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Application of fuzzy logic in medical data interpretation

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Abstract

This paper serves the purpose of presentation of a general view of the current applications of fuzzy logic in medicine and bioinformatics. Using fuzzy logic, we particularly review medical aspects. We then recall the geometrical interpretation of fuzzy sets as points in a fuzzy hypercube and present two concrete illustrations in medicine (drug addictions) and in bioinformatics (comparison of genomes).

Keywords: Drug addictions; Genomes; Bioinformatics; Illness; Sickness, Deal, Inherent; Formalism; Render

Introduction

The diagnosis of disease involves inherent to medicine and involves several levels of uncertainty and imprecision.

Depending on the patient, a single disease may manifest itself quite differently and with different intensities. A single symptom may correspond to different disease on the other hand; several diseases present in patient may interact and interfere with the usual description of any of the diseases.

Disease entities uses linguistic terms that are also imprecise and vague of the best and most precise description. Moreover, the classical concepts of health and disease are mutually exclusive and opposite. However, some recent approaches consider both concepts as complementary processes in the same continuum (Jobe and Helgason, 1998, Helgason and Jobe 2003, Helgason and Malik *et al.*, 2001, Kosko 1992, Kosko 1993, Sadegh-Zadeh 1999). According to the definition issued by the World Health Organization (WHO), health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity.

The loss of health can be seen in the three forms : disease, illness, and sickness. To deal with imprecision and uncertainty we have at our disposal fuzzy logic. It is partial truth values, between true and false introducing Fuzzy logic.

According to Aristotelian logic, for a given proposition or state we only have two logical values : true- false, black-white, 1-0. Things are not either black or white, but most of the times are grey, in real life.

Thus, in many practical situations it is convenient to consider intermediate logical values. Let us show this with a very simple medical example. Consider the statement "You are healthy". Is it true if you have only a broken nail? Is it false if you have a terminal cancer?

Everybody is healthy to some degree h and ill to some degree i . If you are totally healthy, then of course $h = 1$, $i = 0$. Usually, everybody has some minor health problems and $h < 1$, but

$$h + i = 1 \longrightarrow (1)$$

In the other extreme situation, $h = 0$ and $i = 1$ so that you are not healthy at all (you are dead). In the case you have only a broken nail, we may write $h = 0.999$, $i = 0.01$; if you have a painful gastric ulcer, $i = 0.6$, $h = 0.4$, but the case you have a terminal cancer probably $i = 0.95$, $h = 0.05$. As we will see, this is a particular case of Kosko's hypercube : the one dimensional case (Kosko 1992).

Fuzzy logic in medicine

The complexity of medical practice makes traditional qualitative approaches of analysis inappropriate. In

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medicine, the lack of information, and its imprecision, and many times, contradictory nature and common facts. The sources of uncertainty can be classified as follows (Abbod *et al.*, 2001).

Information about the patient; Medical history of the patient, which is usually supplied by the patient and/ or his/ her family. This is usually highly subjective and imprecise; Physical examination: The physician usually obtains objective data, but in some cases the boundary between normal and pathological status is not sharp; Laboratory results and other diagnostic tests, but they are also subject to some mistakes and even to improper behavior of the patient prior to the examination; The patient may include simulated, exaggerated, understated symptoms, or may even fail to mention some of them and we stress the paradox of the growing number of mental disorders versus the absence of a natural classification. The classification in critical (i, e, borderline) cases is difficult, particularly when a categorical system of diagnosis is considered.

