Uncertainty quantification in the fixation of Drug Dosage to cancer-induced Rats – A computational and Mathematical modeling using Fuzzy evidence theory

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Abstract: Results of any working out are of practical use only if statistics about their accuracy is also available. This is commonly correct in the molecular and drug design where the accuracy in each model is of vital importance. Valuation of the efficiency of changes presented in a prototypical and quantifiable evaluation of the presentation of changed models necessitates quantity for calculating the full uncertainty in designing the drug molecules, the collective impact from all improbability causes. To novelty, such a quantity is some of the points of our research. In the fuzzy model, the consequent of the fuzzy rule is often determined with degrees of belief or credibility because of vague information originating from evidence not strong enough and “lack of specificity”. In this paper, we present a fuzzy model incorporated with the fuzzy Dempster-Shafer Theory. A well-known example of drug dosage prediction is tested, the prediction results show that our fuzzy modeling is very efficient and has a strong expressive power to represent the complex system with uncertain situations.

Keywords: Fuzzy focal elements, fuzzy arithmetic, drug dosage, fixation of Drug Dosage, cancer.

1. Introduction

Cancer is the main cause of death universal. The number of patients analyzed through dissimilar forms of cancer has nearly folded in the previous three decades, and is predicted to increase even upper in the upcoming years if new effective management methods are not developed. Skin cancer and Breast Cancer is common cancer identified both in men and women [1]. The complexes of Schiff base...
derivatives have anti-cancer activity. The anti-cancer efficiency of this Schiff – base compound reduced the progression of the tumor and metastatic spreading. A study was made to develop a mathematical model in fuzzy evidence theory with the key influencing parameters like concentration of drug dosage (mole/lit) versus body weight (mg/kg) of the rats to access the efficiency of these compounds in in-vitro studies. This model can be successful, relate the above process parameters with the drug dosage fixation. The main task of medical science is to analyze diseases. Probability theory is proposed only for randomness uncertainty and it is inappropriate to represent epistemic uncertainty. To overcome the constraint of the probabilistic method. Dempster put forward a theory in 1976 and now it is known as evidence theory (or) Dempster Shafer theory (DST). In a finite discrete space, Dempster Shafer Theory can be interpreted as a generalization of probability theory in which probabilities assigned to sets as to mutually exclusive singleton. In traditional probability theory, the evidence is associated with only one possible event. In Dempster Shafer Theory, evidence can be associated with multiple events. A frame of discernment (or simply a frame) usually denoted as $\Theta$ a set of mutually exclusive and exhaustive proportional hypotheses only of which is true. Evidence is based on two dual non-additive measures, namely Belief measure and Plausibility measure. There is one important function in this theory to define Belief measure and Plausibility measure which is known as Basic Probability Assignments (BPA). Method for finding the accurate value of the interval-valued fuzzy set theory has been studied, extensively for the past few decades. However, the significant innovation of this framework is that fuzzy focal elements allow for the allocation of the probability mass sets or intervals. An important aspect of this theory is the combination of evidence obtained from multiple sources and the modeling of conflict between them. Plash Dutta and Trazid Ali [2] proposed a method to combine fuzzy focal elements and their corresponding Basic Probability Assignments (BPA) of two variables. To study the uncertainty, it is essential to study the interval-valued intuitionistic triangular fuzzy sets. Some set-theoretic operations such as union, intersection, and compliment on hesitant fuzzy sets have also been proposed by Torra [3], Xia and Xu [4] made an investigation of hesitant fuzzy information techniques and their applications in decision making. Zhiming Zhang [5] have recently proposed the concept of interval-valued intuitionistic hesitant fuzzy sets, some basic properties, and improved the operators for interval-valued intuitionistic hesitant triangular fuzzy sets to solve multi-attribute group decision making. This research work illustrates new methods in developing possibility distributions from empirical data, and it briefly describes a special kind of relationship between a possibility distribution and a fuzzy set. The evidence available to the medical doctor about his persistence and medical relations, in general, is fundamentals [6]. To expand the problem, there have recommended many methods [7,8]. In terms of indefinite medicinal information, it can be operated for modeling the diagnostic process. An application of a fuzzy set on medical science fields now proposed a fully established relationship modeling theory [9,10]. Despite the technological importance of 5-Methyl Salicylaldehyde with aniline no such studies on drug dosage, are available in the literature. We report here the above-said studies of 5-Methyl Salicylaldehyde and aniline with CCl4 at 303k over the entire composition range. A good procedure among new data and the values predicted by theoretical technique was obtained.

