then Potassium Laboratory Test Temporal Association is *Unlikely*.

Both Potassium Time Duration and Potassium Laboratory Test Temporal Association are fuzzy variables characterized by triangular fuzzy sets. Figure 28 and Figure 29 show the fuzzy sets for both fuzzy variables, respectively. The universe course is set 15 to 130 days. That is, if the apparent ADR occurs between 15 days and 130 days after the drug start date, the pair is considered as having temporal association.

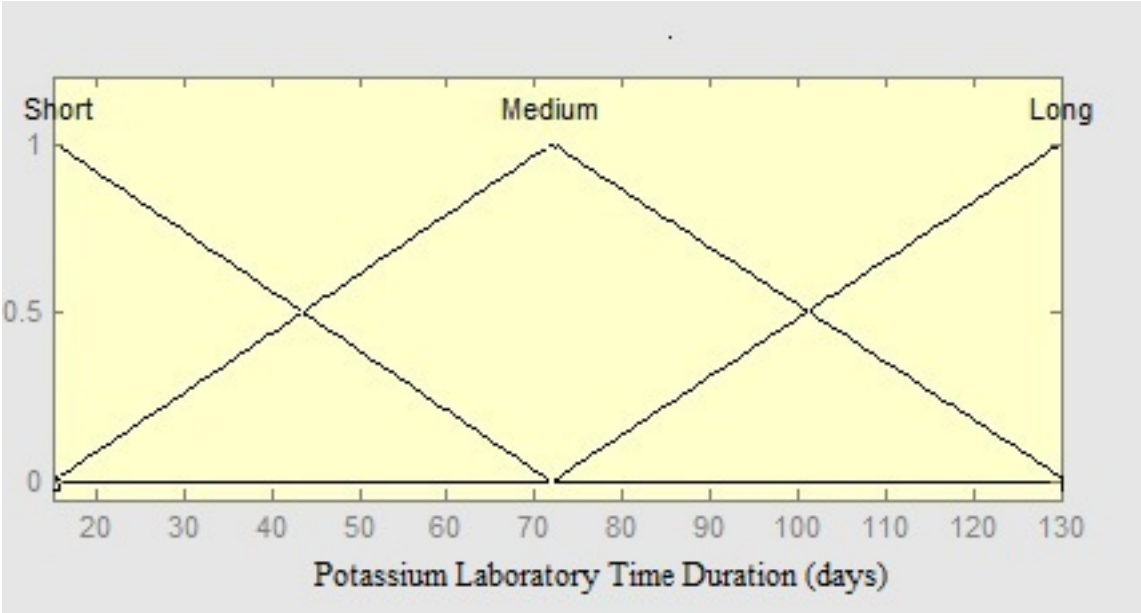


Figure 28. Fuzzy sets for Potassium Laboratory Test Time Duration

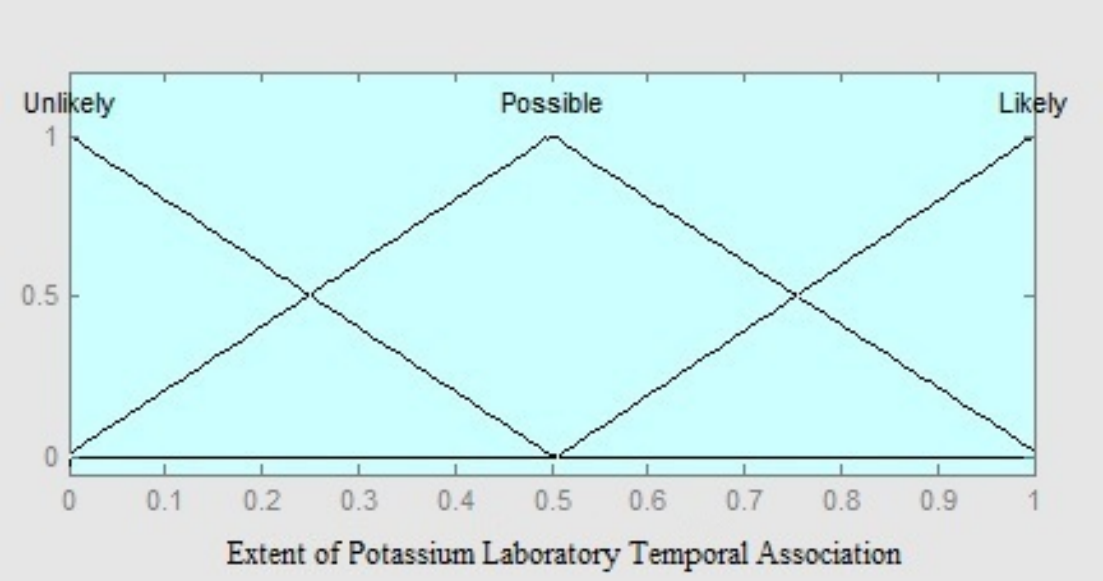


Figure 29. Fuzzy sets for Potassium Laboratory Test Temporal Association

The above rules are used if the laboratory test is done between the drug start date and the drug stop date (if it is available) but if the laboratory test is done after both the drug start date and the drug stop date, another condition should be satisfied in order to use the above fuzzy rules. The laboratory test should be within certain period after the stop date, i.e., 60 days to be considered as a pair with the medication. This period was selected based on the opinion of the physician our team.

Creatinine laboratory test is also used in calculating the ADR signal pair strength. This test measures the amount of Creatinine in blood. This test is used to evaluate kidney function. The rules used to determine Abnormality in Creatinine Laboratory Test are as follows,

- If Creatinine Laboratory Test Value is *Low*, then Abnormality in Creatinine Laboratory Test is *Low*.

- If Creatinine Laboratory Test Value is *High*, then Abnormality in Creatinine Laboratory Test is *High*.

The two fuzzy variables used to determine Abnormality in Creatinine Laboratory Test are characterized by bell fuzzy sets (Figure 30 and Figure 31).

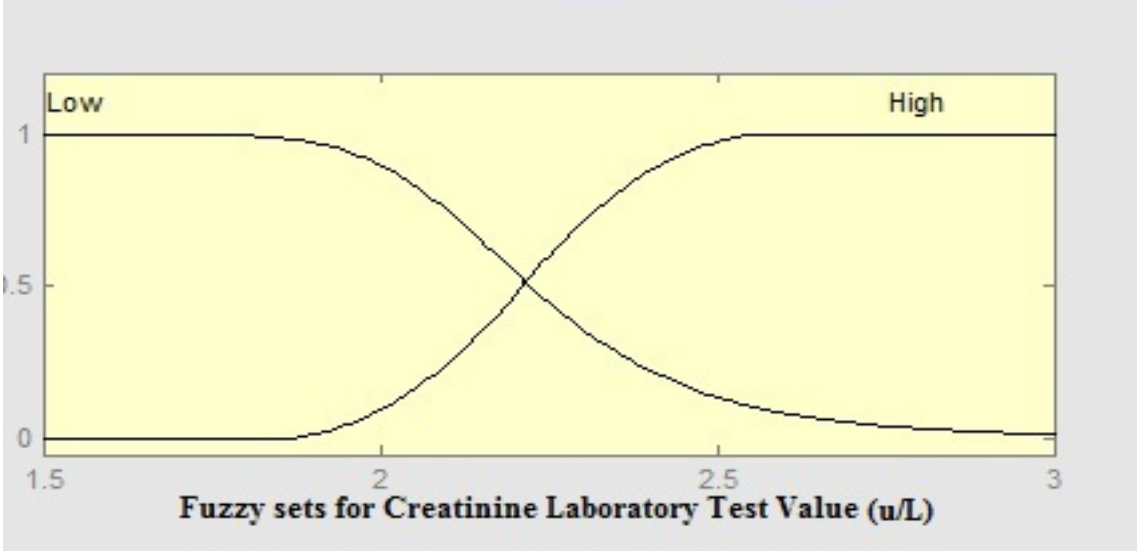


Figure 30. Fuzzy sets for Creatinine Laboratory Test Value.

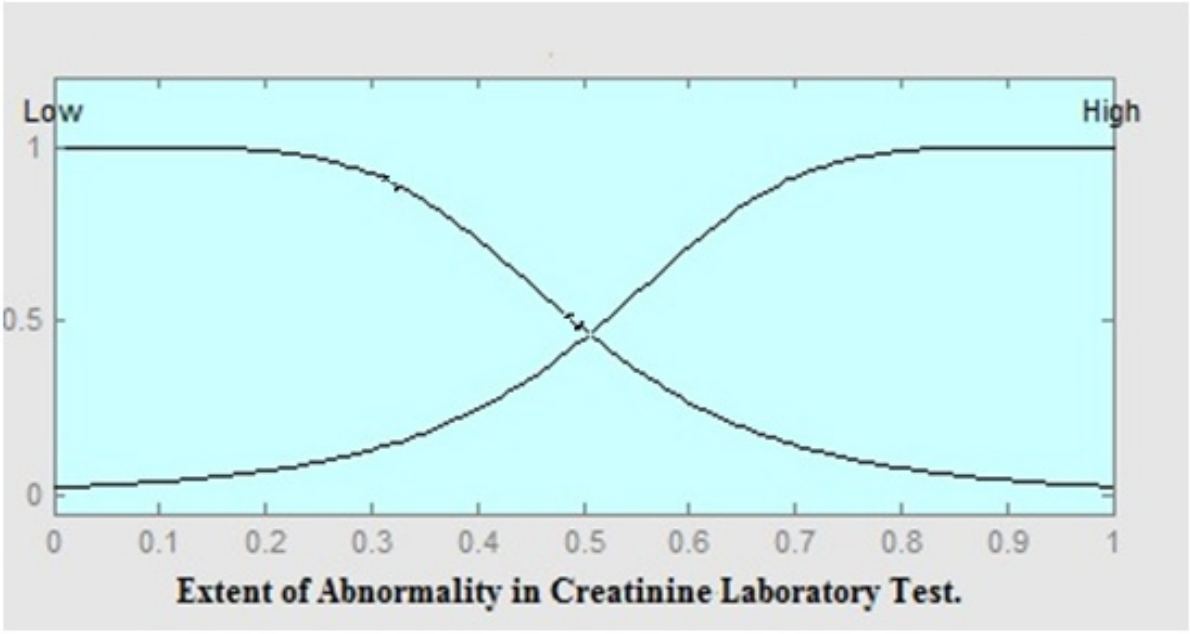


Figure 31. Fuzzy sets for Abnormality in Creatinine Laboratory Test.

The Creatinine Temporal Association is calculated in the same way as the Potassium Temporal Association. Based on the experience of the physicians on the team, I define six fuzzy rules of the Creatinine Laboratory Temporal Association. Here are the rules:

- If Time Duration between drug-taking and the appearance of the elevated Creatinine lab is *Short* and Abnormality in Potassium Laboratory Test is *High,* then Creatinine Laboratory Test Temporal Association is *Likely*.
- If Time Duration between drug-taking and the appearance of the elevated Creatinine lab is *Short* and Abnormality in Creatinine Laboratory Test is *Low*, then Creatinine Laboratory Test Temporal Association is *Possible*.

