

Review Article

Fuzzy Logic in Medicine and Bioinformatics

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The purpose of this paper is to present a general view of the current applications of fuzzy logic in medicine and bioinformatics. We particularly review the medical literature using fuzzy logic. 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).

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INTRODUCTION

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

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

The best and most precise description of disease entities uses linguistic terms that are also imprecise and vague. 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 [1–6]. 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 its three forms: disease, illness, and sickness.

To deal with imprecision and uncertainty, we have at our disposal fuzzy logic. Fuzzy logic introduces partial truth values, between *true* and *false*.

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

$$h + i = 1. \quad (1)$$

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 $h = 0.999$, $i = 0.001$; if you have a painful gastric ulcer, $i = 0.6$, $h = 0.4$, but in 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 [4].

Uncertainty is now considered essential to science and fuzzy logic is a way to model and deal with it using natural language. We can say that fuzzy logic is a qualitative computational approach.

Since uncertainty is inherent in fields such as medicine and massive data in bioinformatics, and fuzzy logic takes into account such uncertainty, fuzzy set theory can be considered as a suitable formalism to deal with the imprecision intrinsic to many biomedical and bioinformatics problems. Fuzzy logic is a method to render precise what is imprecise in the world of medicine. Several examples and illustrations are mentioned below.

FUZZY LOGIC IN MEDICINE

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. The sources of uncertainty can be classified as follows [7].

- (1) Information about the patient.
- (2) Medical history of the patient, which is usually supplied by the patient and/or his/her family. This is usually highly subjective and imprecise.
- (3) Physical examination. The physician usually obtains objective data, but in some cases the boundary between normal and pathological status is not sharp.
- (4) Results of laboratory and other diagnostic tests, but they are also subject to some mistakes, and even to improper behavior of the patient prior to the examination.
- (5) The patient may include simulated, exaggerated, understated symptoms, or may even fail to mention some of them.
- (6) We stress the paradox of the growing number of mental disorders versus the absence of a natural classification [8]. The classification in critical (ie, borderline) cases is difficult, particularly when a categorical system of diagnosis is considered.

Fuzzy logic plays an important role in medicine [7, 9–14]. Some examples showing that fuzzy logic crosses many disease groups are the following.

- (1) To predict the response to treatment with citalopram in alcohol dependence [15].
- (2) To analyze diabetic neuropathy [16] and to detect early diabetic retinopathy [17].
- (3) To determine appropriate lithium dosage [18, 19].
- (4) To calculate volumes of brain tissue from magnetic resonance imaging (MRI) [20], and to analyze functional MRI data [21].
- (5) To characterize stroke subtypes and coexisting causes of ischemic stroke [1, 3, 22, 23].
- (6) To improve decision-making in radiation therapy [24].
- (7) To control hypertension during anesthesia [25].
- (8) To determine flexor-tendon repair techniques [26].
- (9) To detect breast cancer [27, 28], lung cancer [28], or prostate cancer [29].
- (10) To assist the diagnosis of central nervous systems tumors (astrocytic tumors) [30].
- (11) To discriminate benign skin lesions from malignant melanomas [31].
- (12) To visualize nerve fibers in the human brain [32].
- (13) To represent quantitative estimates of drug use [33].
- (14) To study the auditory P50 component in schizophrenia [34].
- (15) Many other areas of application, to mention a few, are
 - (a) to study fuzzy epidemics [35],
 - (b) to make decisions in nursing [36],
 - (c) to overcome electroacupuncture accommodation [37].

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 1. The data is from 1991 to 2002 and

TABLE 1: Number of papers per year in medicine using fuzzy logic.

Year	Number
≤ 1990	13
1991	2
1992	14
1993	24
1994	38
1995	66
1996	58
1997	76
1998	66
1999	68
2000	76
2001	128
2002	175

includes also the number of those publications in 1990 and before. It results in a total of 804 articles and agrees essentially with the numbers indicated in [7, 13]. 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.

Figure 1 indicates an exponential growth in the number of articles in medicine making use of fuzzy technology. The preliminary data we have for 2003 and 2004 [38] supports this tendency.

FUZZY LOGIC IN BIOINFORMATICS

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 (and hence imprecision) from various sources, patient statistics, and scientific literature. Bioinformatics combines computer science, biology, physical and chemical principles, and tools for analysis and modeling of large sets of biological data, the managing of chronic diseases, the study of molecular computing, cloning, and the development of training tools of bio-computing systems [39]. Bioinformatics is a very active and attractive research field with a high impact in new technological development [40].