Fuzzy logic plays an important role in medicine (Abbod *et al.*, 2001) (Barro and Marin 2002, Boegl *et al.*, 2004, Mahfouf *et al.*, 2001, Mordeson *et al.*, 2000, Szczepaniak *et al.*, 2000). Some examples showing that fuzzy logic crosses many disease groups are the following:

To predict the response to treatment with citalopram in alcohol dependence (Naronjo *et al.*, 1997); analyze diabetic neuropathy (Lascio *et al.*, 2002) and to detect early diabetic retinopathy (Zahlm *et al.*, 2000); determine appropriate lithium dosage (Sproule *et al.*, 1997, Stip *et al.*, 2001); calculate volumes of brain tissue from magnetic resonance imaging (MRI) (Brandt *et al.*, 1994) and to analyze functional MRI data (Lu *et al.*, 2003.); characterize stroke subtypes and coexisting causes of ischemic stroke (Jobe and Helgason 1998, Helgason *et al.*, 2001). (Dickerson and Helgason 1997, Helgason and Jobe 1999); improve decision- making in radiation therapy (Papageorgiou *et al.*, 2003); control hypertension during anesthesia (Oshita *et al.*, 1994); determine flexor- tendon repair techniques (Johnson *et al.*, 2001); detect breast cancer (Hassanien AE. 2003), lung cancer (Seker *et al.*, 2003) assist the diagnosis of central nervous systems tumors (astrocytic tumors) (Belacel 2004); visualize nerve fibers in the human brain (Axer *et al.*, 2003); study the auditory P50 component in schizophrenia (Zouridakis *et al.*, 1997) and Many other areas of application, to mention a few, are (a)

(Massad to make decisions in nursing (Im and Chee, 2003); (b) to overcome electro acupuncture accommodation (Zhu *et al.*, 2001).

We used the database MEDLINE to identify the medical publications using fuzzy logic. We used as keywords fuzzy logic and grade of membership. The total number of articles per year appears in Table-I. The data is from 2001 to 2012 and

Table I. Number of Papers per year in medicine using fuzzy logic.

	Year	Number
≤	2000	375
	2001	76
	2002	128
	2003	175
	2004	186
	2005	198
	2006	212
	2007	208
	2008	201
	2009	213
	2010	223
	2011	276
	2012	295

includes also the number of those publications in 2000 and before. It is table of 2766 articles and agrees essentially with the numbers indicated. We plan to screen databases in the engineering literature that covers medicine related articles since it is difficult to publish medical results using a fuzzy logic approach. In the future we will compare the figures obtained.

Fig. 1. indicates an exponential growth in the number of articles in medicine making use of fuzzy technology.

Fuzzy Logic in Bioinformatics

Fuzzy logic and fuzzy technology are now frequently used in bioinformatics. The following are some examples:

To increase the flexibility of protein motifs (Chang *et al.*, 2002); study differences between polynucleotide (Torres and Nieto 2003); analyze experimental expression data (Tomida *et al.*, 2002). using fuzzy adaptive resonance theory; align

functional and ancestral relationships between proteins via fuzzy alignment methods (Blankenbe Cler *et al.* 2003), or using a generalized radial basis function neural network architecture that generates fuzzy classification rules (Wang *et al.* 2003.); analyze the relationships between genes and decipher a genetic network (Ressom *et al.* 2003); process complementary deoxyribonucleic acid (cDNA) microarray images (Lukac *et al.*, 2003). The procedure should be automated due to the large number of spots and it is achieved using a fuzzy vector filtering framework and classify amino acid sequences into different super families (Bandyopadhyay 2005).