- If Time Duration between drug-taking and the appearance of the elevated Creatinine lab is *Medium* and Abnormality in Creatinine Laboratory Test is *High,* then Creatinine Laboratory Test Temporal Association is *Likely*.

- If Time Duration between drug-taking and the appearance of the elevated Creatinine lab is *Medium* and Abnormality in Creatinine Laboratory Test is *Low,* then Creatinine Laboratory Test Temporal Association is *Possible*

- If Time Duration between drug-taking and the appearance of the elevated Creatinine lab is *Long* and Abnormality in P Creatinine Laboratory Test is *High*, then Creatinine Laboratory Test Temporal Association is *Possible*.

- If Time Duration between drug-taking and the appearance of the elevated Creatinine lab is *Long* and Abnormality in Creatinine Laboratory Test is *Low,* then Creatinine Laboratory Test Temporal Association is *Unlikely*.

Both Creatinine Time Duration and Creatinine Laboratory Test Temporal Association are fuzzy variables characterized by triangular fuzzy sets. Figure 32 and Figure 33 show the fuzzy sets for both fuzzy variables, respectively.

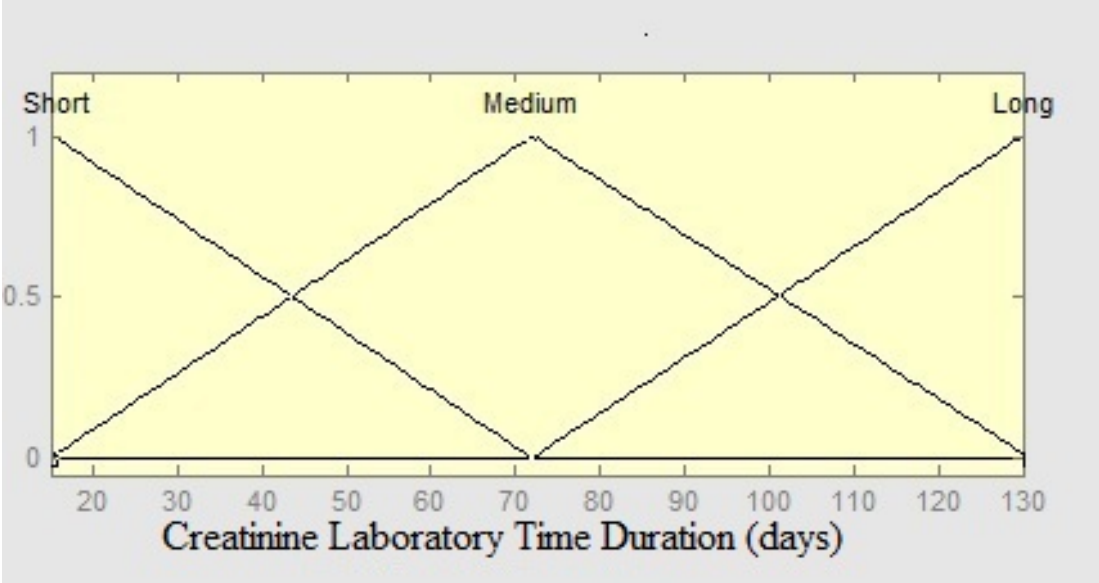


Figure 32. Fuzzy sets for Creatinine Laboratory Test Time Duration.

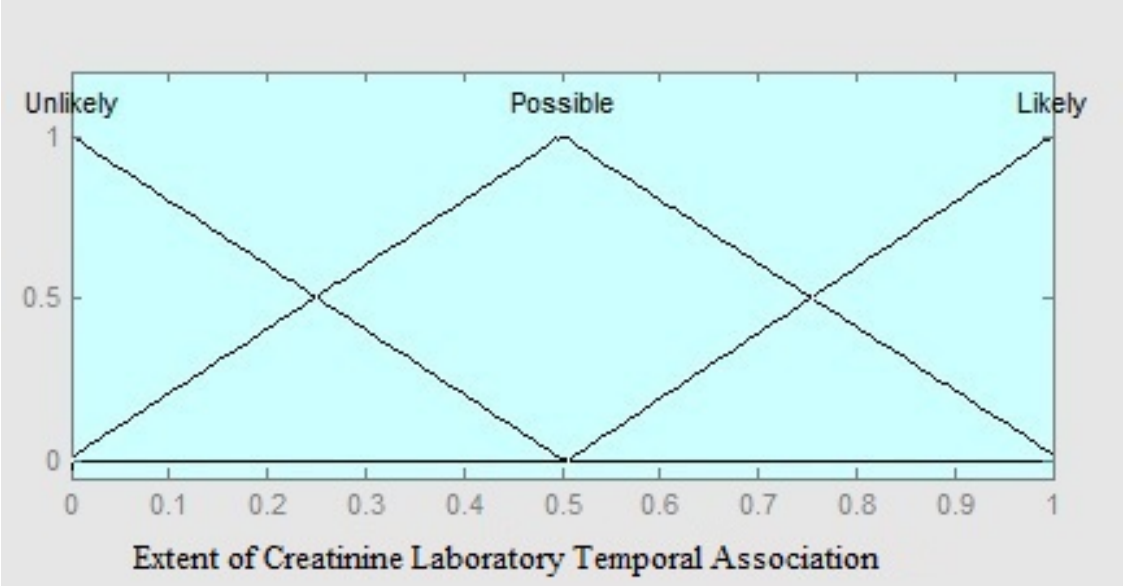


Figure 33. Fuzzy sets for Creatinine Laboratory Test Temporal Association.

The strength of Total Laboratory Test Temporal Association is founded using ten fuzzy rules. Here are the rules:

- If Potassium Laboratory Test Temporal Association is *Likely* and Creatinine Laboratory Test Temporal Association is available and it is *Likely,* then Total Laboratory Test Temporal Association is *Likely*.

- If Potassium Laboratory Test Temporal Association is *Likely* and Creatinine Laboratory Test Temporal Association is available and it is *Possible,* then Total Laboratory Test Temporal Association is *Probable*.

- If Potassium Laboratory Test Temporal Association is *Likely* and Creatinine Laboratory Test Temporal Association is available and it is *Unlikely,* then Total Laboratory Test Temporal Association is *Possible*.

- If Potassium Laboratory Test Temporal Association is *Possible* and Creatinine Laboratory Test Temporal Association is available and it is *Likely,* then Total Laboratory Test Temporal Association is *Likely*.

- If Potassium Laboratory Test Temporal Association is *Possible* and Creatinine Laboratory Test Temporal Association is available and it is *Possible,* then Total Laboratory Test Temporal Association is *Probable*.

- If Potassium Laboratory Test Temporal Association is *Possible* and Creatinine Laboratory Test Temporal Association is available and it is *Unlikely,* then Total Laboratory Test Temporal Association is *Possible*.

- If Potassium Laboratory Test Temporal Association is *Unlikely* and Creatinine Laboratory Test Temporal Association is available and it is *Likely,* then Total Laboratory Test Temporal Association is *Probable*.

- If Potassium Laboratory Test Temporal Association is *Unlikely* and Creatinine Laboratory Test Temporal Association is available and it is *Possible,* then Total Laboratory Temporal Association is *Possible*.

- If Potassium Laboratory Test Temporal Association is *Unlikely* and Creatinine Laboratory Test Temporal Association is available and it is *Unlikely,* then Total Laboratory Test Temporal Association is *Unlikely*.

- If Creatinine Laboratory Test Temporal Association is unavailable, then Total Laboratory Test Temporal Association is equal to Potassium Laboratory Test Temporal Association.

The total Laboratory Test Temporal Association which is composed of Potassium laboratory test and Creatinine laboratory test is a fuzzy variable represented by four Gaussian membership functions categorized as ”Likely,” ”Probable,” ”Possible,” and ”Unlikely” as shown in Figure 34.

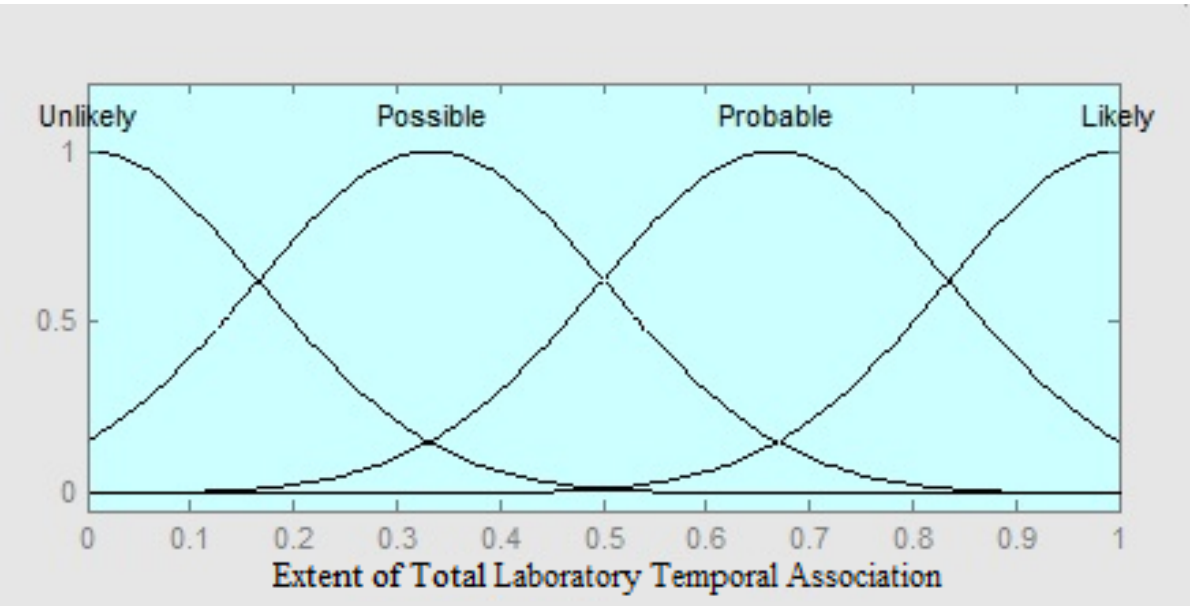


Figure 34. Fuzzy sets for Total Laboratory Test Temporal Association.

If the Creatinine laboratory test is elevated before and after taking the suspect medication, then the elevation of the Creatinine laboratory test will be considered as another explanation for the elevated potassium and this will decreases the ADR causality by certain value specified by the agent and his physician.

4.1.3 Medication Dechallenge

Medication Dechallenge refers to the relationship between discontinuity of the drug and abatement of the apparent ADR. Dechallenge is a fuzzy variable characterized by triangular fuzzy sets labeled as ”*Unlikely*,” ”*Possible*,” ”*Probable*,” and ”*Likely*” as shown in Figure 35.