Molecular biologists are currently engaged in some of the most impressive data collection projects. Recent genome-sequencing projects are generating an enormous amount of data related to the function and the structure of biological molecules and sequences. Other complementary high-throughput technologies, such as DNA microarrays, are rapidly generating large amounts of data that are too overwhelming for conventional approaches to biological data analysis. We have at our disposal a large number of genomes, protein structures, genes with their corresponding expressions monitored in experiments, and single-nucleotide polymorphisms (SNPs) [41]. For example, the EMBL Nucleotide Sequence Database (<http://www.ebi.ac.uk/embl>) has

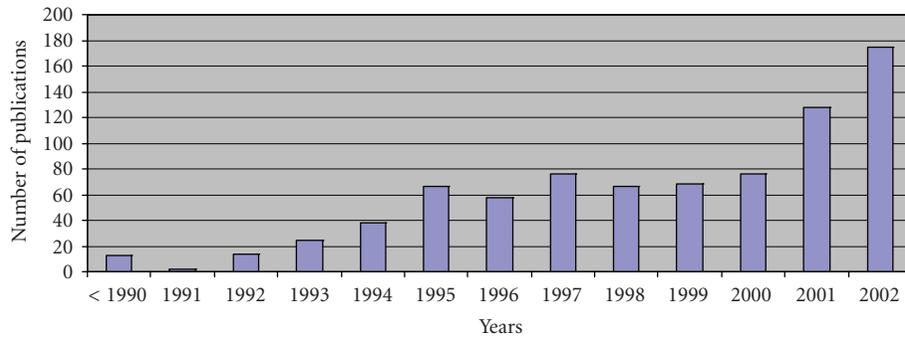


FIGURE 1: Number of publications per year indexed in MEDLINE using fuzzy logic.

increased in 12 months from 18.3 million entries comprising 23 Gb (Release 71, September 2002) to 27.2 million entries comprising over 33 Gb (Release 76, September 2003) as indicated in [42].

Handling this massive amount of data, in many cases imprecise and fuzzy, requires powerful integrated bioinformatics systems and new technologies.

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

- (1) To increase the flexibility of protein motifs [43].
- (2) To study differences between polynucleotides [44].
- (3) To analyze experimental expression data [45] using fuzzy adaptive resonance theory.
- (4) To align sequences based on a fuzzy recast of a dynamic programming algorithm [46].
- (5) DNA sequencing using genetic fuzzy systems [47].
- (6) To cluster genes from microarray data [48].
- (7) To predict proteins subcellular locations from their dipeptide composition [49] using fuzzy k-nearest neighbors algorithm.
- (8) To simulate complex traits influenced by genes with fuzzy-valued effects in pedigreed populations [50].
- (9) To attribute cluster membership values to genes [51] applying a fuzzy partitioning method, fuzzy C-means.
- (10) To map specific sequence patterns to putative functional classes since evolutionary comparison leads to efficient functional characterization of hypothetical proteins [52]. The authors used a fuzzy alignment model.
- (11) To analyze gene expression data [53].
- (12) To unravel functional and ancestral relationships between proteins via fuzzy alignment methods [54], or using a generalized radial basis function neural network architecture that generates fuzzy classification rules [55].
- (13) To analyze the relationships between genes and decipher a genetic network [56].
- (14) To process complementary deoxyribonucleic acid (cDNA) microarray images [57]. The procedure should be automated due to the large number of spots and it is achieved using a fuzzy vector filtering framework.

- (15) To classify amino acid sequences into different superfamilies [58].

THE FUZZY HYPERCUBE

In 1992, Kosko [4] introduced a geometrical interpretation of fuzzy sets as points in a hypercube. In 1998, Helgason and Jobe [1] used the unit hypercube to represent concomitant mechanisms in stroke. Indeed, for a given set

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

a fuzzy subset is just a mapping

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

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

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, μ (John) gives the grade of healthiness of John, or the *grade of membership* of John to the set of *healthy subjects*. If λ is the fuzzy set that describes the grade of depression, then λ (Mary) is the degree of depression of Mary.

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 $P = (\mu(x_1), \dots, \mu(x_n))$. Reciprocally, any point $A = (a_1, \dots, a_n) \in I^n$ generates a fuzzy subset μ defined by $\mu(x_i) = a_i$, $i = 1, \dots, n$. 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 to [59].

