Fuzzy Rule-Based Approach for Detecting Adverse Drug Reaction Signal Pairs

Ayman Mansour[1,*], Hao Ying[2], Peter Dews[3], Yanqing Ji[4], R. Michael Massanari[5]

[1] Department of Electrical and Computer Engineering, Tafila Technical University, Tafila, Jordan
[2] Department of Electrical and Computer Engineering, Wayne State University, Detroit, Michigan, USA
[3] Department of Internal Medicine, St John Health Providence Hospital, Southfield, Michigan, USA
[4] Department of Electrical and Computer Engineering, Gonzaga University, Spokane, Washington, USA
[5] The Critical Junctures Institute, Bellingham, Washington, USA

* Corresponding Author: mansour@ttu.edu.jo

Abstract— **Detecting Adverse Drug Reactions (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 paper we have designed and developed a fuzzy inference engine for finding the causal relationship between a drug and an adverse reaction. The reasoning is based on a fuzzy inference system implemented using the freeware FuzzyJess. Fuzzy logic is used to represent, interpret, and compute vague and/or subjective information which is very common in medicine. The Detector is a fuzzy rule-based system. Using clinical information of more than 10,000 patients treated at the Detroit Veterans Affairs Medical Center, we have generated preliminary simulated detection results.**

I. INTRODUCTION

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]. 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 [2,3]. 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 [2]. 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.

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] some rare or serious ADRs are likely to remain unnoticed during the clinical trial program. 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 [3,4,5]. 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 [3]. Even if the report does suggest labeling changes, the information provided will be kept for further investigated especially when more information became available. 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. In this paper Fuzzy logic [6] is used to represent, interpret, and compute vague and/or subjective information of ADR factors. Fuzzy logic is a well-established methodology that is effective for systematic handling of *deterministic uncertainty* and *subjective* information. It has been successfully used to solve challenging industrial and medical problems in practice, some of which are very difficult to solve without it. Using Fuzzy rule based approach will enhance the post-marketing ADR detection performance. In this paper the reasoning is implemented using the freeware FuzzyJess [7].

II. THE DEVELOPED FUZZY RULE APPROACHED FOR DETECTION OF ADR SIGNAL PAIRS

The developed 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 summarized in Table 1.

Table1. 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.

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. The fuzzy sets used in fuzzifying the Input and Output variables are shown in Table 2.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 2.Definitions of Fuzzy Sets

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

The detection rules that use the above cues were acquired through the joint efforts of the engineering and medical team members. The detection rules are mentioned in details the following sections.

a) 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).

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 shows an example of such situation.

Figure 1. Sample start dates out of refills dates.

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 2), and three fuzzy sets for the output variable Abnormality in Potassium Laboratory Test- Low, Medium, and High (Figure 3). 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*.
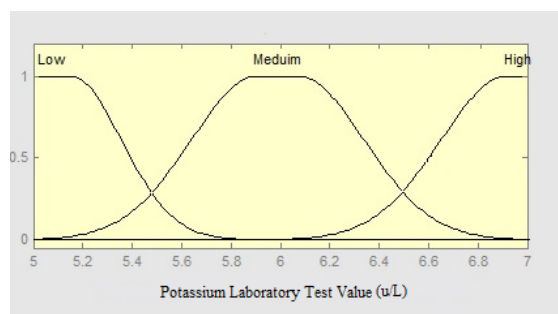- If Potassium Laboratory Test Value is *High*, then Abnormality in Potassium Laboratory Test is *High*.