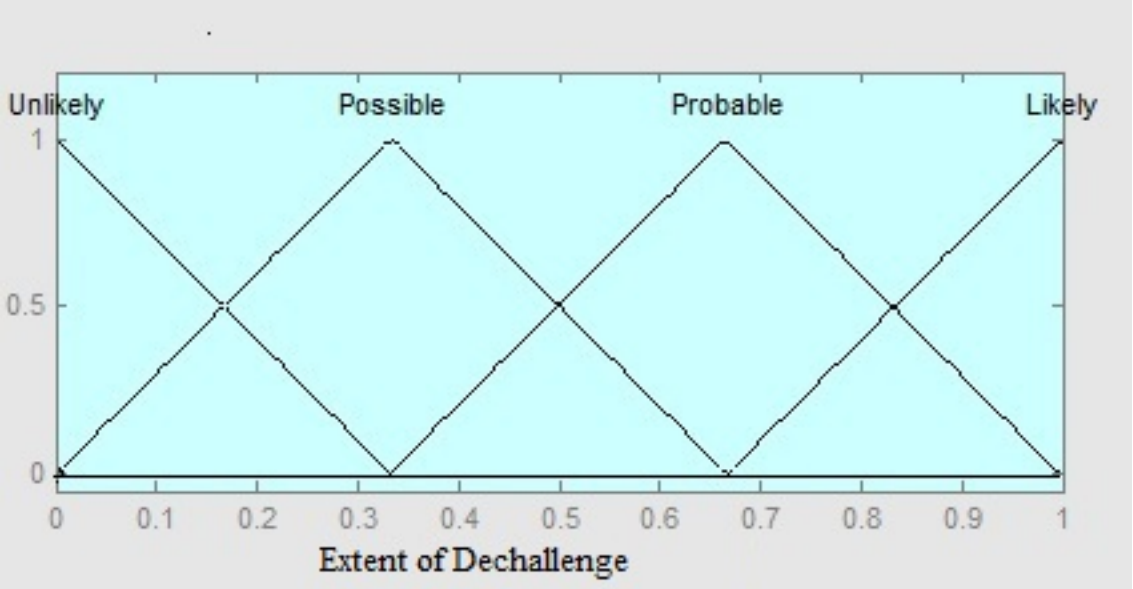


Figure 35. Fuzzy sets for Dechallenge

We cannot directly evaluate dechallenge of a pair since the drug stop date is usually unavailable in electronic health databases. However, we can indirectly assess the existence of dechallenge of a pair if a symptom occurs after the drug start date and another drug in the same class was prescribed after the appearance of the symptom. This is because the physicians often stop a drug and prescribe another drug in the same class to avoid apparent adverse effect found on a patient.

Also, if the temporal association is *Unlikely*, then Dechallenge is *Unlikely*. In some cases the patient stops taking the drug for a period greater than 150 days then the stop date can be considered as the previous start date plus the number of days the patient took that medication. In such cases six fuzzy rules will be applied to get the strength of dechallenge. Here are the rules:

- If Time Duration between stopping the drug and the abatement of the apparent symptoms is *Very Small*, then Dechallenge is *Likely*.
- If Time Duration between stopping the drug and the abatement of the apparent symptoms is *Small*, then Dechallenge is *Probable*.
- If the Time Duration between stopping the drug and the abatement of the symptoms is Large then Dechallenge is Possible.
- If the Time Duration between stopping the drug and the abatement of the symptoms is Very Large then Dechallenge is Unlikely.
- If the reaction does not abate after withdrawal of drug then Dechallenge is Unlikely.
- If the reactions occurred again after the drug was discontinued then Dechallenge is Unlikely.

Time Duration between stopping the drug and the abatement of the symptoms is a fuzzy variable represented by triangular membership functions (Figure 36).

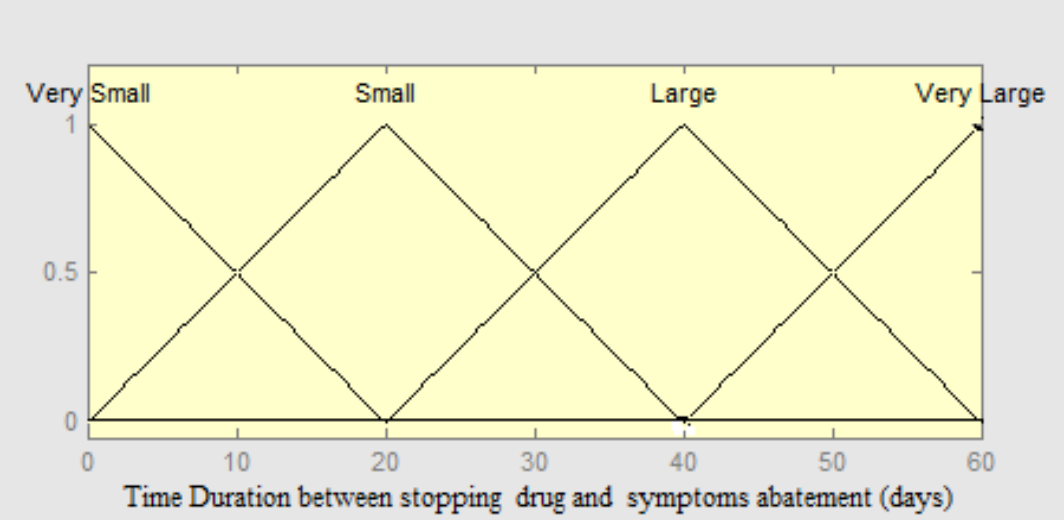


Figure 36. Fuzzy sets for Time Duration between stopping drug and symptom abatement

4.1.4 Medication Rechallenge

Medication Rechallenge depicts the relationship between re-introduction of the drug discontinued before and recurrence of an ADR. Rechallenge is determined by the temporal associations of the two consecutive occurrences of the same pair one after taking the medication and the other one after the reintroduction of the medication. Let Temporal Association of time t_1 and Temporal Association of time t_2 represent the two temporal associations, respectively. Then the following fuzzy rules are used to assess the value of the Rechallenge of a pair.

- If Temporal Association of time t_1 is *Likely* and Temporal Association of time t_2 is *Likely* Then Rechallenge is *Likely*.

- If Temporal Association of time t_1 1 is *Likely* and Temporal Association of time t_2 is *Possible* Then Rechallenge is *Likely*.

- If Temporal Association of time t_1 is *Likely* and Temporal Association of time t_2 is *Unlikely* Then Rechallenge is *Possible*.

- If Temporal Association of time t_1 is *Possible* and Temporal Association of time t_2 is *Likely* Then Rechallenge is *Likely*.

- If Temporal Association of time t_1 is *Possible* and Temporal Association of time t_2 is *Possible* Then Rechallenge is *Possible*.

- If Temporal Association of time t_1 is *Possible* and Temporal Association of time t_2 is *Unlikely* Then Rechallenge is *Possible*.

- If Temporal Association of time t_1 is *Unlikely* and Temporal Association of time t_2 is *Likely* Then Rechallenge is *possible*.

- If Temporal Association of time t_1 is *Unlikely* and Temporal Association of time t_2 is *Possible* Then Rechallenge is *Possible*.

- If Temporal Association of time t_1 is *Unlikely* and Temporal Association of time t_2 is *Unlikely* Then Rechallenge is *Unlikely*.

Both Temporal Association and Rechallenge are fuzzy variables. The Temporal Association is defined in Figure 29. Rechallenge is fuzzified by three fuzzy sets Likely, Possible and Unlikely (Figure 37)

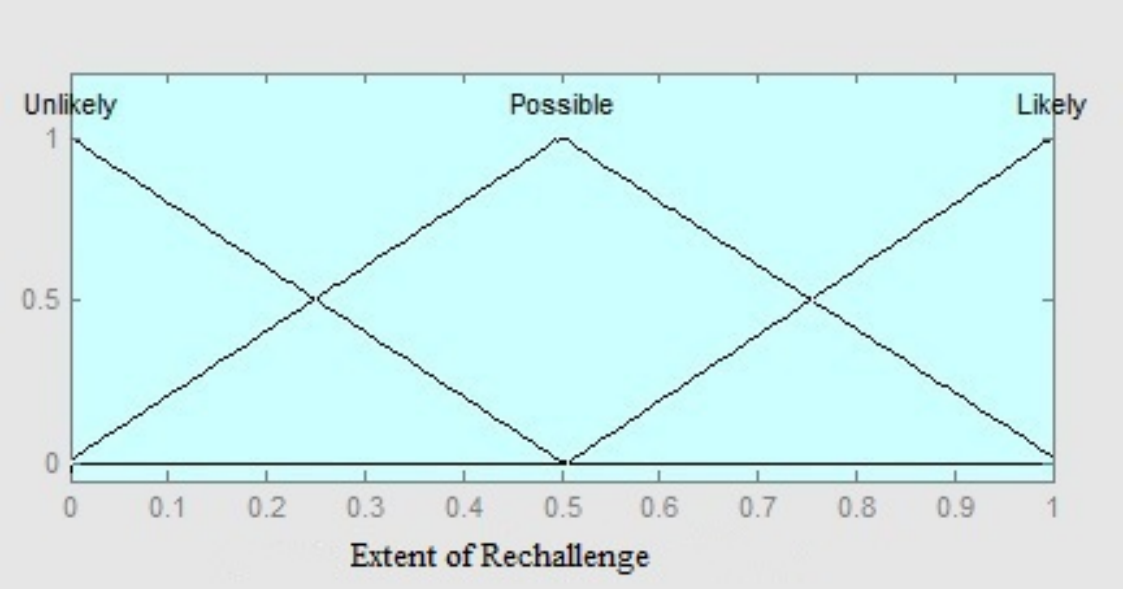


Figure 37. Fuzzy sets for Rechallenge.

4.1.5 Causality Assessment

Causality assessment determines the likelihood that a drug causes a suspected ADR. The strength of the Causality assessment between the drug and an adverse effect is called Degree of Causality. The Degree of Causality is calculated as a linear combination of the effect of the cues. The aggregated Degree of Causality is calculated as the following:

Degree of Causality = w_1 x Laboratory Temporal Association + w_2 x Dechallenge + w_3 x Rechallange

where $w_1 + w_2 + w_3 = 1$

The selection of the coefficients for combining similarities is a crucial issue. The weights control the importance of the corresponding cues. In case of equally importance,

the weights will have the value 1/3. The causality scores are between 0 and 1 and a higher score represents a higher similarity.

4.2 Other Factors in Causality Assessment

Degree of Causality can be affected by other reasons that can lead to the same apparent ADR symptom. This includes two factors - other medications and other ICD-9 codes.

4.2.1 Other Medications

Excess potassium in the bloodstream can result from certain medications. Examples of such medications are:

- Potassium supplements.
- Spironolactone (diuretic drug group).
- Triamterene (diuretic drug group).
- Amiloride (Diuretic drug group).
- Eplerenone.
- Pentamidine (antimicrobial drug group).
- Trimethoprim (trimethoprim/sulfa – antimicrobial drug group).
- Ketoconazole (antimicrobial drug group).
- NSAIDS – non-steroidal anti-inflamatory agents.
- Heparin.
- Cyclosporin.