Given,

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

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

$$d(p, q) = \frac{\sum_{i=1}^n |p_i - q_i|}{\sum_{i=1}^n \max\{p_i, q_i\}}. \quad (5)$$

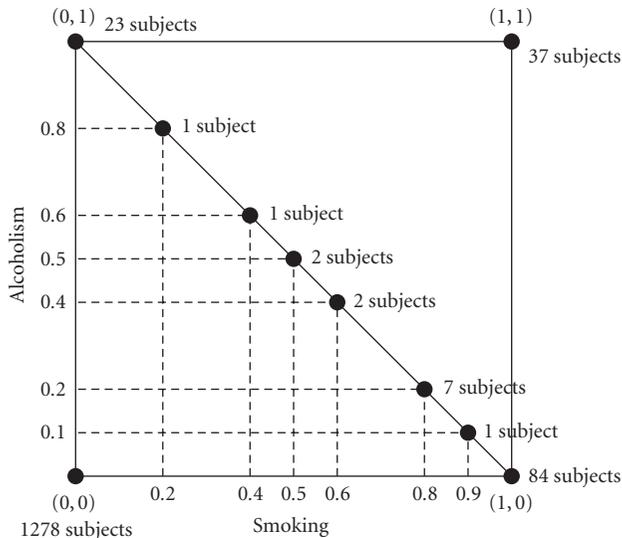


FIGURE 2: Number of subjects in the two-dimensional fuzzy hypercube I^2 .

Of course $d(\emptyset, \emptyset) = 0$. We know that d is indeed a metric [60]. Hypercubical calculus has been described in [61], while some biomedical applications of the fuzzy unit hypercube are given in [1, 6, 59]. Recently, the fuzzy hypercube has been utilized to study differences between polynucleotides [59] and to compare genomes [44, 62].

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.

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 [63, Figure 3.8] 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 possibly 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 disor-

TABLE 2: Number of nucleotides at the three base sites of a codon in the coding sequence of *Mycobacterium tuberculosis*.

	T	C	A	G
First base	216 051	409 011	228 244	470 868
Second base	269 638	416 457	233 472	404 607
Third base	217 803	458 256	210 892	437 223

TABLE 3: Fractions of nucleotides at the three base sites of a codon in the coding sequence of *Mycobacterium tuberculosis*.

	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

ders (Lewinsohn et al [64]; Nelson and Wittchen [65]). 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 (or 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 teetotaler. 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 Figure 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 [1] and agrees with its results ($29/30 \approx 96.66\%$).

We refer to [59] for details on the general theory of fuzzy midpoints and their applications. It has been used recently to average biopolymers [66].

AN APPLICATION TO THE COMPARISON OF GENOMES

Whole genome sequence comparison is important in bioinformatics [44, 67].

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 4 411 529 base pairs, contains around 4000 genes, and has a very high guanine+cytosine

TABLE 4: Number of nucleotides at the three base sites of a codon in the coding sequence of *Aquifex aeolicus*.

	T	C	A	G
First base	82 722	77 800	157 096	167 050
Second base	159 068	84 092	168 591	72 917
Third base	103 692	119 016	147 956	114 004

TABLE 5: Fractions of nucleotides at the three base sites of a codon in the coding sequence of *Aquifex aeolicus*.

	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

content [68]. Computing [44] the number of the nucleotides at the three base sites of a codon in the coding sequences of *M tuberculosis* (Table 2), and then calculating the corresponding fractions, we have the fuzzy set of frequencies of the genome sequence of *M tuberculosis* (Table 3). This set can be considered as a point in the hypercube I^{12} . Indeed, the point

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

Aquifex aeolicus was one of the earliest diverging, and is one of the most thermophilic, bacteria known [69]. 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 one-third the size of the *E coli* genome.

The corresponding data for *A aeolicus* was obtained from <http://www.ncbi.nlm.nih.gov> with accession number NC_000918, and is presented in Tables 4 and 5, respectively. The complete genome sequence has 1 551 335 base pairs. The fuzzy set of frequencies of the genome of *A aeolicus* is

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

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*:

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

In [44] we calculate the difference between *M tuberculosis* and *E coli K-12* obtaining