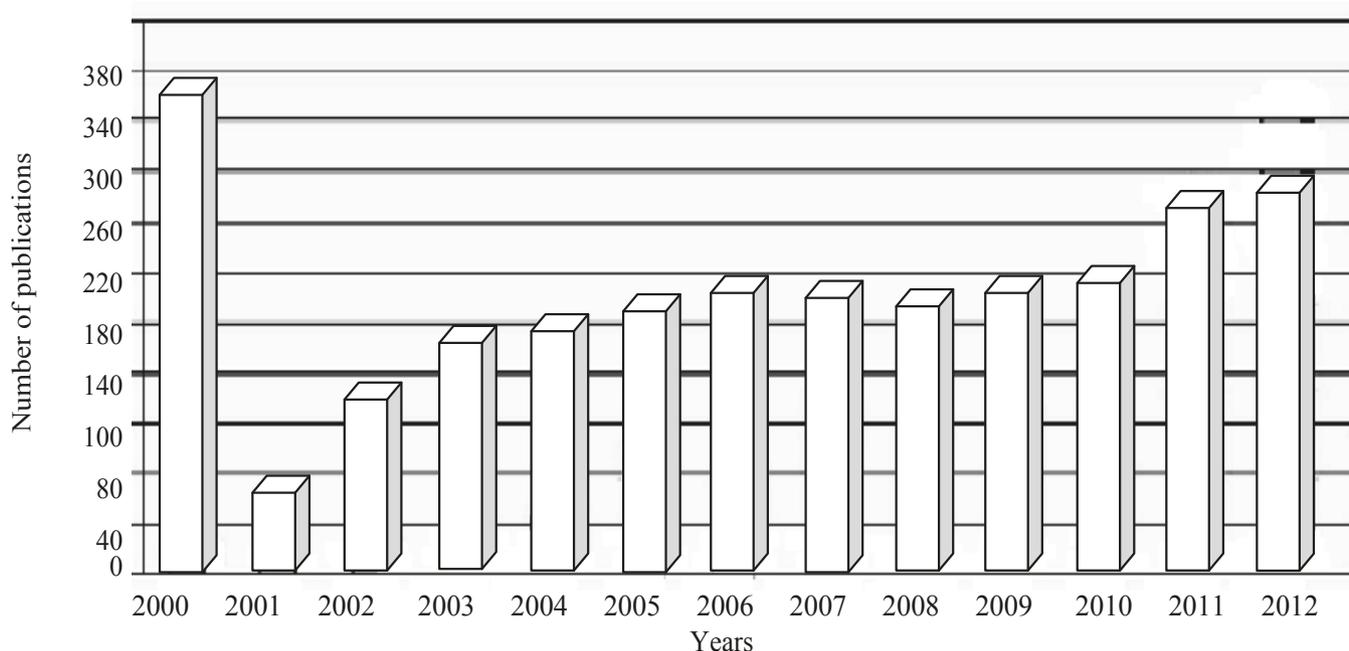


Fig. 1. Number of Publications per year indexed in MEDLINE using fuzzy logic.

sequences based on a fuzzy recast of a dynamic programming algorithm (Schlosshauer and Ohlsson 2002); DNA sequencing using genetic fuzzy systems (Cordon *et al.*, 2004.); cluster genes from microarray data (Belacel *et al.*, 2009) predict proteins subcellular locations from their dipeptide composition (Huang and Li, 2004). using fuzzy k-nearest neighbors algorithm; simulate complex traits influenced by genes with fuzzy- valued effects in pedigreed populations (Carleos *et al.*, 2003). attribute cluster membership values to genes (Dembale and Kastner 2003) applying a fuzzy partitioning method, fuzzy C-means; map specific sequence patterns to putative functional classes since evolutionary comparison leads to efficient functional characterization of hypothetical proteins (Heger and Holm, 2003). The authors used a fuzzy alignment model; analyze gene expression data (Woolf and Wang 2000). unravel

Fuzzy Hypercube

In 1992, Kosko (Kosko 1993) introduced a geometrical interpretation of fuzzy sets as points in a hypercube. In 1998, Helgason and Jobe (Jobe and Helgason 1998.) used the unit hypercube to represent concomitant mechanisms in stroke. Indeed, for a given set

$$X = \{x_1, x_2, \dots, x_n\} \rightarrow (2)$$

a fuzzy subset is just a mapping

$$\mu : X \rightarrow I = [0, 1] \rightarrow (3)$$

and the value $\mu(x)$ expresses the grade of membership of the element to the fuzzy subset.

For example, let X be the set of persons of some population and let the fuzzy set μ be defined as healthy subjects. If John is a member of the population (the set X), then, (Rubel) gives the grade of healthiness of Rubel, or the grade of membership of John to the set of healthy subjects. If μ is the fuzzy set that describes the grade of depression, then (Maya) is the degree of depression of Maya.