Having such medications in the patient database will lower the strength of Degree of Causality.

The reduction is based on the following rules:

- If one medication was founded beside the interested drug then Degree of Causality will be lowered by 0.5
- If two medications were founded beside the interested drug then Degree of Causality will be lowered by 0.25
- If more than two medications were founded, no ADR signal pair will be considered.

4.2.2 Concurrent Diseases

Diseases of the kidneys or adrenal glands will affect the strength of Degree of Causality. Diseases are found in patients Databases as ICD-9 codes so the existence of certain ICD-9 codes will affect the Degree of Causality.

The ICD-9 provides codes to classify diseases and a wide variety of signs, symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or disease. For example, if a patient is diagnosed with Hepatitis C, it will be given the ICD-9 code (070.51). The ICD-9 codes will stay in the patient databases no matter the diagnosis is for something acute or chronic.

Since different ICD-9 codes may represent the same (or similar) diagnoses, we also clustered them into a manageable number of categories based on the Clinical Classifications System (CCS). Searching patient CCS codes can lead to Other Explanation.

For example most cases of hyperkalemia are caused by disorders that reduce the kidney's ability to get rid of potassium. This may result from disorders such as acute kidney failure (CCS code 157) or chronic kidney failure (CCS code 158). Having such a CCS category will reduce the Degree of Causality by 0.50. This is because such a CCS Category will offer another explanation of the manifest symptoms. Here are the rules of score reduction:

- If one CCS code that gives other explanation to the suspect ADR appears in the patient records then the Degree of Causality will be reduced by 0.5.
- If two CCS codes that give other explanations to the suspect ADR appears in the patient records then the Degree of Causality will be reduced by 0.75.
- If more than two CCS codes that give other explanation to the suspect ADR appears in the patient records then the Degree of Causality will be reduced to 0 (meaning no signal pairs found).

Some CCS categories such as hyperkalemia (CCS code 55) will support and increase the Degree of Causality if it has been reported after taking the medication of this study. However this category shouldn't appear prior to medication-taking. The increase of the Degree of Causality is based on CCS Temporal Association value which describes the time duration between taking the drug and the appearance of the symptoms (i.e., the ICD-9 code) which is CCS Time Duration. There are four triangular fuzzy sets for the variable CCS Time Duration – *Very Short, Short, Long* and *Very Long* and four triangular fuzzy

sets to define the variable CCS Temporal Association: *Likely, Probable, Possible* and *Unlikely.*

Figure 38 and Figure 39 show the fuzzy sets for CCS Time Duration and CCS Temporal Association, respectively.

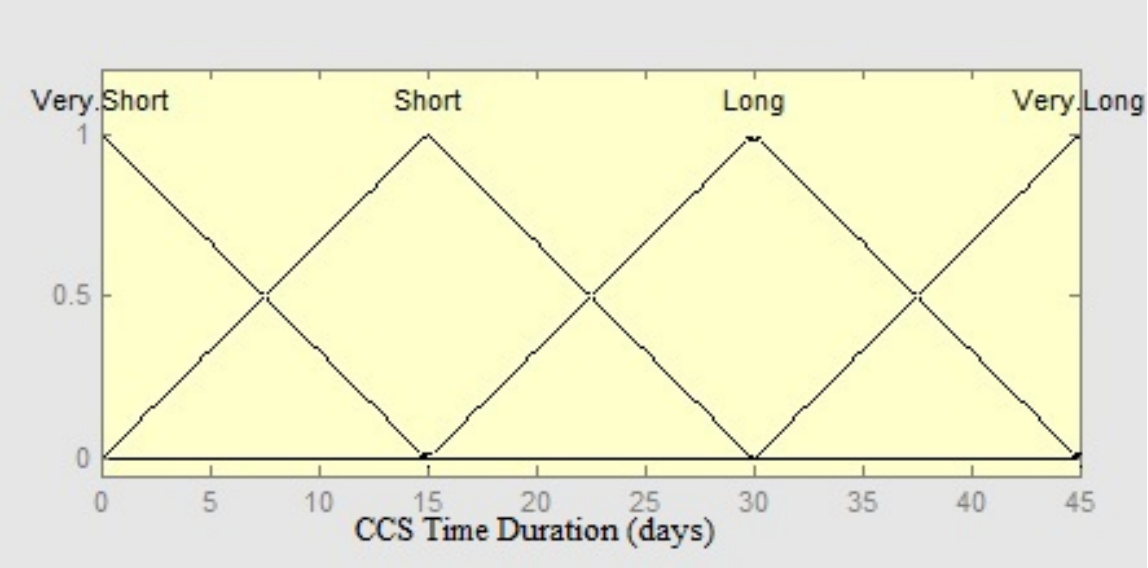


Figure 38. Fuzzy sets for CCS Time Duration.

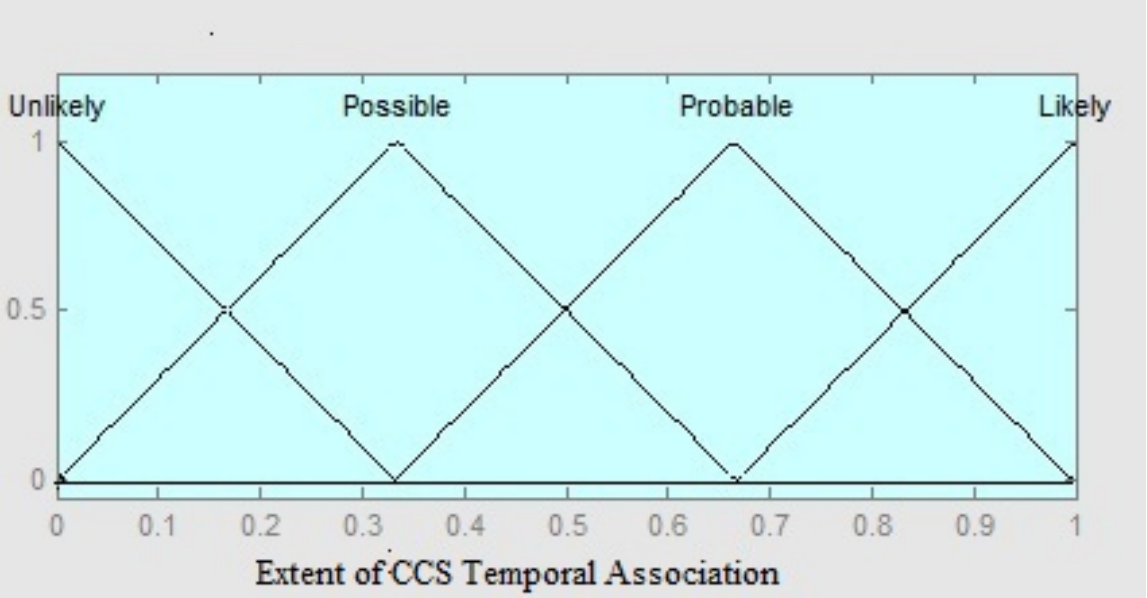


Figure 39. Fuzzy sets for CCS Temporal Association.

CCS Temporal Association will be calculated using four fuzzy rules. Here are the rules:

If the Time Duration between taking the drug and the appearance of the CCS code is Very *Short* then CCS Temporal Association is *Likely*.

- If the Time Duration between taking the drug and the appearance of the CCS code is *Short* then CCS Temporal Association is *Probable*

- If the Time Duration between taking the drug and the appearance of CCS code is *Long* then CCS Temporal Association is *Possible*.

- If the Time Duration between taken the drug and the appearance of CCS code is *Very Long* then CCS Temporal Association is *Unlikely*.

- The defuzzified CCS Temporal Association value will be weighted by 0.5 in order to get the increment value of the Degree of Causality.

The CCS categories that support the ADR signal strength should be reported after taking the studied medication. If it has been reported before the start date of the medication, then it will not support the strength of ADR signal anymore. It will rather decrease the ADR Signal by 0.25 because such categories will be considered as other explanation.

Figure 40 shows an example of such situation. The patient took the medication LISIOPRIL on 5/16/2008 and the potassium laboratory test was elevated on 06/05/2008 while the Hyperkalemia, ICD-9 267.7, was reported on 01/29/2007. This finding will decrease Degree of Causality of that patient by 0.25 because this gives indication that the elevation could be from a reason other than the medication.

PATIENT DRUG TABLE

DRUG NAME	START DATE
ISOSORBIDE DINITRATE 20MG (	1/27/2009
ISOSORBIDE DINITRATE 20MG (	4/15/2009
ISOSORBIDE DINITRATE 20MG (	6/15/2009
ISOSORBIDE MONONITRATE 30	5/16/2008
ISOSORBIDE MONONITRATE 30	11/11/2008
ISOSORBIDE MONONITRATE 30	5/29/2008
LISINOPRIL 2.5MG TAB	5/16/2008
LISINOPRIL 2.5MG TAB	5/29/2008
methylPREDNISolone 4MG TAB [	1/17/2010

PATIENT LAB TABLE

LAB DATE	TEST NMAE	RESULT
NOV 3,2009 10:34:28	POTASSIUM	6.4
AUG 19,2008 12:49:47	POTASSIUM	6.6
FEB 12,2009 10:29:39	POTASSIUM	5.0
NOV 9,2008 09:14:07	POTASSIUM	5.5
NOV 3,2009 15:18:32	POTASSIUM	6.3
AUG 6,2008 08:30:06	POTASSIUM	5.2
MAY 9,2008 11:33:48	POTASSIUM	6.0
JUN 5,2008 17:01:06	POTASSIUM	5.8
MAY 16,2008 08:04:06	POTASSIUM	4.9

PATIENT ICD9 TABLE

ICD9 C	ICD9 DESCRIPTION	DIAG DATE
389.9	Hard of Hearing (ICD-9-CM 389.9)	1/29/2007
401.9	HTN (ICD-9-CM 401.9)	1/29/2007
272.0	Hypercholesterolemia (ICD-9-CM 272.0)	1/30/2007
276.7	Hyperkalemia (ICD-9-CM 276.7)	2/12/2008
276.7	Hyperkalemia (ICD-9-CM 276.7)	6/5/2008
272.4	Hyperlipidemia (ICD-9-CM 272.4)	1/29/2007
799.02	HYPOXEMIA (ICD-9-CM 799.02)	10/30/2008

Figure 40. Patient Case for Other Explanation Scenario.

In all cases the “Degree of Causality” value should stay between 0 and 1. In case the value is greater than 1 or less than 0 then it will rounded to 1 or 0 respectively.

Patient cases vary in the strength of the possible causal association between the drug and an event based on (1) the temporal association; (2) evidence for dechallenge; (3) evidence for rechallenge; (4) presence or absence of an alternative explanation for the adverse event; and (5) presence or absence of abnormality in the laboratory tests.