2. Synthesis of Drug material 5-Methyl Salicylaldehyde with Aniline in CCl4 solvent

Analytical grade reagents were recycled without any additional purification. Materials having reasonable to high solubility in the temperature range ambient to room temperature 303k at atmospheric pressure; form the complexes when their samples were carefully mixed. In the current methods, the many concentrations of the ternary liquid mixes were prepared in terms of mole fractions out of which the mole elements of the first component 5-Methyl Salicylaldehyde are varied from 0.01 to 0.05 ml and the second element aniline were varied from ml. The required solute concentrations of
the above title mixture in 5ml CCl4 was prepared. The construction of the complex was noticed by its pale color and also the absence of precipitation of solid [11]

3. Simplified fuzzy model in drug dosage

Dempster-Shafer Theory of Evidence
We introduce some basic concepts and mechanisms of the Dempster-Shafer theory of evidence [12-15] which required for our procedure. The Dempster-Shafer theory is a formal framework for plausible reasoning providing methods to represent and combine weights of evidence. Let $\Theta$ be a finite set of mutually exclusive and exhaustive events or hypotheses about the problem domain, called the frame of discernment.

A Dempster-Shafer belief structure, information granule $m$, is a collection of non-null subsets of $\Theta$, $Ai$, $i = 1, \ldots, n$, called focal elements, and a set of associated weights $m(Ai)$, called basic probability assignment (BPA). This PBA must be such that

$$m(Ai) \in [0, 1], \quad m(Ai) \neq 0, \quad \sum_{i} m(Ai) = 1 \quad ------ (1)$$

When our knowledge is of the form of a Dempster-Shafer theory belief, because of the imprecision in the information, when attempting to try to find the probabilities associated with arbitrary subsets of $\Theta$ we can’t find exact probabilities but lower and upper probabilities.

Firstly one measure, $\text{Bel}$, is introduced to capture the relevant information. Let $B$ be a subset of $\Theta$, we define

$$\text{Bel}(B) = \sum_{Ai \subseteq B} m(Ai) \quad ------ (2)$$

Then we define $\text{Pl}$

$$\text{Pl}(B) = 1 - \text{Bel}(B). \quad ------ (3)$$

One advantage of Dempster-Shafer theory is its capability to express degrees of ignorance, that is the belief in an event and the belief in its opposite do not necessarily add up to one like in probability theory. A situation of total ignorance is characterized by $m(\Theta) = 1$.

Assume that $m1$ and $m2$ are two independent belief structures on a frame of discernment $\Theta$, with focal elements $Ai$, $i = 1, \ldots, n1$, and $Bj$, $j = 1, \ldots, n2$. Then the conjunction of $m1$ and $m2$ is another belief structure $m = m1 \cap m2$ whose focal elements are all the subsets $Fk$ of $\Theta$, where $Fk = Ai \cap Bj$ and $Fk \neq \emptyset$

The basic probability numbers associated with each $Fk$ are defined as

$$m(Fk) = \frac{1}{1-T} (m1(Ai) \times m2(Bj)) \quad ------ (4)$$

where

$$T = \sum_{Ai \cap Bj} m1(Ai) \times m2(Bj)$$

Now the concept of the fuzzy Dempster-Shafer belief structure can be introduced.

A fuzzy Dempster-Shafer belief structure is a Dempster-Shafer belief structure with fuzzy sets as focal elements [6]. When we combine two fuzzy Dempster-Shafer belief structures using a set operation $\cap$, we simply use its fuzzy version.

Some basic concepts of D-S theory are briefly introduced as follows,

3.1.2 Frame of Discernment:

Let $\Theta = \{\theta_1, \theta_2, \ldots, \theta_n\}$ be a set called frame of discernment, if it contains mutually exclusive and exhaustive events.

3.1.3 Basic Probability Assignments (BPA):

A function $m : 2^\Theta \rightarrow [0,1]$ is called a Basic Probability Assignment (BPA) on $\Theta$ if it satisfies the following three properties (i) $m(\emptyset) = 0$ (ii) $m(A) \geq 0$ (iii) $\sum_{A \subseteq \Theta} m(A) = 1$, $A \in 2^\Theta$ is called a focal element of being’ satisfies $m(A) \geq 0$
3.1.4 Belief Function:
From the BPA, a function $Bel(A) : 2^\Theta \rightarrow [0,1]$ is defined as $Bel(A) = \sum_{B \subseteq A} m(B)$.

3.1.5 Plausibility Function:
From the BPA, a function $Pls(A) : 2^\Theta \rightarrow [0,1]$ is defined as $Pls(A) = \sum_{A \subseteq B \neq \emptyset} m(B)$.

3.1.6 Dempster Rule of Combination:
Let $m_1$ & $m_2$ be two mass functions defined on the same frame of discernment, $\Theta$ and then a combined BPA can be obtained by using Dempster’s combination rule, the combined BPA

$$m = m_1 \oplus m_2$$

is defined as follows

$$m = \begin{cases} \sum_{B \subseteq C \subseteq A} m_1(B) m_2(C), & \forall \phi \subseteq \Theta \\ 1 - \sum_{B \subseteq C \neq \phi} m_1(B) m_2(C), & \text{otherwise} \\ 0, & \text{otherwise} \end{cases}$$

This is known as the Dempster rule of combination [9,10,12].