Thus, the set of all fuzzy subsets (of X) is precisely the unit hypercube $I^n = [0, 1]^n$, as any fuzzy subset μ determines a point $p \in I^n$ given by $p = (\mu(x_1), \mu(x_2), \dots, \mu(x_n))$. Reciprocally, any point $A = (a_1, a_2, \dots, a_n) \in I^n$ generates a fuzzy subset μ defined by $\mu(x_i) = a_i, i = 1, 2, \dots, n$.

Nonfuzzy or crisp subsets of X are given by mappings $\mu: X \rightarrow \{0, 1\}$, and are located at the 2^n corners of the n -dimensional unit hypercube I^n . For graphic representations of the two-dimensional and three-dimensional hypercube, we refer (Nieto JJ, Torres A., 2003):

$$p = (p_1, p_2, \dots, p_n), q = (q_1, q_2, \dots, q_n) \in I^n \rightarrow (4)$$

not both equal to the empty set $\phi(0, 0, \dots, 0)$, we define the difference between p and q as

$$d(p, q) = \dots \rightarrow (5)$$

$$\frac{\sum_{i=1}^n |p_i - q_i|}{\sum_{i=1}^n \max\{p_i, q_i\}}$$

Of course. We know that d is indeed a metric (Nieto and Torres A. *et al.*, 2003), Hypercubical calculus has been described in (Zaus 1999), while some biomedical applications of the fuzzy unit hypercube has been utilized to study differences between polynucleotides (Nieto and Torres 2003) and to compare genomes (Torres and Nieto, 2003, Nieto *et al.*, 2003).

An application to drug addictions

We now present an example of the use of the fuzzy hypercube in a medical case of consumption of drugs.

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hypercube in a medical case of consumption of drugs.

Consider the following fuzzy variables : Smoking and alcohol drinking. If you do not smoke, then your degree of being a smoker is evidently 0. If you smoke, for example, six cigarettes per day, we say that your degree of being a smoker is 0.8. If the consumption is ten or more, the degree is 1. See (Kasabov *et al.*, 1996). for a geometrical representation of the fuzzy concept of being a smoker.

With respect to the other fuzzy variable, if you drink no alcohol, the degree of this variable is 0. If you drink more than 75 cc of alcohol per day, the degree of alcoholism is 1. For 25 cc/d, the degree could be 0.4 and for 50 cc/d, 0.8.

Thus, the fuzzy set $\mu=(0,0)$ corresponds to a nonsmoker and teetotaler. Some further examples are the following : the set $\mu=(1,0)$ represents a heavy smoker, but a teetotaler, and the set $\mu = (0.8,1)$ is a person who smokes about six cigarettes a day and is a risk consumer of alcohol.

Suppose you correspond to the fuzzy set $\lambda=(1,1)$, have recently had some health problems, and your physician has advised you to reduce your consumption of cigarettes and alcohol by half. The ideal situation for your health is, of course, the point $\mu=(0,0)$, but it is possible difficult to achieve.

Cigarette smoking and alcohol drinking during adolescence have been shown to be associated with a greater possibility of concurrent and future substance-related disorders (Lewinsohn P., *et al.*, 1999) and (Nelson and Wittchen 1998).

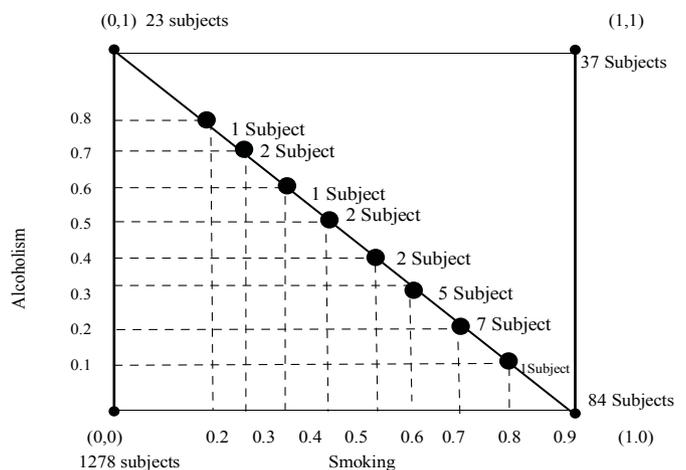


Fig. 2. Number of subjects in the two-dimensional fuzzy hypercube I^2 .