The final “Degree of Causality” score is represented by 4 levels whose values are labeled as, Level 1 = “No Signal Pairs,” Level 2 = “Unlikely,” Level 3 = “Possible,” and Level 4=“Likely.”

- Level 1: “Degree of Causality” score from 0.00 to 0.25 represents No Signal Pairs.
- Level 2: “Degree of Causality” score from 0.25 to 0.50 represents Unlikely.
- Level 3: “Degree of Causality” score from 0.50 to 0.75 represents Possible.
- Level 4: “Degree of Causality” score from 0.75 to 1.00 represents Likely.

4.3 Experiments

4.3.1 Experiment Settings

The purpose of the simulation experiment is to preliminarily examine whether the PAAs work together in identifying ADR signal pairs. A suspect case will be given to one of the PAAs (i.e., PAA1). Then, PAA1 will contact the White Board in order to locate other agents available to assist in the case of interest. The White Board will inform the PAA about the availability of other PAAs (i.e., PAA2, PAA3 and PAA4). The PAAs will then work with each other in order to update their detection rules. Finally, each PAA will

evaluate its own patient's cases and assign causal link strengths for them. The evaluation outcome of each case will be forwarded to PAA1. To evaluate the effectiveness of the developed system, we retrieved the electronic data of all patients who received at least one of the 11 drugs of interest in the Veterans Affairs Medical Center in Detroit during the time period from January 1, 2005 to December 31, 2008. The interested drugs include 6 statin drugs (i.e., rosuvastatin, atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) and 5 inhibitors (angiotensin-converting enzyme inhibitor) drugs (i.e., benazepril, captopril, enalapril, fosinopril and lisinopril). Statin is a type of drug that helps patients improves their cholesterol level. Inhibitors are a type of drug that treats high blood pressure. Event data such as demographic data, patient visit data, diagnostic data, drug-related data, and laboratory data was retrieved for all the patients. For each event certain details were obtained. For example, the data for dispensing of drug includes name of the drug, subject ID, quantity of the drug dispensed, dose of the drug, drug start date, drug schedule, and the number of refills. The total number of retrieved patients was 20,000 (19,102 males and 898 females). Their average age was 68.0. All the data was stored in a 2007 Microsoft Access database. As mentioned above, we selected Lisinopril as the target drug for this ADR signal study. This reduced the number of patients to 10,048.

The experiment setting has three steps as shown below:

Step 1: Selection of the patients

Since I need two physicians to evaluate the multi-agent intelligent system performance .we need to minimize the number of patients to a certain acceptable number since the evaluation of such high number will take long time from them. The biostatistician suggested selecting randomly 2% out of the 10.048 patient. We cannot apply the systematic sampling we used in finding similar patient here since we are dealing evaluating a rare event. Otherwise we may miss one of the levels (i.e. Level 4) since the appearance probability of such level in real medical life is around 0.2%. The used way to get the 2% out of the 10,048 patients is by evaluating the 10.048 using a centralized system developed by me that contains all the detection rules. The resulting causal link strengths provided by the centralized system are shown in Table 15. A biostatistician in the team suggests sampling each level by certain percentage as shown in Table 15. This will produce 194 patients randomly selected from each Level. Some levels the biostatistician suggested a 100% sampling which means use all the patients in that level. This sampling is needed since this level has the highest association between the drug and the potential adverse events which is rear in real life data (i.e. 0.1 to 0.2 percent).

Table 15. Number of patients provided by the centralized system, Sample Percentages and Number of Patients after sampling in each level.

Level	**Number of Patients**	**Sample Percentage**	**Number of Patients After Sampling**
Level 1	9492	%0.8	75
Level 2	276	%12	33
Level 3	254	%24	60
Level 4	26	%100	26
Total Number of Patients	10048	N/A	194

Figure 41 shows the centralized methodology for Identifying ADR signal pairs.

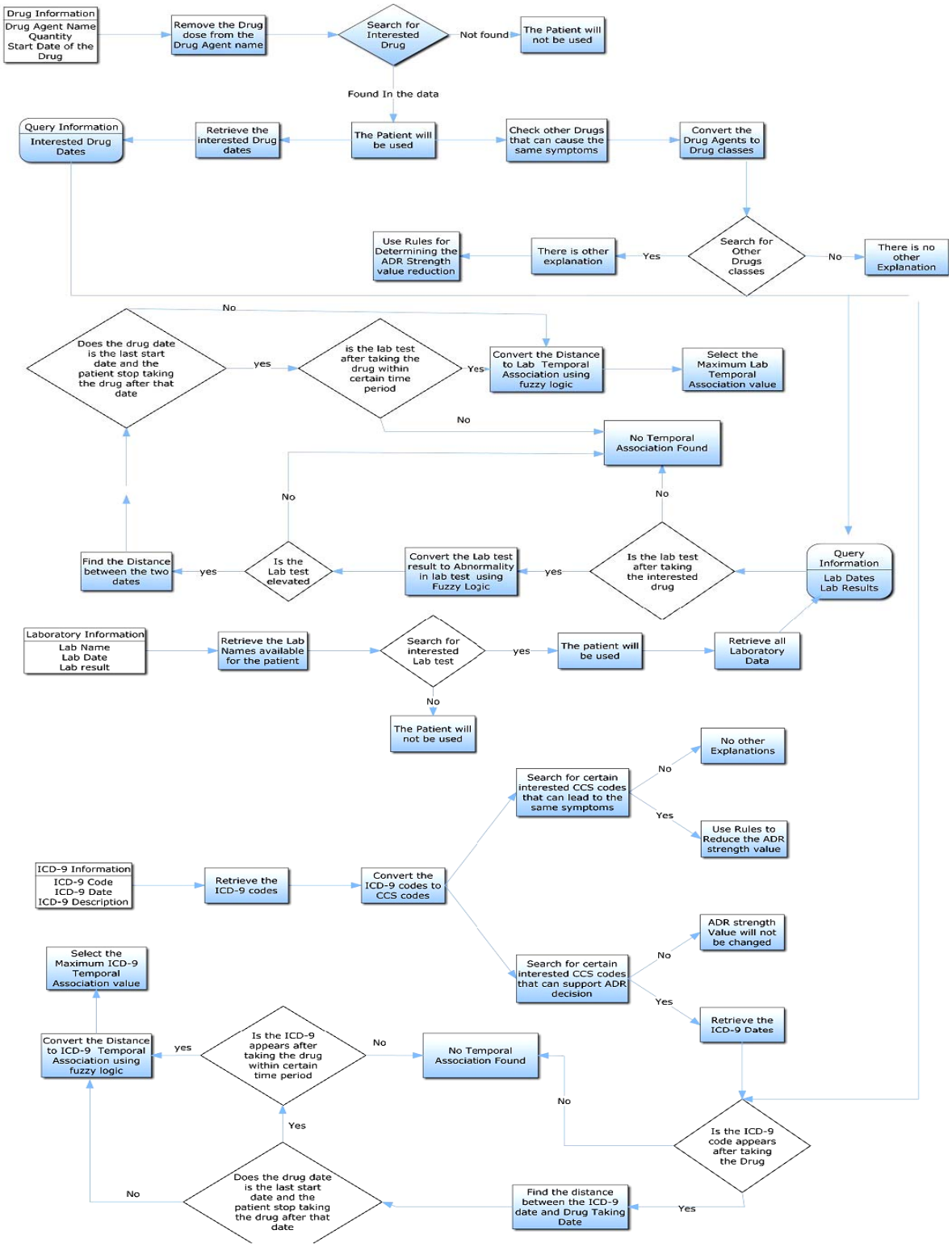


Figure 41. The Centralized Methodology for Identifying ADR Signal Pairs.

Step 2: Distribution of the patients and the detection rules among the PAAs

I formed the agent system by implementing four PAAs (I choose four because it is representative enough while computing time is still reasonable). I divided the 194 patients randomly among the agents as follows: PAA1 to PAA4 had 10 (5%), 29 (15%), 58 (30%), and 97 (50%) patients, respectively. Having different number of patients for each PAA will lead to PAA with different levels of experiences as in real life problem. Each PAA had part of the rules. The total number of the rules is 52. Some of these rules are key rules that all the agents will have. In this experiment the key rules are made up of Potassium Temporal Association rules and Potassium Test Abnormality. The remaining fuzzy rules, which were randomly distributed, are classified into two classes: unique rules and overlapping rules. The numbers of each class that an agent has depended on the number of patients it had. The numbers of unique rules and overlapping rules shared between the PAAs are shown in Table 16.

Table 16. Numbers of Unique and Overlapping Rules used by PAAs.

Agents	Number of Unique Rules	Number of Overlapped Rules	Total Number of Rules
PAA1	6	12	18
PAA2	8	12	20
PAA3	10	12	22
PAA4	16	12	28

Step 3: run the program and send a suspect signal pairs to PAA1 and getting the result

The process of starting the agents involved their registration with the JADE Main Container, which assigned a unique name to each PAA. Then, a suspect signal pair case was sent by PAA1 to the other three PAAs. The case was "patient has elevated potassium laboratory test result while taking Lisinopril". Then, PAA1 will contact White Board in order to locate other PAAs available to assist in the suspect signal pairs. White Board will inform the PAA about the availability of other PAAs (i.e., PAA2, PAA3 and PAA4). The PAAs will then work with each other in order to update their detection rules. Finally, each PAA will evaluate its own patient's cases and assign a causality score for each of the cases. The evaluation outcome of each case will be forwarded to PAA1 and then his physician.

4.3.2 Experiment Results

The four PAAs worked with each other and produced a Degree of Causality for each one of the patients. The causal link strength of each patient is assigned as a level that belongs to one of the four levels, i.e., Level 1 = "No Signal Pairs," Level 2 = "Unlikely," Level 3 = "Possible," and Level 4="Likely." The resulting causal link strengths provided by the four PAAs are shown in Table 17.

Table 17. Results of Causal Link Founded by the 4-PAAs System.

Number of patients / Agents	Category "Likely" Level 4	Category "Possible" Level 3	Category "Unlikely" Level 2	Category "No Signal Pairs" Level 1	Total Number of Patients
PAA1	0	3	2	5	10
PAA2	4	5	5	15	29
PAA3	7	15	11	25	58
PAA4	16	38	17	26	97
Total number of patients	27	61	35	71	194

As shown in the table, the total number of patients in the categories "Likely", " "Possible", "Unlikely", and "No Signal Pairs" was found to be 27, 61, 35, and 71, respectively. For example PAA2, PAA3, and PAA4 provided PAA1 with 4, 7 and 16 "Likely" patients, respectively. At the same time PAA1 searched its patients' database and it found one patient with "Likely" decision in its database. The multi-agent system took 9 hours to evaluate the 194 patients. From the software standpoint, the four agents collaboratively worked one another as designed. They updated their detection rules in proactive way and used the updated rules in evaluating the cases. Two physicians were participated in this study. They were asked to independently review each of the 194 patient cases and assigned a causality level. In this evaluation, patient cases were retrieved one by one from Databases using a visual basic program done for that purpose.