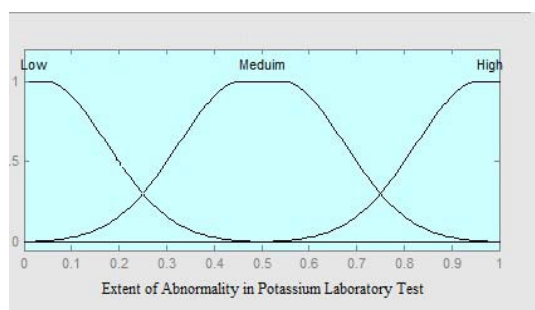Figure 2. Fuzzy sets for Potassium Laboratory Test Value

Figure 3. Fuzzy sets for Abnormality in Potassium Laboratory Test

b)   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, we 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 4 and Figure 5 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.
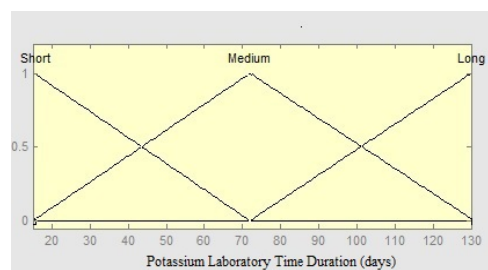

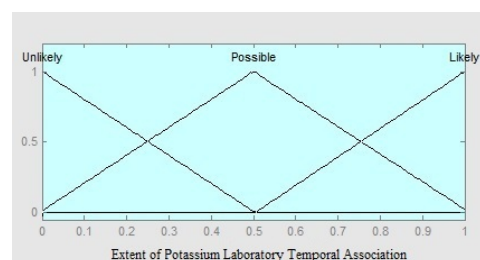Figure 4. Fuzzy sets for Potassium Laboratory Test Time Duration

Figure 5. 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 6 and Figure 7).
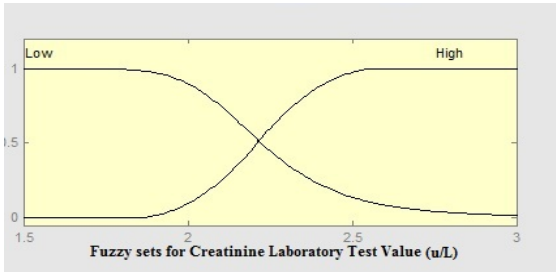

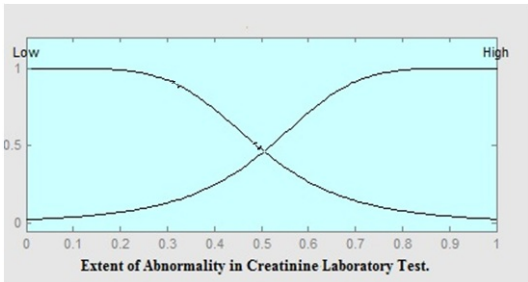Figure 6. Fuzzy sets for Creatinine Laboratory Test Value.

Figure 7. 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, we 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 and Figure show the fuzzy sets for both fuzzy variables, respectively.
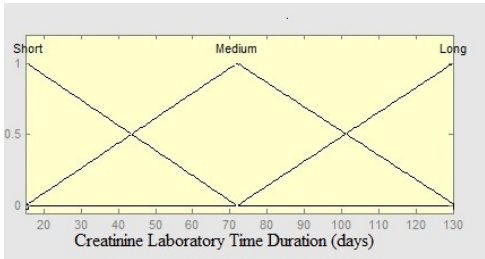

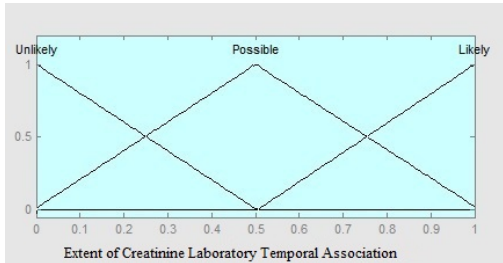Figure 8. Fuzzy sets for Creatinine Laboratory Test Time Duration.