In order to report patterns of drug use and to describe factors associated with substance use in adolescents, a cross-sectional survey was carried out in a representative population sample of 2550 adolescents, aged 12 to 17 years, from Galicia (an autonomous region located in the Northwest of Spain). The original survey covered the use of alcohol, tobacco, illicit drugs, and other psychoactive substances. For tobacco smoking and alcohol drinking, each subject of the population sample was assigned a fuzzy degree of addiction (risk use) and mapped into the two-dimensional hypercube I^2 by an expert.

Several subjects occupy the same point in the two-dimensional hypercube. For example Figure- 2 represents the number of subjects in the cross-sectional survey according to the two fuzzy degrees of addiction.

The reader can see that there are 1278 subjects corresponding to the point (0,0), that is, nonsmoker and teetotalor. Also 7 adolescents are at the point (0.8, 0.2). There are 121 subjects on the line of probability

$$x_1 + x_2 = 1$$

Indeed (See Fig. 2.), $23+1+1+2+2+7+1+84 = 121$.

Most subjects were inside the hypercube but outside the line of probability. This means that the vast majority of subjects ($2429/2550 \approx 95.25\%$) are outside the line of probability. This is in agreement with the fundamental limitation of probability theory with respect to clinical science in general (Jobe and Helgason 1998) and agrees with its results ($29/30 \approx 6.66\%$).

We refer to (Nieto and Torres 2003), for details on the general theory of fuzzy midpoints and their applications. It has been used recently to average biopolymers (Casasnovas and Rossello 2005).

An application to the comparison of genomes

Definition: Nitrogenous Base: In nitrogenous base, there are two elements i, e, DNA (T→Thianine, C→Cytosine, A→Adenine, G→Guanine) and RNA (A→Adenine, G→Guanine, C→Cytosine, U→Uracil).

Definition: Nucleotide: Nucleotide is made by three components i, e, Base, Sugar, and phosphate.

Definition: Codon: The correspondence between specific DNA base sequence, and the amino acids they specify

called genetic code. Each nucleotide triplet is called a codon. A codon is made by three letters.

Whole genome sequence comparison is important in bioinformatics (Torres and Nieto 2003, Castelli et al. 2004).

The complete genome sequence of *Mycobacterium tuberculosis* H37Rv is available at <http://www.ncbi.nlm.nih.gov> with accession number NC_000962.

The genome comprises 4411529 base pairs, contains around 4000 genes, and has a very high guanine+cytosine content (Cole et al., 1998).

Table II. Number of nucleotides at the three base sites of a codon in the coding sequence of *Mycobacterium tuberculosis*.

	T	C	A	G
First base	216051	409011	228244	470868
Second base	269638	416457	233472	404607
Third base	217803	458256	210892	437223

Table III. Fractions of nucleotides at the three base sites of a codon in the coding sequence of *Mycobacterium tuberculosis*. (Multiplying the above numbers by 7.54×10^{-7} , where PH = 7.54 and PH of $H_2O = 10^{-7}$).

	T	C	A	G
First base	0.1632	0.3089	0.1724	0.3556
Second base	0.2036	0.3145	0.1763	0.3056
Third base	0.1645	0.3461	0.1593	0.3302

Table IV. Number of nucleotides at the three base sites of a codon in the coding sequence of *Aquifex aeolicus*.

	T	C	A	G
First base	82722	77800	157096	167050
Second base	159068	84092	168591	72917
Third base	103692	119016	147956	114004

Table V. Fractions of nucleotides at the three base sites of a codon in the coding sequence of *Aquifex aeolicus*. (According to above method).