The physician checked the patient and assigned the causality score in a numerical score between 1 and 4 to show the strength of similarity. Where 1 = 'No Signal Pairs,' 2 =

'Unlikely,' 3 = 'Possible,' and 4='Likely.' The causality results generated by the multi-agent system and the two physicians (Physician 1 and physician 2) are shown in Table 18.

Table 18. Degree of Causality Results Generated by the Multi-Agent System and the Decisions of the Two Physicians (Physician 1 and Physician 2)

Patient ID	The System Decision	Physician 1 Decision	Physician 2 Decision
1	1	1	1
2	3	4	3
3	2	1	3
4	3	3	2
5	1	1	1
6	1	1	1
7	3	3	3
8	1	1	1
9	2	1	2
10	1	1	1
11	1	1	2
12	1	1	2
13	1	1	2
14	1	1	2
15	1	1	1
16	2	2	3
17	1	1	1
18	1	1	1
19	3	3	3
20	1	1	2
21	1	1	1
22	3	3	3
23	1	1	1
24	3	1	3
25	1	1	1
26	1	1	2
27	1	1	2
28	2	2	2
29	3	3	4
30	1	1	1

31	1	1	1
32	1	1	1
33	1	1	1
34	1	1	1
35	2	2	3
36	2	2	2
37	2	2	2
38	1	1	1
39	1	1	1
40	2	3	2
41	1	1	1
42	1	1	1
43	3	1	2
44	1	1	1
45	1	1	1
46	1	1	1
47	1	1	1
48	1	1	1
49	3	3	3
50	1	1	1
51	3	3	2
52	2	1	2
53	1	1	1
54	2	1	3
55	1	1	1
56	1	1	1
57	1	1	1
58	1	1	1
59	1	1	1
60	1	1	1
61	1	1	1
62	2	1	2
63	1	1	1
64	2	1	2
65	2	1	2
66	1	1	1
67	1	1	1
68	2	3	2
69	2	1	2

70	1	1	1
71	1	1	1
72	2	1	3
73	1	1	1
74	1	1	2
75	1	1	1
76	1	1	1
77	1	1	1
78	1	1	1
79	4	4	4
80	1	1	1
81	1	1	1
82	2	3	4
83	1	1	1
84	1	1	1
85	1	1	1
86	1	1	1
87	1	1	1
88	1	1	1
89	1	1	1
90	1	1	1
91	1	1	1
92	1	1	1
93	1	1	2
94	2	1	3
95	3	3	3
96	3	3	3
97	3	3	3
98	1	1	1
99	3	3	3
100	2	3	2
101	3	3	3
102	3	3	2
103	3	3	3
104	3	3	3
105	4	3	4
106	2	1	2
107	3	3	2
108	3	3	3

109	3	3	3
110	3	3	3
111	3	3	2
112	4	4	4
113	2	1	2
114	2	3	2
115	3	3	2
116	4	3	4
117	4	4	4
118	2	2	3
119	3	3	3
120	4	3	4
121	4	4	4
122	2	2	2
123	3	3	3
124	1	1	1
125	2	2	2
126	2	2	2
127	3	3	3
128	3	3	2
129	3	3	3
130	3	3	3
131	4	4	4
132	4	3	3
133	3	3	3
134	3	3	3
135	3	3	3
136	3	3	3
137	2	3	2
138	3	3	3
139	3	3	3
140	3	3	3
141	3	3	3
142	4	4	4
143	3	3	3
144	4	4	4
145	1	1	1
146	3	3	3
147	3	3	3

148	4	4	4
149	3	3	3
150	3	3	3
151	1	1	1
152	3	3	3
153	3	3	3
154	4	4	4
155	3	3	3
156	2	2	3
157	4	4	4
158	2	3	2
159	3	3	4
160	3	3	3
161	2	3	2
162	4	4	4
163	2	1	3
164	4	4	4
165	3	4	4
166	4	4	3
167	4	4	3
168	2	2	3
169	3	4	3
170	3	3	3
171	3	4	4
172	4	4	3
173	3	3	3
174	4	4	4
175	1	1	1
176	2	3	2
177	3	3	3
178	2	1	2
179	1	1	1
180	2	3	2
181	3	3	2
182	3	3	3
183	3	3	3
184	4	4	4
185	4	4	4
186	4	4	4

187	3	3	2
188	3	3	4
189	3	4	3
190	4	4	4
191	4	4	4
192	4	4	4
193	4	4	4
194	3	3	3

4.3.3 Analysis of the Results

In this section will examine the agreement between the causality levels generated by the developed algorithm and those by each of the two physicians. I have utilized Kappa statistic to estimate the levels of agreement. The Kappa coefficient as mentioned before is an estimate of the agreement between two raters. Table 19, 20 and 21 summarizes the number of matches between the decision of the system and the two physicians.

Table 19.Confusion Matrix of System by Physician 1.

	Physician 1					
MAS System	**Frequency**	**1**	**2**	**3**	**4**	**Total**
	1	71	0	0	0	71
	2	14	11	10	0	35
	3	2	0	54	5	61
	4	0	0	4	23	27
	Total	87	11	68	28	194

Table 20. Confusion Matrix of System by Physician 2.

		Physician 2				
MAS System	Frequency	1	2	3	4	Total
	1	62	9	0	0	71
	2	0	24	10	1	35
	3	0	10	46	5	61
	4	0	0	4	23	27
	Total	62	43	60	29	194

Table 21. Confusion Matrix of Physician 1 by Physician 2.

		Physician 2				
Physician 1	Frequency	1	2	3	4	Total
	1	62	19	6	0	87
	2	0	6	5	0	11
	3	0	18	43	7	68
	4	0	0	6	22	28
	Total	62	43	60	29	194

The estimate of agreements is as follows: Kappa = 0.8448 for physician 1 and the developed system; Kappa = 0.8274 for physician 2 and the developed system; Kappa = 0.7196 for physician 1 and physician 2. These coefficients suggest excellent agreement between the system and the physicians. The asymptotic standard error (ASE) is also computed, as well as 95% confidence bounds. Those values are computed using Weighted Kappa which considers disagreement close to the diagonals less heavily than disagreement further away from the diagonals. The simple Kappa is also provided. The results of these two methods are shown in Table 22, 23, and 24.

Table 22. Kappa Statistics between Physician 1 vs. MAS System.

Kappa Statistics between Physician 1 vs. MAS System				
Statistic	**Value**	**ASE**	**95% Confidence Limits**	
Simple Kappa	0.7405	0.0379	0.6663	0.8148
Weighted Kappa	**0.8448**	0.0250	0.7958	0.8938

Table 23. Kappa Statistics between Physician 2 vs. MAS System.

Kappa Statistics between Physician 2 vs. MAS System				
Statistic	**Value**	**ASE**	**95% Confidence Limits**	
Simple Kappa	0.7227	0.0391	0.6461	0.7993
Weighted Kappa	**0.8274**	0.0262	0.7760	0.8789

Table 24. Kappa Statistics between Physician 1 vs. Physician 2.

Kappa Statistics between Physician 1 vs. Physician 2				
Statistic	**Value**	**ASE**	**95% Confidence Limits**	
Simple Kappa	0.5597	0.0433	0.4748	0.6446
Weighted Kappa	**0.7196**	0.0331	0.6547	0.7844

4.4 Summary

I have developed a collaborative, team agent framework that aims to achieve earlier detection of ADR signal pairs. In this framework, a group of collaborative agents would search and track relevant patient information, update their knowledge and learn from each other in proactive way. I implemented a four-agent system using JADE and FuzzyJess software packages. Using real patient data, the results show that the agents worked together in identifying ADR signal pairs.

CHAPTER 5
CONCLUSION AND FUTURE DIRECTIONS

5.1 Conclusion

In this dissertation, I developed a novel intelligent multi agent system for identifying adverse drug reaction signal pairs. The system offers an implementation that enables the agents, equipped with decision rules, to interact with each other, share their experiences and exchange information in a proactive way in order to identify ADR signal pairs. Through the study, we encounter the interesting problem of how the agents should collaborate to find patients in their patient databases that are similar to any given patient provided by one of the agents as a prototype. This leads me to develop a methodology that enables agents in the multi-agent system to find similar patients in agents' databases. The agents are equipped with intelligent decision maker that arms them with the rule-based reasoning capability. The rules used in the intelligent decision maker were developed in this dissertation. The agents have been supported with a cooperative learning mechanism. The basic idea of the learning mechanism is that the agents need to collaborate with one another and sharing their knowledge for the benefit of the entire agents. The agents start collaboration by providing their detection rules and similarity rules to the other agents. I proposed using a confidence level that effectively reflects the experience level of an agent for a given rule. This leads to a collection of rules that are the best and the most insightful rules which lead to improve the agents' decision performance. The system has been tested using four agents. I choose four because it is representative enough while computing time is still reasonable. I implemented the multi agent system using JADE and FuzzyJess

software packages. In the dissertation the architecture, design and implementation of the system has been described**.** Using real patient data that involved over 20,000 patients treated at the Veterans Affairs Medical Center in Detroit between 2005 and 2008, two experiments have been performed to show how the four agents can effectively work together. The experiments' results were evaluated independently by two physicians on our team. Kappa statistics has been to evaluate the system results. The kappa coefficients show excellent agreement between the decision of physicians and the agents. This indicates that the agents can successfully collaborate in finding ADR signal pairs and in finding similar patients.

5.2 Future Directions

The multi-agent system can be extended step by step to move towards the developed MAS. Health Organization Agent and Hospital Pharmacist Assistant Agent could be the first two agents to be added into the system core. Health Organization Agent (HOA) is a broker and controller for each health organization. A HOA is the entrance point through which all the databases in a health organization could be accessed by outside institutes. Pharmacists Assistant Agents would be helpful by collecting useful information that help PAAs identify ADR signals. The pharmacist's Assistant Agent role could be to support other agents with drugs information, ADR reporting from drug companies, and monitor ongoing evaluation of certain potential ADR. By having a clinical Pharmacist Assistant Agent, the detection and assessment of ADRs may be greatly enhanced. We can also develop an agent that has a role of establishing contacts with the medical records. The

agent should have the ability to recommend relative articles to the physicians especially when a decision is not certain about an ADR case. Establishing this contact may add significant value to the ADR detection process. Those medical documents will help the PAAs and hence its physicians in making decision.

Another future direction is to use fuzzy measures instead of classical measures. Because we are dealing with deferent types of uncertain information, fuzzy measures can be used for the representation of uncertain information instead of classical measures. For example instead of using normal averaging we can use Ordered Weighted Averaging operators. Ordered Weighted Averaging operators change the aggregation from the `pessimistic' minimum-type aggregation, to the `optimistic' maximum-type aggregations. Also we can use type 2 fuzzy sets or interval type 2 fuzzy instead of type 1 fuzzy sets in order to get more precise decision. We can also use more of machine learning techniques, for example classification and clustering, to make agents adaptive to their users and context. This may enhance the detection speed of the PAAs.