Figure 9. 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 10.
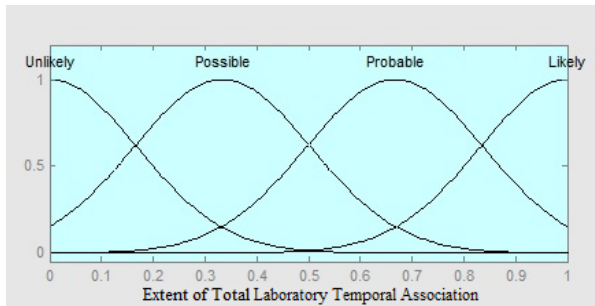

Figure 10. Fuzzy sets for Total Laboratory Test Temporal Association.

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. This issue will be explained in other explanation section.

c) 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 .
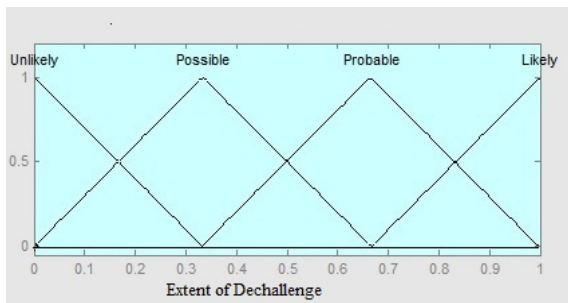

Figure 11. Fuzzy sets for Dechallenge

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 12).
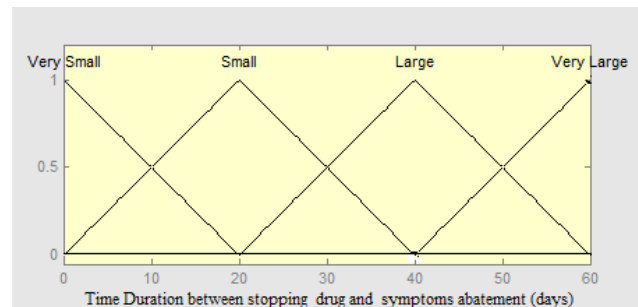

Figure 12. Fuzzy sets for Time Duration between stopping drug and symptom abatement

d) 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. Rechallenge is fuzzified by three fuzzy sets Likely, Possible and Unlikely (Figure 13).
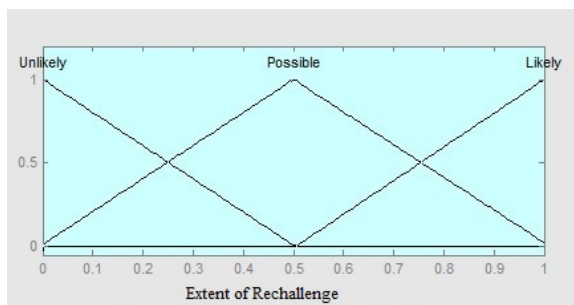

Figure 13. Fuzzy sets for Rechallenge.

e) 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.

f) 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.

f-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.

f-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 *International Classification of Diseases, 9th Revision, and Clinical Modification* (ICD-9-CM) code 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) [8]. 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 14 and Figure 15 show the fuzzy sets for CCS Time Duration and CCS Temporal Association, respectively.
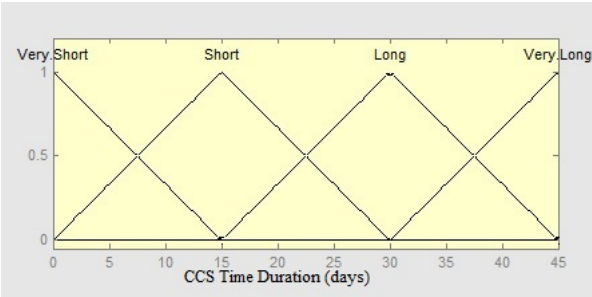

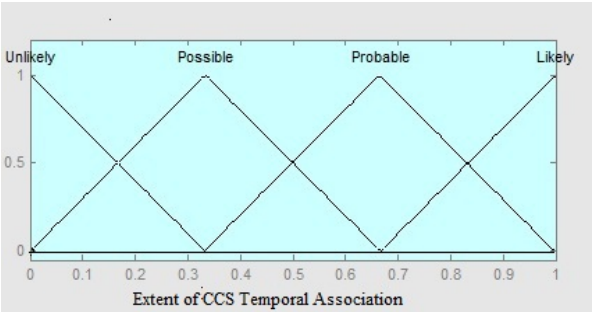Figure 14. Fuzzy sets for CCS Time Duration.