	T	C	A	G
First base	0.1706	0.1605	0.3241	0.3446
Second base	0.3282	0.1735	0.3478	0.1504
Third base	0.2139	0.2455	0.3052	0.2352

Computing (Torres and Nieto 2003) the number of the nucleotides at the three base sites of a codon in the coding sequences of *M. tuberculosis* (Table II.), and then calculating the corresponding fractions, we have the fuzzy set of frequencies of the genome sequence of *M. tuberculosis* (Table III.).

This set can be considered as a point in the hypercube I^2 . Indeed, the point

$$(0.1632, 0.3089, 0.1724, 0.3556, 0.2036, 0.3145, 0.1763, 0.3056, 0.1645, 0.3461, 0.1593, 0.3302) \in I^{12}. \rightarrow(6)$$

Aquifex aeolicus was one of the earliest diverging, and is one of the most thermophilic, bacteria known (Deckert *et al.*, 1998). It can grow on hydrogen, oxygen, carbon dioxide and mineral salts. The complex metabolic machinery needed for *A. aeolicus* to function as a chemolithoautotroph (an organism which uses an inorganic carbon source for biosynthesis and an inorganic chemical energy source) is encoded within a genome that is only 1/3 the size of the *E. coli* genome.

The corresponding data for *A. aeolicus* was obtained from <http://www.ncbi.nih.gov> with accession number NC_000918, and is presented in Table 4 and 5, respectively. The complete genome sequence has 1551 335 base pairs. The fuzzy set of frequencies of the genome of *A. aeolicus* is

$$(0.1706, 0.1605, 0.3241, 0.3446, 0.3282, 0.1735, 0.3478, 0.1504, 0.2139, 0.2455, 0.3052, 0.2352) \in I^{12}. \rightarrow(7)$$

Using the distance given in (5), it is possible to compute the distance between these two fuzzy sets representing the frequencies of the nucleotides of *A. aeolicus* and *M. tuberculosis* :

$$d(A. aeolicus, M. tuberculosis) = \frac{2.2125}{6.106} \approx 0.3623 \rightarrow(8)$$

In (Torres and Nieto 2003.), we calculate the difference between *M. tuberculosis* and *E. coli* K-12 obtaining

$$d(M. tuberculosis, E. coli) = \frac{0.8506}{3.4253} \approx 0.2483 \rightarrow(9)$$

Using the corresponding data for *E. coli*, (Torres and Nieto 2003),

we get,

$$d(A. aeolicus, E. coli) = \frac{0.8514}{5.0161} \approx 0.1697 \rightarrow(10)$$

Conclusion

The complexity of medical practice makes traditional quantitative approaches of analysis inappropriate. In medicine the lack of information, and its imprecision, and many times contradictory nature are common facts. We classified the sources of these uncertainty. Thus fuzzy logic plays an important role in medicine. We indicate on exponential growth in the number of articles in medicine making use of fuzzy technology.

Bioinformatics derives Knowledge from computer analysis of biological data. This data can consist of the information stored in the genetic code, and also experimental results from various sources, patient statistics, and scientific literature. We discussed fuzzy logic and fuzzy technology are now frequently used in bioinformatics.

The researcher introduced a geometrical interpretation of fuzzy sets as points in a hypercube. Recently, the fuzzy hypercube has been utilized to study differences between polynucleotide and to compare genomes.

We present the use of the fuzzy hypercube in a medical case of consumption of drugs. We refer to details on the general theory of fuzzy midpoints and their applications. It has been used recently to average biopolymers.

Whole genome sequence comparison is important in bioinformatics. Using the distance given in (5), it is possible to compute the distance between these two fuzzy sets representing the frequencies of the nucleotides.

In both case, either drug addiction or comparison of genomes, we find out the result in fuzzy values.

Smoking and alcohol drinking are very effected harmfully to a subjects health. Mycobacterium

Tuberculosis, *Aquifex Aeolicus*, and *Escherichia coli* are very harmful to a patient. In this paper, we study using fuzzy logic about such kind of these drug and genomes which are important for the expert and statistical purpose in the various part of health and diagnosis.

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