BIBLIOGRAPHY

[1] I. R. Edwards and J. K. Aronson, "Adverse drug reactions: definitions, diagnosis, and management," *Lancet,* vol. 356, pp. 1255-9, Oct 7 2000.

[2] U. S. F. a. D. Administration. (December 31, 2010). *AERS Patient Outcomes by Year*. Available: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070461.htm

[3] M. D. B. Stephens, J. C. C. Talbot, and P. Waller, *Stephens' detection of new adverse drug reactions*, 5th ed. Chichester ; Hoboken, NJ: Wiley, 2004.

[4] M. P. Couig, "Reporting adverse events and product problems. MedWatch provides comprehensive resource for health professionals," *AWHONN lifelines / Association of Women's Health, Obstetric and Neonatal Nurses,* vol. 4, pp. 22-4, Aug-Sep 2000.

[5] M. Hauben, "Early postmarketing drug safety surveillance: data mining points to consider," *The Annals of pharmacotherapy,* vol. 38, pp. 1625-30, Oct 2004.

[6] A. Serenko and B. Detlor, "Agent toolkit satisfaction and use in higher education," *Journal of Computing in Higher Education,* vol. 15, pp. 65-88, 2003.

[7] R. Orchard, "Fuzzy reasoning in Jess: the Fuzzy J toolkit and Fuzzy Jess," 2001.

[8] D. C. Classen, S. L. Pestotnik, R. S. Evans, J. F. Lloyd, and J. P. Burke, "Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality," *JAMA : the journal of the American Medical Association,* vol. 277, pp. 301-6, Jan 22-29 1997.

[9] J. Lazarou, B. H. Pomeranz, and P. N. Corey, "Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies," *JAMA : the journal of the American Medical Association,* vol. 279, pp. 1200-5, Apr 15 1998.

[10] H. Dormann, M. Criegee-Rieck, A. Neubert, T. Egger, A. Geise, S. Krebs, T. Schneider, M. Levy, E. Hahn, and K. Brune, "Lack of awareness of community-acquired adverse drug reactions upon hospital admission : dimensions and consequences of a dilemma," *Drug safety : an international journal of medical toxicology and drug experience,* vol. 26, pp. 353-62, 2003.

[11] D. W. Bates, N. Spell, D. J. Cullen, E. Burdick, N. Laird, L. A. Petersen, S. D. Small, B. J. Sweitzer, and L. L. Leape, "The costs of adverse drug events in hospitalized patients. Adverse Drug Events Prevention Study Group," *JAMA : the journal of the American Medical Association,* vol. 277, pp. 307-11, Jan 22-29 1997.

[12] J. M. Drazen, Institute of Medicine (U.S.). Forum on Drug Discovery Development and Translation., and Institute of Medicine (U.S.). Board on Health Sciences Policy., *Adverse drug event reporting : the roles of consumers and health-care professionals : workshop summary*. Washington, D.C.: National Academies Press, 2007.

[13] R. Patterson, R. D. DeSwarte, P. A. Greenberger, L. C. Grammer, J. E. Brown, and A. C. Choy, "Drug allergy and protocols for management of drug allergies," *Allergy proceedings : the official journal of regional and state allergy societies,* vol. 15, pp. 239-64, Sep-Oct 1994.

[14] B. H. Stricker and B. M. Psaty, "Detection, verification, and quantification of adverse drug reactions," *BMJ,* vol. 329, pp. 44-7, Jul 3 2004.

[15] M. B. Aspinall, J. Whittle, S. L. Aspinall, R. L. Maher, Jr., and C. B. Good, "Improving adverse-drug-reaction reporting in ambulatory care clinics at a Veterans Affairs hospital," *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists,* vol. 59, pp. 841-5, May 1 2002.

[16] J. P. Ioannidis and J. Lau, "Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas," *JAMA : the journal of the American Medical Association,* vol. 285, pp. 437-43, Jan 24-31 2001.

[17] T. Brewer and G. A. Colditz, "Postmarketing surveillance and adverse drug reactions: current perspectives and future needs," *JAMA : the journal of the American Medical Association,* vol. 281, pp. 824-9, Mar 3 1999.

[18] B. Mukherjee and T. Shivakumar, "A case of sensorineural deafness following ingestion of sildenafil," *The Journal of laryngology and otology,* vol. 121, pp. 395-7, Apr 2007.

[19] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[20] U.K. yellow card ADR Reporting System, http://yellowcard.mhra.gov.uk/.

[21] Canadian ADR Reporting System, http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/index-eng.php.

[22] Cental Drugs Standard Control Organization ADR Reporting System of India, http://www.cdsco.nic.in/html/pharmaco.html.

[23] N. J. Gogtay, S. S. Mangalvedhekar, and N. A. Kshirsagar, "Adverse drug reaction (ADR) monitoring in India and the postal survey as a useful tool for ADR detection," *Pharmacoepidemiology and Drug Safety,* vol. 9, pp. 235-6, May 2000.

[24] L. Landow, "Monitoring adverse drug events: the Food and Drug Administration MedWatch reporting system," *Regional anesthesia and pain medicine,* vol. 23, pp. 190-3, Nov-Dec 1998.

[25] T. D. Piazza-Hepp and D. L. Kennedy, "Reporting of adverse events to MedWatch," *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists,* vol. 52, pp. 1436-9, Jul 1 1995.

[26] R. W. Amar Gupta , Igor Crk and Surendra Sarnikar, "An Information Technology Architecture for Drug Effectiveness Reporting and Post-Marketing Surveillance," *IJHISI,* vol. 2, pp. 65-80, 2007.

[27] M. C. Danovaro-Holliday, A. L. Wood, and C. W. LeBaron, "Rotavirus vaccine and the news media, 1987-2001," *JAMA : the journal of the American Medical Association,* vol. 287, pp. 1455-62, Mar 20 2002.

[28] M. Zolezzi and N. Parsotam, "Adverse drug reaction reporting in New Zealand: implications for pharmacists," *Therapeutics and clinical risk management,* vol. 1, pp. 181-8, Sep 2005.

[29] K. K. Kelly M, Davis SR, et al, "Factors influencing adverse drug reaction reporting in New South Wales teaching hospitals.

," *J Pharm Pract Res,* vol. 34, pp. 32–5, 2004.

[30] (1996, 5/2/2011). *THE CLINICAL IMPACT OF ADVERSE EVENT REPORTIN*. Available: http://www.fda.gov/downloads/safety/medwatch/ucm168505.pdf

[31] E. van Puijenbroek, W. Diemont, and K. van Grootheest, "Application of quantitative signal detection in the Dutch spontaneous reporting system for adverse drug reactions," *Drug safety : an international journal of medical toxicology and drug experience,* vol. 26, pp. 293-301, 2003.

[32] S. J. Evans, P. C. Waller, and S. Davis, "Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports," *Pharmacoepidemiology and Drug Safety,* vol. 10, pp. 483-6, Oct-Nov 2001.

[33] A. Bate, M. Lindquist, I. R. Edwards, S. Olsson, R. Orre, A. Lansner, and R. M. De Freitas, "A Bayesian neural network method for adverse drug reaction signal generation," *European journal of clinical pharmacology,* vol. 54, pp. 315-21, Jun 1998.

[34] A. Szarfman, S. G. Machado, and R. T. O'Neill, "Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database," *Drug safety : an international journal of medical toxicology and drug experience,* vol. 25, pp. 381-92, 2002.

[35] R. Harpaz, H. S. Chase, and C. Friedman, "Mining multi-item drug adverse effect associations in spontaneous reporting systems," *BMC bioinformatics,* vol. 11 Suppl 9, p. S7, 2010.

[36] K. Kubota, D. Koide, and T. Hirai, "Comparison of data mining methodologies using Japanese spontaneous reports," *Pharmacoepidemiology and Drug Safety,* vol. 13, pp. 387-94, Jun 2004.

[37] D. E. Lilienfeld, "A challenge to the data miners," *Pharmacoepidemiology and Drug Safety,* vol. 13, pp. 881-4, Dec 2004.

[38] (1998, Agent Communication Language, FIPA 97 Specification, Version 2.0, Part 2.

[39] Y. Labrou, T. Finin, and P. Yun, "Agent communication languages: the current landscape," *Intelligent Systems and their Applications, IEEE,* vol. 14, pp. 45-52, 1999.

[40] J. Ferber, *Multi-agent systems : an introduction to distributed artificial intelligence*. Harlow: Addison-Wesley, 1998.

[41] H. Lin, *Architectural design of multi-agent systems : technologies and techniques*. Hershey: Information Science Reference, 2007.

[42] F. T. f. o. i. p. agents., "See http://www.fipa.org."

[43] K. Decker and L. Jinjiang, "Coordinated hospital patient scheduling," in *Multi Agent Systems, 1998. Proceedings. International Conference on*, 1998, pp. 104-111.

[44] A. Aldea, B. López, A. Moreno, D. Riaño, and A. Valls, "A Multi-Agent System for Organ Transplant Co-ordination," in *Artificial Intelligence in Medicine*. vol. 2101, S. Quaglini, P. Barahona, and S. Andreassen, Eds., ed: Springer Berlin / Heidelberg, 2001, pp. 413-416.

[45] J. Vázquez-Salceda, J. A. Padget, U. Cortés, A. López-Navidad, and F. Caballero, "Formalizing an electronic institution for the distribution of human tissues," *Artificial Intelligence in Medicine,* vol. 27, pp. 233-258, 2003.

[46] M. Calisti, P. Funk, S. Biellman, and T. Bugnon, "A Multi-Agent System for Organ Transplant Man-agement," *Applications of Software Agent Technology in the Health Care Domain,* 2003.

[47] M. Beer, I. Anderson, and W. Huang, "Using agents to build a practical implementation of the INCA (intelligent community alarm) system," presented at the Proceedings of the fifth international conference on Autonomous agents, Montreal, Quebec, Canada, 2001.

[48] M. S. Devi and V. Mago, "Multi-agent model for Indian rural health care," *International journal of health care quality assurance incorporating Leadership in health services,* vol. 18, pp. suppl i-xi, 2005.

[49] O. Baujard, V. Baujard, S. Aurel, C. Boyer, and R. D. Appel, "MARVIN, multi-agent softbot to retrieve multilingual medical information on the Web," *Medical informatics = Medecine et informatique,* vol. 23, pp. 187-91, Jul-Sep 1998.

[50] S. Barro, J. Presedo, D. Castro, M. Fernandez-Delgado, S. Fraga, M. Lama, and J. Vila, "Intelligent telemonitoring of critical-care patients," *IEEE engineering in*

medicine and biology magazine : the quarterly magazine of the Engineering in Medicine & Biology Society, vol. 18, pp. 80-8, Jul-Aug 1999.

[51] S. M. Alhashmi, "Design of an Internet-Based Advisory System: A Multi-agent Approach," presented at the Proceedings of the 11th Pacific Rim International Conference on Multi-Agents: Intelligent Agents and Multi-Agent Systems, Hanoi, Vietnam, 2008.