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

Using the corresponding data for *E coli* (see [44, Tables 3 and 4]), we get

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

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REFERENCES

- [1] Jobe TH, Helgason CM. The fuzzy cube and causal efficacy: representation of concomitant mechanisms in stroke. *Neural Networks*. 1998;11(3):549–555.
- [2] Helgason CM, Jobe TH. Perception-based reasoning and fuzzy cardinality provide direct measures of causality sensitive to initial conditions in the individual patient (Invited paper). *International Journal of Computational Cognition*. 2003;1(2):70–104.
- [3] Helgason CM, Malik DS, Cheng S-C, Jobe TH, Mordeson JN. Statistical versus fuzzy measures of variable interaction in patients with stroke. *Neuroepidemiology*. 2001;20(2):77–84.
- [4] Kosko B. *Neural Networks and Fuzzy Systems*. Englewood Cliffs, NJ: Prentice-Hall; 1992.
- [5] Kosko B. *Fuzzy Thinking: The New Science of Fuzzy Logic*. New York, NY: Hyperion Press; 1993.
- [6] Sadegh-Zadeh K. Fundamentals of clinical methodology: 3. Nosology. *Artificial Intelligence in Medicine*. 1999;17(1):87–108.
- [7] Abbod MF, von Keyserlingk DG, Linkens DA, Mahfouf M. Survey of utilisation of fuzzy technology in Medicine and Healthcare. *Fuzzy Sets and Systems*. 2001;120(2):331–349.
- [8] Marchais P. De l'esprit et des modes de classification en psychiatrie [Classification in psychiatry: principles, modes and ways of thinking]. *Annales Medico-Psychologiques*. 2002;160(3):247–252.
- [9] Barro S, Marin R. *Fuzzy Logic in Medicine*. Heidelberg, Germany: Physica; 2002.
- [10] Boegl K, Adlassnig KP, Hayashi Y, Rothenfluh TE, Leitich H. Knowledge acquisition in the fuzzy knowledge representation framework of a medical consultation system. *Artificial Intelligence in Medicine*. 2004;30(1):1–26.
- [11] Mahfouf M, Abbod MF, Linkens DA. A survey of fuzzy logic monitoring and control utilisation in medicine. *Artificial Intelligence in Medicine*. 2001;21(1–3):27–42.
- [12] Mordeson JN, Malik DS, Cheng S-C. *Fuzzy Mathematics in Medicine*. Heidelberg, Germany: Physica; 2000.
- [13] Steimann F. On the use and usefulness of fuzzy sets in medical AI. *Artificial Intelligence in Medicine*. 2001;21(1–3):131–137.
- [14] Szczepaniak PS, Lisoba PJG, Kacprzyk J. *Fuzzy Systems in Medicine*. Heidelberg, Germany: Physica; 2000.
- [15] Naranjo CA, Bremner KE, Bazoon M, Turksen IB. Using fuzzy logic to predict response to citalopram in alcohol dependence. *Clinical Pharmacology and Therapeutics*. 1997;62(2):209–224.
- [16] Lascio LD, Gisolfi A, Albulia A, Galardi G, Meschi F. A fuzzy-based methodology for the analysis of diabetic neuropathy. *Fuzzy Sets and Systems*. 2002;129(2):203–228.
- [17] Zahlmann G, Kochner B, Ugi I, et al. Hybrid fuzzy image processing for situation assessment. *IEEE Engineering in Medicine and Biology Magazine*. 2000;19(1):76–83.
- [18] Sproule BA, Bazoon M, Shulman KI, Turksen IB, Naranjo CA. Fuzzy logic pharmacokinetic modeling: application to lithium concentration prediction. *Clinical Pharmacology and Therapeutics*. 1997;62(1):29–40.

- [19] Stip E, Dufresne J, Boulerice B, Elie R. Accuracy of the Pepin method to determine appropriate lithium dosages in healthy volunteers. *Journal of Psychiatry & Neuroscience*. 2001;26(4):330–335.
- [20] Brandt ME, Bohan TP, Kramer LA, Fletcher JM. Estimation of CSF, white and gray matter volumes in hydrocephalic children using fuzzy clustering of MR images. *Computerized Medical Imaging and Graphics*. 1994;18(1):25–34.
- [21] Lu Y, Jiang T, Zang Y. Region growing method for the analysis of functional MRI data. *NeuroImage*. 2003;20(1):455–465.
- [22] Dickerson JA, Helgason CM. The characterization of stroke subtype and science of evidence-based medicine using fuzzy logic. *Journal of Neurovascular Disease*. 1997;2(4):138–144.
- [23] Helgason CM, Jobe TH. Causal interactions, fuzzy sets and cerebrovascular “accident”: the limits of evidence-based medicine and the advent of complexity-based medicine. *Neuroepidemiology*. 1999;18(2):64–74.
- [24] Papageorgiou EI, Stylios CD, Groumpos PP. An integrated two-level hierarchical system for decision making in radiation therapy based on fuzzy cognitive maps. *IEEE Transactions on Biomedical Engineering*. 2003;50(12):1326–1339.
- [25] Oshita S, Nakakimura K, Sakabe T. Hypertension control during anesthesia. Fuzzy logic regulation of nicardipine infusion. *IEEE Engineering in Medicine and Biology Magazine*. 1994;13(5):667–670.
- [26] Johnson M, Firoozbakhsh K, Moniem M, Jamshidi M. Determining flexor-tendon repair techniques via soft computing. *IEEE Engineering in Medicine and Biology Magazine*. 2001;20(6):176–183.
- [27] Hassanien AE. Intelligent data analysis of breast cancer based on rough set theory. *International Journal on Artificial Intelligence Tools*. 2003;12(4):465–479.
- [28] Seker H, Odetayo MO, Petrovic D, Naguib RN. A fuzzy logic based-method for prognostic decision making in breast and prostate cancers. *IEEE Transactions on Information Technology in Biomedicine*. 2003;7(2):114–122.
- [29] Schneider J, Peltri G, Bitterlich N, et al. Fuzzy logic-based tumor marker profiles including a new marker tumor M2-PK improved sensitivity to the detection of progression in lung cancer patients. *Anticancer Research*. 2003;23(2A):899–906.
- [30] Belacel N, Boulassel MR. Multicriteria fuzzy classification procedure PROCFTN: methodology and medical application. *Fuzzy Sets and Systems*. 2004;141(2):203–217.
- [31] Stanley RJ, Moss RH, Van Stoecker W, Aggarwal C. A fuzzy-based histogram analysis technique for skin lesion discrimination in dermatology clinical images. *Computerized Medical Imaging and Graphics*. 2003;27(5):387–396.
- [32] Axer H, Jantzen J, Keyserlingk DG, Berks G. The application of fuzzy-based methods to central nerve fiber imaging. *Artificial Intelligence in Medicine*. 2003;29(3):225–239.
- [33] Matt GE, Turingan MR, Dinh QT, Felsch JA, Hovell MF, Gehrman C. Improving self-reports of drug-use: numeric estimates as fuzzy sets. *Addiction*. 2003;98(9):1239–1247.
- [34] Zouridakis G, Boutros NN, Jansen BH. A fuzzy clustering approach to study the auditory P50 component in schizophrenia. *Psychiatry Research*. 1997;69(2-3):169–181.
- [35] Massad E, Ortega NR, Struchiner CJ, Burattini MN. Fuzzy epidemics. *Artificial Intelligence in Medicine*. 2003;29(3):241–259.
- [36] Im EO, Chee W. Fuzzy logic and nursing. *Nursing Philosophy*. 2003;4(1):53–60.
- [37] Zhu QM, Sun XW, Pipe AG. A fuzzy controller to overcome EA accommodation, In: Proceedings of IFAC conference on new technologies for computer control. 2001; Hong Kong, China. 493–498.
- [38] Torres A, Nieto JJ. Fuzzy logic and technology in medicine and psychiatry. preprint, 2004.
- [39] Bourbakis NG. Bio-imaging and bio-informatics. *IEEE Transactions on Systems, Man and Cybernetics, Part B: Cybernetics*. 2003;33(5):726–727.
- [40] Fuchs R. From sequence to biology: the impact on bioinformatics. *Bioinformatics*. 2002;18(4):505–506.
- [41] Valencia A. Bioinformatics: biology by other means. *Bioinformatics*. 2002;18(12):1551–1552.
- [42] Kulikova T, Aldebert P, Althorpe N, et al. The EMBL nucleotide sequence database. *Nucleic Acids Research*. 2004;32(database issue):D27–D30.
- [43] Chang BC, Halgamuge SK. Protein motif extraction with neuro-fuzzy optimization. *Bioinformatics*. 2002;18(8):1084–1090.
- [44] Torres A, Nieto JJ. The fuzzy polynucleotide space: basic properties. *Bioinformatics*. 2003;19(5):587–592.
- [45] Tomida S, Hanai T, Honda H, Kobayashi T. Analysis of expression profile using fuzzy adaptive resonance theory. *Bioinformatics*. 2002;18(8):1073–1083.
- [46] Schlosshauer M, Ohlsson M. A novel approach to local reliability of sequence alignments. *Bioinformatics*. 2002;18(6):847–854.
- [47] Cordón O, Gomide F, Herrera F, Hoffmann F, Magdalena L. Ten years of genetic fuzzy systems: current framework and new trends. *Fuzzy Sets and Systems*. 2004;141(1):5–31.
- [48] Belacel N, Čuperlović-Culf M, Laflamme M, Ouellette R. Fuzzy J-Means and VNS methods for clustering genes from microarray data. *Bioinformatics*. 2004;20(11):1690–1701.
- [49] Huang Y, Li Y. Prediction of protein subcellular locations using fuzzy k-NN method. *Bioinformatics*. 2004;20(1):21–28.
- [50] Carleos C, Rodriguez F, Lamelas H, Baro JA. Simulating complex traits influenced by genes with fuzzy-valued effects in pedigreed populations. *Bioinformatics*. 2003;19(1):144–148.
- [51] Dembélé D, Kastner P. Fuzzy C-means method for clustering microarray data. *Bioinformatics*. 2003;19(8):973–980.
- [52] Heger A, Holm L. Sensitive pattern discovery with ‘fuzzy’ alignments of distantly related proteins. *Bioinformatics*. 2003;19(suppl 1):i130–i137.
- [53] Woolf PJ, Wang Y. A fuzzy logic approach to analyzing gene expression data. *Physiological Genomics*. 2000;3(1):9–15.
- [54] Blankenbecler R, Ohlsson M, Peterson C, Ringnér M. Matching protein structures with fuzzy alignments. *Proceedings of the National Academy of Sciences of the United States of America*. 2003;100(21):11936–11940.
- [55] Wang DH, Lee NK, Dillon TS. Extraction and optimization of fuzzy protein sequence classification rules using GRBF neural networks. *Neural Information Processing—Letters and Reviews*. 2003;1(1):53–59.
- [56] Resson H, Reynolds R, Varghese RS. Increasing the efficiency of fuzzy logic-based gene expression data analysis. *Physiological Genomics*. 2003;13(2):107–117.
- [57] Lukac R, Plataniotis KN, Smolka B, Venetsanopoulos AN. cDNA microarray image processing using fuzzy vector filtering framework. *Fuzzy Sets and Systems*. 2005;152(1):17–35.
- [58] Bandyopadhyay S. An efficient technique for superfamily classification of amino acid sequences: feature extraction, fuzzy clustering and prototype selection. *Fuzzy Sets and Systems*. 2005;152(1):5–16.

-
- [59] Nieto JJ, Torres A. Midpoints for fuzzy sets and their application in medicine. *Artificial Intelligence in Medicine*. 2003;27(1):81–101.
- [60] Nieto JJ, Torres A, Vázquez-Trasande MM. A metric space to study differences between polynucleotides. *Applied Mathematics Letters*. 2003;16(8):1289–1294.
- [61] Zaus M. *Crisp and Soft Computing With Hypercubical Calculus*. Heidelberg, Germany: Physica; 1999.
- [62] Nieto JJ, Torres A, Georgiou DN, Karakasidis T. Fuzzy polynucleotide spaces and metrics. to appear in *Bulletin of Mathematical Biology*.
- [63] Kasabov NK. *Foundations of Neural Networks, Fuzzy Systems and Knowledge Engineering*. Cambridge, Mass: MIT Press; 1996.
- [64] Lewinsohn PM, Rohde P, Brown RA. Level of current and past adolescent cigarette smoking as predictors of future substance use disorders in young adulthood. *Addiction*. 1999;94(6):913–921.
- [65] Nelson CB, Wittchen HU. DSM-IV alcohol disorders in a general population sample of adolescents and young adults. *Addiction*. 1998;93(7):1065–1077.
- [66] Casanovas J, Rosselló F. Averaging fuzzy biopolymers. *Fuzzy Sets and Systems*. 2005;152(1):139–158.
- [67] Castelli V, Aury J-M, Jaillon O, et al. Whole genome sequence comparisons and “full-length” cDNA Sequences: a combined approach to evaluate and improve *Arabidopsis* genome annotation. *Genome Research*. 2004;14(3):406–413.
- [68] Cole ST, Brosch R, Parkhill J, et al. Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature*. 1998;393(6685):537–544.
- [69] Deckert G, Warren PV, Gaasterland T, et al. The complete genome of the hyperthermophilic bacterium *Aquifex aeolicus*. *Nature*. 1998;392(6674):353–358.