**Division**

$$A/B = [a_1, a_2]/[b_1, b_2] = [a_1, a_2] \cdot \left[\frac{1}{b_2}, \frac{1}{b_1}\right]$$

$$= \{m(A) m(B) - k, \ (m(A) m(B)) + k\}$$

Where

$$k = \min \{(m(A) m(B)) - \alpha, \beta - m(A) m(B)\}$$

3.1.7 Algebraic combination of fuzzy focal elements:
Let $X_1$ and $X_2$ be two variables whose values are represented by Dempster-Shafer structure with focal elements $A_1, A_2, A_3, \ldots, A_n$ and $B_1, B_2, B_3, \ldots, B_m$ corresponding Basic Probability Assignments (BPA) are as follows:

$$m(A_i) = a_i \quad \text{and} \quad m(B_j) = b_j, \ i = 1, 2, 3, \ldots, n \quad \text{and} \quad j = 1, 2, 3, \ldots, m \quad \text{respectively.}$$

where $\sum_{i=1}^{n} a_i = 1$ and $\sum_{j=1}^{m} b_j = 1$

Initially, we combine all the fuzzy focal elements using fuzzy arithmetic which will produce several fuzzy focal elements and thereafter the corresponding basic probability assignments of resulting fuzzy focal elements will be calculated as follows

4.1 Division:

$$m(C_{ij}) = m(A_i / B_j) = \frac{m(A_i) / m(B_j)}{\sum_{i} \sum_{j} (m(A_i) / m(B_j))}$$

4.2 Numerical example:
Basic Probability Assignments (BPA) of two parameters is assigned by an expert and which are given in the following tables:

| Interval Valued Fuzzy Focal Elements | Basic Probability Assignments |
|-------------------------------------|-------------------------------|
| Weight of Rats (mg/kg) | Drug Dosage (mole/lr) | (BPA) |
| [1,3] | [0.75,0.65] | 0.15 |
| [3,5] | [0.65,0.55] | 0.20 |
4.3 Division of Focal Elements:

Now tabulated the resulting fuzzy focal elements and their corresponding basic probability assignments below.

| Weight of Rats (mg/kg) | Drug Dosage (mole/lr) | BPA Partially Recovered | Drug Dosage (mole/lr) | BPA Completely Recovered |
|------------------------|-----------------------|-------------------------|-----------------------|--------------------------|
| [1,3]                  | [0.75,0.65]           | 0.9427                  | [0.15,0.35]           | 0.3429                   |
| [3,5]                  | [0.65,0.55]           | 0.7642                  | [0.35,0.5]            | 0.2675                   |
| [5,7]                  | [0.55,0.45]           | 0.6429                  | [0.5,0.75]            | 0.2475                   |
| [7,9]                  | [0.45,0.35]           | 0.5426                  | [0.75,0.9]            | 0.1421                   |

It is observed that the arithmetic operators have the advantages of simple calculations and high accuracy (complete recovery of rats) in the division. Those results are Promising and interesting as it is addressed for the first time. An algorithm was developed for the above model.

4.4 Algorithm

Calculate the Division of Intuitionistic Pentagon Fuzzy Focal Elements

Step: A1 Start the Program
Step: A2 Declare and initialize the variable X1 and X2
- X1 mole fractions of 5 Methyl salicylaldehyde
- X2 mole fractions of Aniline
Step: A3 Input the variable
- Input “5 Methyl salicylaldehyde”
- Input “Aniline”, X2
Step: A4 Compute the following

\[
X = \frac{m(A_i)}{m(B_j)}
\]
\[
Y = \sum_{i=1}^{n} \left( \frac{m(A_i)}{m(B_j)} \right)
\]
\[
m \times C_{ij} = \frac{m(A_i)}{m(B_j)} = \frac{X}{Y}
\]
Where \(A_i, (B_j), m, \sum_{i=1}^{\infty} \sum_{j=1}^{\infty}\).

Step: A5 Output the program \(C = X/Y\)

Step: A6 Stop the Program

Numerical example

Step B1: Start the Program

Step B2: Declare and initialize the variables
- Parameter “PARAMETER”
- Drug Dosage

Step B3: Input the parameters; EXPERT A
- Weight of Rats

Step B4: Compute the following
\[
X = m(A_i) / m(B_j) \\
Y = \sum_{i=1}^{\infty} \sum_{j=1}^{\infty} (m(A_i) / m(B_j)) \\
m \times C_{ij} = m(A_i) / m(B_j) = X / Y
\]

Step: B5 Output the program
Step: B6 Stop the Program

5. Conclusion

In this research work, a new technique to quantify the accuracy of models for the above-said applications using the available best databases presented. Also, a new method to quantify and improve the precision of these applications where no best models one available is suggested. Both techniques rely on the mathematical tools of evidence theory, which are customized here for an application to the total uncertainty in designing them. Applications of this approach to design drug molecules have provided encouraging results. The basic probability number of each focal element is interpreted as the conditional probability of the focal element given by the system.

6. Reference

[1] © 2019 American Cancer Society, Inc. All rights reserved. The American Cancer Society is a qualified 501(c)(3) tax-exempt organization. Cancer.org is provided courtesy of the Leo and Gloria Rosen’s family.

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