[52] T. Alsinet, C. Ansotegui, R. Bejar, C. Fernandez, and F. Manya, "Automated monitoring of medical protocols: a secure and distributed architecture," *Artificial Intelligence in Medicine,* vol. 27, pp. 367-92, Mar 2003.

[53] L. Godo, J. Puyol-Gruart, J. Sabater, V. Torra, P. Barrufet, and X. Fabregas, "A multi-agent system approach for monitoring the prescription of restricted use antibiotics," *Artificial Intelligence in Medicine,* vol. 27, pp. 259-82, Mar 2003.

[54] M. Hospers, E. Kroezen, A. Nijholt, R. op den Akker, and D. Heylen, "An agent-based intelligent tutoring system for nurse education," *Applications of Software Agent Technology in the Health Care Domain},* pp. 143-159.

[55] B. M. Balachandran, E. Alhashel, and M. Mohammedian, "An Agent-Mediated Collaborative Negotiation in E-Commerce: A Case Study in Travel Industry," presented at the Proceedings of the 13th International Conference on Knowledge-Based and Intelligent Information and Engineering Systems: Part II, Santiago, Chile, 2009.

[56] B. M. Balachandran and M. Enkhsaikhan, "Development of a Multi-Agent System for Travel Industry Support," in *Computational Intelligence for Modelling, Control*

and Automation, 2006 and International Conference on Intelligent Agents, Web Technologies and Internet Commerce, International Conference on, 2006, pp. 63-63.

[57] G. Ligon, B. Bala, and S. Dharmendra, "Personalised Search on Electronic Information," in *Knowledge-Based Intelligent Information and Engineering Systems*. vol. 3684, R. Khosla, R. Howlett, and L. Jain, Eds., ed: Springer Berlin / Heidelberg, 2005, pp. 907-907.

[58] G. Ligon, M. Balachandran, and D. Sharma, "Personalisation of Web Search: An Agent Based Approach," in *Knowledge-Based Intelligent Information and Engineering Systems*. vol. 4253, B. Gabrys, R. Howlett, and L. Jain, Eds., ed: Springer Berlin / Heidelberg, 2006, pp. 1192-1200.

[59] L. V. Massawe, J. Kinyua, and F. Aghdasi, "An implementation of a multi-agent based RFID middleware for asset management system using the JADE platform," in *IST-Africa, 2010*, 2010, pp. 1-8.

[60] K. I. Wang, W. H. Abdulla, and Z. Salcic, "A multi-agent system for intelligent environments using JADE," *IEE Seminar Digests,* vol. 2005, pp. v2-86-v2-86, 2005.

[61] A.-h. Suhayya, T. Mansour, and W. Tony, "A Multi-Agent Systems Approach for Fraud Detection in Personal Communication Systems," ed, 2007.

[62] J. M. G. a. A. Fernández-Caballero, "An Agent-Based Intelligent Tutoring System for Enhancing E-Learning / E-Teaching," *International Journal of Instructional Technology and Distance Learning*, vol. 2 Novembe 2005.

[63] A. Fern\, \#225, ndez-Caballero, V. L\, \#243, pez-Jaquero, F. Montero, P. Gonz\, and lez, "Adaptive interaction multi-agent systems in E-learning/E-teaching on the web," presented at the Proceedings of the 2003 international conference on Web engineering, Oviedo, Spain, 2003.

[64] M. Pipattanasomporn, H. Feroze, and S. Rahman, "Multi-agent systems in a distributed smart grid: Design and implementation," in *Power Systems Conference and Exposition, 2009. PSCE '09. IEEE/PES*, 2009, pp. 1-8.

[65] S. D. J. McArthur, E. M. Davidson, V. M. Catterson, A. L. Dimeas, N. D. Hatziargyriou, F. Ponci, and T. Funabashi, "Multi-Agent Systems for Power Engineering Applications—Part I: Concepts, Approaches, and Technical Challenges," *Power Systems, IEEE Transactions on,* vol. 22, pp. 1743-1752, 2007.

[66] A. Mansour, H. Ying, P. Dews, Y. Ji, and R. M. Massanari, "Identifying adverse drug reaction signal pairs by a multi-agent intelligent system with fuzzy decision model," in *Fuzzy Information Processing Society (NAFIPS), 2012 Annual Meeting of the North American*, 2012, pp. 1-6.

[67] A. Mansour, Y. Hao, P. Dews, J. Yanqing, M. S. Farber, J. Yen, R. E. Miller, and R. M. Massanari, "A multi-agent system for detecting adverse drug reactions," in *Fuzzy Information Processing Society (NAFIPS), 2010 Annual Meeting of the North American*, 2010, pp. 1-6.

[68] M. P. Singh, "Agent communication languages: rethinking the principles," *Computer,* vol. 31, pp. 40-47, 1998.

[69] A. Mansour, H. Ying, P. Dews, Y. Ji, J. Yen, R. E. Miller, and R. M. Massanari, "Finding similar patients in a multi-agent environment," in *Fuzzy Information Processing Society (NAFIPS), 2011 Annual Meeting of the North American*, 2011, pp. 1-6.

[70] J. Yanqing, Y. Hao, M. S. Farber, J. Yen, P. Dews, R. E. Miller, and R. M. Massanari, "A Distributed, Collaborative Intelligent Agent System Approach for Proactive Postmarketing Drug Safety Surveillance," *Information Technology in Biomedicine, IEEE Transactions on,* vol. 14, pp. 826-837, 2010.

[71] U.S. National Library of Medicine, National Institutes of help, http://www.nlm.nih.gov.

[72] M. Esteva, J. A. Rodriguez-Aguilar, J. L. Arcos, C. Sierra, and P. Garcia, "Institutionalising open multi-agent systems," in *MultiAgent Systems, 2000. Proceedings. Fourth International Conference on*, 2000, pp. 381-382.

[73] J. Vazquez-Salceda, "The role of norms and electronic institutions in multi-agent systems applied to complex domains. The HARMONIA framework," *Ai Communications,* vol. 16, pp. 209-212, 2003.

[74] National Drug Code Directory, USA, http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm.

[75] F. L. Bellifemine, G. Caire, and D. Greenwood, *Developing multi-agent systems with jade*. Hoboken, NJ: John Wiley, 2007.

[76] C. C. S. C. f. ICD-9-CM, "see http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp."

[77] E. V. Granowitz and R. B. Brown, "Antibiotic adverse reactions and drug interactions," *Critical care clinics,* vol. 24, pp. 421-442, 2008.

[78] C. W. J. Granger and P. L. Siklos, "Systematic sampling, temporal aggregation, seasonal adjustment, and cointegration theory and evidence," *Journal of Econometrics,* vol. 66, pp. 357-369, 1995.

[79] J. R. Landis and G. G. Koch, "The measurement of observer agreement for categorical data," *Biometrics,* vol. 33, p. 159, 1977.

ABSTRACT

A MULTI-AGENT INTELLIGENT SYSTEM FOR DETECTING UNKNOWN ADVERSE DRUG REACTIONS THROUGH COMMUNICATION AND COLLABORATION

by

AYMAN MANSOUR

December 2012

Advisor: Prof. Hao Ying

Major: Electrical Engineering

Degree: Doctor of Philosophy

Several thousands of drugs are currently available on the U.S. market. A complete understanding of the safe use of drugs is not possible at the time when drug is developed or marketed. At that time, the safety information is only obtained from a few thousand people in a typical pre-marketing clinical trial. Clinical trials are not capable of detecting rare adverse drug reactions (ADRs) because of limitations in sample size and trial duration. Early detection of unknown ADRs could save lives and prevent unnecessary hospitalizations. Current methods largely rely on spontaneous reports which suffer from serious underreporting, latency, and inconsistent reporting. Thus they are not ideal for rapidly identifying rare ADRs. In this dissertation, I developed a team-based multi-agent intelligent system approach for proactively detecting potential ADR signal pairs (i.e., potential links between drugs and apparent adverse reactions). The basic idea is that intelligent agents are capable of collaborating with one another by sharing information and

knowledge which will accelerate the process of detecting ADR signal pairs. Each agent is equipped with a fuzzy inference engine, which enables it to find the causal relationship between a drug and a potential ADR (i.e., a signal pair). The fuzzy inference uses detection rules developed by me in this dissertation. The detection rules are based on different factors. I have also developed a methodology to find similar patients in the multi-agents system. The developed methodology uses similarity fuzzy rules in order to find similar patients in each agent's patient database.

In this dissertation, I developed a cooperative learning mechanism that was used by the agents in identifying ADR signal pairs and finding similar patients. The basic idea is that the agents are capable of collaborating with one another by sharing their knowledge. The agents start collaboration by providing their knowledge (i.e. rules) to the other agents. Using confidence level, the most important and insightful detection rules will be found and used for the benefit of the entire agent system. The new updated rules will lead to improve the agents' decision performance. To evaluate our approach, I designed a four–agent system and implemented it using JADE and FuzzyJess software packages. I choose four because it is representative enough while computing time is still reasonable. To assess the performance of the developed system, I conducted two simulation experiments that involved over 20,000 patients treated at the Veterans Affairs Medical Center in Detroit between 2005 and 2008. From the software standpoint, the four agents collaboratively worked one another as designed. Two physicians on the team independently reviewed the multi-agent system results. The results indicate that the agents can successfully collaborate in finding ADR signal pairs and finding similar patients.

AUTOBIOGRAPHICAL STATEMENT
AYMAN MANSOUR

EDUCATION

- Doctor of Philosophy (Electrical Engineering), December 2012, Wayne State University, Detroit, Michigan, United States.
- Master of Science in Electrical Engineering, 2006, University of Jordan, Amman, Jordan.
- Bachelor of Science in Electrical and Electronics Engineering, 2004, University of Sharjah, Sharjah, United Arab Emirates.

AWARDS AND HONORS

- Best Paper Award, given *at 31th North American Fuzzy Information Processing Society Conference*, Berkeley, CA, Aug 06-08, 2012.
- Outstanding Graduate Teaching Assistant Award, Wayne State University, 2012.
- Eta Kappa Nu, Electrical and Computer Engineering Honor society, honor was given from Board of Governor, 2012.
- Inclusion in Marquis Who's Who in the World, 2012.
- Sigma Xi, The Scientific Honor Research Society, honor was given from the Board of Governor, 2012.
- Tau Beta Pi, Engineering Honor Society, 2011.
- Golden Key Honor Society, 2011.
- Thomas C. Rumble University Graduate Fellowships, Wayne State University, 2010.
- Graduate Student Professional Travel Award, Wayne State University, (2010, 2011, 2012).
- Graduate Teaching Assistant Scholarship, University of Jordan 2004.
- Excellence Honor Award, the Best Student Rank in the Engineering College, University of Sharjah, UAE, 2004.
- University of Sharjah Honor List (5 times 1999-2003).
- Sharjah Prize for Brilliant Student, UAE, 1997, 1998 and 1999.