Figure 15. 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 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.

Figure 16. 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.

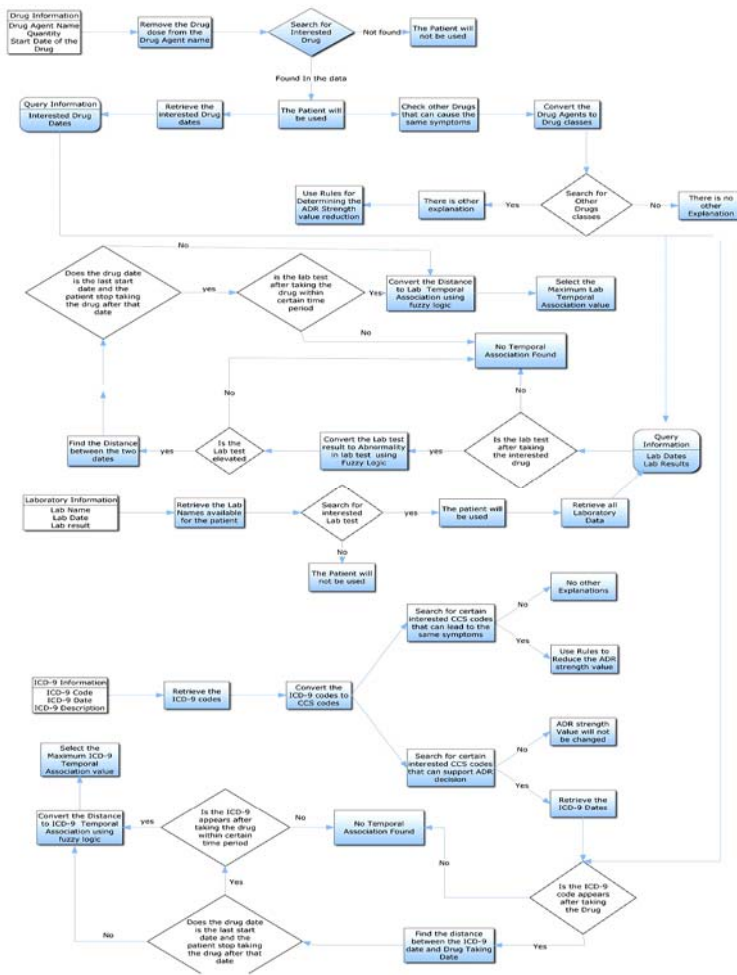The developed Fuzzy Rule-based Algorithm is shown in the Figure 17.

Figure 17: The developed Fuzzy Rule-based Algorithm

III. EXPERIMENTS

The purpose of the simulation experiment is to preliminarily examine the proposed approach. A suspect case will be provided to the developed rule-based system. 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. We selected Lisinopril as the target drug for this ADR signal study. This reduced the number of patients to 10,048. The resulting causal link strengths provided by the proposed system are shown in Table 3.

Table 3. Number of patients provided by the system

Level	Number of Patients
Level 1	9492
Level 2	276
Level 3	254
Level 4	26
Total Number of Patients	10048

IV. CONCLUSION

In this paper, we have developed a fuzzy ruled based approach that can be used in postmarketing surveillance systems to enhance the detection of ADRs signal pairs. The fuzzy system has been implemented using FuzzyJess software packages. Using real patient data the detection performance of the approach has been assessed.

REFERENCES

[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]L. A. Zadeh, "Fuzzy sets," Information and Control, vol. 8, pp. 338-353, 1965.
[7] R. Orchard, "Fuzzy reasoning in Jess: the Fuzzy J toolkit and Fuzzy Jess," 2001.
[8] ICD-9-CM, "see http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp."