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Fuzzy Relationships and Fuzzy Control in Medical Knowledge-Based Systems

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Abstract

Some of the first knowledge-based systems to be introduced were medical knowledge-based systems, namely MYCIN, INTERNIST, CASNET, PIP, EXPERT, and CADIAG. The latter is one of the first to use the theory of fuzzy sets. It was developed to assist the physician in diagnostics.

The present article delineates two specific pathways resulting from a bifurcation in the history of applied fuzzy systems in medicine. This bifurcation occurred in the 1970's in the history of the theory of fuzzy sets and systems, when Lotfi A. Zadeh published the "rule of max-min composition" and other researchers applied this rule in different areas. This was the origin of two research areas: fuzzy control, initiated by Sedrak Assilian and Ebrahim Mamdani in London, and fuzzy relations, introduced by Elie Sanchez in Marseille. Later on both concepts were used to construct medical knowledge-based systems in medicine. We present two Viennese systems representing these concepts: the "fuzzy version" of the Computer-Assisted DIAGnostic System (CADIAG) which was developed at the end of the 1970s, and a fuzzy knowledge-based control system, FuzzyKBWean, which was established as a real-time application based on the use of a Patient Data Management System (PDMS) in the intensive care unit (ICU)in 1996.

1 Introduction

The history of fuzzy knowledge-based systems in medicine can be viewed in a selective manner. The earliest beginnings can be traced back to *general non-fuzzy* knowledge-based systems. Medical knowledge-based systems were introduced very early, the first of these being MYCIN, INTERNIST, CASNET, PIP, EXPERT, and CADIAG. Knowledge-based systems were also developed and applied in several other areas, but these will not be dealt with here.

The present article delineates two specific pathways through an eventful history. They result from a bifurcation in the development of fuzzy systems developed to assist the physician in medical science. This branching occurred in the 1970's in the history of the theory of fuzzy sets and systems, when Lotfi A. Zadeh's "rule of max-min composition" (Arnold Kaufmann termed it meta-implication) was applied in different areas. *Fuzzy control* was initiated by Sedrak Assilian and Ebrahim Mamdani in London, UK, [1], whereas *fuzzy relations* were generally introduced by Zadeh [2] and into medical sciences by Elie Sanchez in Marseille, France [3, 4].

Today, both concepts are used to construct medical knowledge-based systems in medicine. The branch of fuzzy relations has been used to model "medical knowledge" expressing associations between symptoms and diseases. Using this approach, a "fuzzy version" of the *C*omputer-*A*ssisted *DIAG*nostic System was developed in 1980 at the University of Vienna Medical School in collaboration with the Vienna General Hospital. The version is based on Klaus-Peter Adlassnig's *Fuzzy Logical Model of Computer-Assisted Medical Diagnosis* [5].

The branch of fuzzy control is being implemented in medical application systems since the 1990's, as real-time applications are being adequately executed by computers since this time. Scientists and physicians at the University of Vienna Medical School and the Vienna General Hospital established the fuzzy knowledge-based control system FuzzyKBWean as a real-time application, based on the use of a Patient Data Management System (PDMS) in the intensive care unit (ICU) in 1996.

2 Fuzzy Sets, Fuzzy Relations, and Fuzzy Control

Any history of *fuzzy* knowledge-based systems in medicine must take the development of the fuzzy set theory into account. This important branch of mathematics originated in the second half of the 20th century (1960's). Zadeh, a professor of electrical engineering at the University of California, Berkeley, defined fuzzy sets by their characteristic function (membership function), which is allowed to assume any value in the interval [0,1]. The space of all fuzzy sets in a given set becomes a Boolean algebra; thus, a propositional logic with fuzzy concepts constitutes fuzzy logic.

In 1973, Zadeh defined *fuzzy* relations: If $L(A\times B)$ is the set of all fuzzy sets in the Cartesian product $A \times B$ of crisp sets A and B, than a fuzzy relation is a subset of $L(A\times B)$ [2].

Having three sets A, B, and C, to compose fuzzy relations $Q \subseteq L(A\times B)$ and $R \subseteq L(B\times C)$ to get another fuzzy relation $T \subseteq L(A\times C)$, Zadeh introduced the combination rule of a *max-min-composition*: $T = Q * R$ is defined by the following membership function

$$\mu_T(x, y) = \max_{y\in B} \min\{\mu_Q(x, y); \mu_R(y, z)\},\ x\in A\ y\in B\ z\in C.$$

Using this composition formula as an inference rule, Assilian and Mamdani developed the concept of *fuzzy control* in the early 1970s [1, 7]. Fuzzy control can be described as "control with sentences rather than equations". In many cases, it is more natural to use sentences, or rules, for instance in operator-controlled systems, with the control strategy written in terms of if-then clauses. If the controller further adjusts the control strategy without human intervention, it is *adaptiv*e. The adaptive *fuzzy* controller, invented by Assilian and Mamdani, is known as the *self-organising fuzzy controller*. An adaptive controller is a controller with adjustable parameters and a mechanism for adjusting the parameters [6]. Despite the lack of a formal definition, an adaptive controller has a distinct architecture consisting of two loops: a control loop and a parameter adjustment loop (see figure 1).

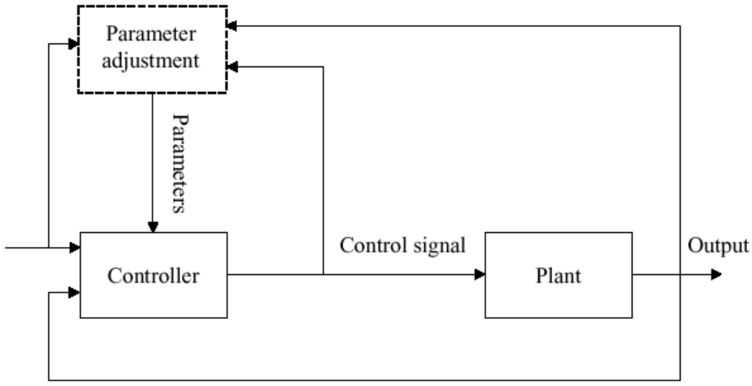

Figure 1: Adaptive control system

In other words, fuzzy control is based on an I/O function that maps each very low-resolution quantization interval of the input domain into a very low-low resolution quantization interval of the output domain. As there are a few fuzzy quantization intervals covering the input domains, the mapping relationship can be very easily expressed using the "if-then" formalism. (In some applications this leads to a simpler solution in less designing time.) The overlapping of these fuzzy domains and their usually linear membership functions will eventually allow a rather high-resolution I/O function between crisp input and output variables to be achieved. Mamdani's development of fuzzy controllers in 1974 [7] gave rise to the utilization of these fuzzy controllers in ever-expanding capacities.

3 Fuzzy Systems in Medicine

Four years after his first paper on fuzzy sets, Zadeh suggested their application in medical science. He wrote: "A human disease, e.g., diabetes, may be regarded as a fuzzy set in the following sense. Let $X = \{x\}$ denote the collection of human beings. Then diabetes is a fuzzy set, say D, in X, characterized by a membership function $\mu_D(x)$ which associates with each human being x his grade of membership in the fuzzy set of diabetes" ([8], p. 205).

Merle Anne Albin, a mathematician in Berkeley wrote her doctoral thesis *Fuzzy Sets and Their Applications to Medical Diagnosis and Pattern Recognition* in 1975 [9], and a year later in Toronto, Canada, Alonso Perez-Ojeda wrote his master thesis *Medical Knowledge Network. A Database for Computer Aided Diagnosis* [10]. Harry Wechsler published his *Applications of Fuzzy Logic to Medical Diagnosis* [11] while Augustine O. Esogbue and Robert C. Elder published two parts of a *fuzzy model* of a physician's decision process in the new journal *Fuzzy Sets and Systems* in 1979 and 1980 [12, 13]. All these articles took no notice of Zadeh's thoughts on the application of his fuzzy sets in medicine!

3.1 "Medical Knowledge" as a Fuzzy Relation

In the cited article [8], Zadeh formulated his thoughts on medical applications of the theory of fuzzy sets very accurately: "In some cases, it may be more convenient to characterize a fuzzy set representing a disease not by its membership function but by its relation to various symptoms which in themselves are fuzzy in nature. For example, in the case of diabetes a fuzzy symptom may be, say, a hardening of the arteries. If this fuzzy set in X is denoted by A, then we can speak of the fuzzy inclusion relation between D and A and assign a number in the interval [0,1] to represent the "degree of containment" of A in D. In this way, we can provide a partial characterization of D by specifying the degrees of containment of various fuzzy symptoms A_1, …, A_k in D. When arranged in a tabular form, the degrees of containment constitute what might be called a *containment table*” ([8], p. 205).

When four years later Perez-Ojedas considered the “particular area of medical diagnosis ... in order to develop a prototype system to be used in the search for an adequate strategy for the simulation of an approximate reasoning model in medical decision-making”, he proposed to represent “medical knowledge” as a network of symptoms and diseases which are connected to each other by logical relations ([10], p. INTRO.1). He gave examples of typical elements of this “medical knowledge” ([10], p. 3.2):

- “Acute pyelonephritis *usually* presents bladder irritation and infection. ”
- “Acute pyelonephritis presents *occasionally* fever, or chills, and malaise.”
- “A runny nose is *almost always* present in a common cold. ”

The abbreviations D_1 and D_2 represent the diseases *acute pyelonephritis* und *common cold* and S_1 to S_6 mean *runny nose*, *fever*, *bladder irritation*, *infection*, *chills*, and *malaise*. Therefore the “network of medical knowledge” could be graphically constructed by elementary knots and arcs. However, Perez-Ojeda modeled the relations (*usually*, *occasionally*, and *almost*) by mathematical probability modifiers:

$$D_1 \xrightarrow{\textit{almost always}} S_1$$

$$D_2 \xrightarrow{\textit{usually}} S_3 \text{ AND } S_4$$

$$D_2 \xrightarrow{\textit{occasionally}} (S_2 \text{ OR } S_5) \text{ AND } S_6$$

Figure 2: Examples of elements of the network “medical knowledge”.

A more far-reaching concept of modeling relationships between symptoms and diseases was introduced in 1974 by Elie Sanchez from Marseille, France, in his human biological doctoral thesis “Equations de Relations Floues” [3]. Sanchez planned “to investigate medical aspects of fuzzy relations at some future time” ([4], p. 47). In 1979 he introduced the relationship between symptoms and diagnoses by the concept of ‘medical knowledge’: “In a given pathology, we denote by S a set of symptoms, D a set of diagnoses and P a set of patients. What we call “medical knowledge” is a fuzzy relation, generally denoted by R, from S to D expressing associations between symptoms, or syndromes, and diagnoses, or groups of diagnoses” ([14], p. 438).

Sanchez adopted Zadeh’s *compositional rule of inference* as an inference mechanism. It accepts fuzzy descriptions of the patient’s symptoms and infers fuzzy descriptions of the patient’s diseases by means of the fuzzy relationships described earlier. If a patient’s symptom is S_i then the patient’s state in terms of diagnoses is a fuzzy set D_j with the following membership function:

$$\mu_{D_i}(d) = \max_{s\in S} \min\{\mu_{S_i}(s); \mu_R(s,d)\}, \; s\in S, \; d\in D.$$

$\mu_R(s,d)$ is the membership function of the fuzzy relation ‘medical knowledge’.

With P, a set of patients, and a fuzzy relation Q from P to S, and by 'max-min composition' we get the fuzzy relation $T = Q * R$ with the membership function

$$\mu_T(p,d) = \max_{s \in S} \min\{\mu_Q(p,s); \mu_R(s,d)\}, p \in P, s \in S, d \in D.$$

3.2 Computer-Assisted Diagnostic

In the nineteen-sixties and seventies, the Department of Medical Computer Sciences at the University of Vienna Medical School and the Vienna General Hospital envisaged the development of a computer-assisted diagnostic system that did not use stochastic methods. To systemize and formalize medical knowledge and to store it in a suitable form, Georg Grabner (professor of gastroenterology and hepatology and both head of the University Department of Medical Computer Sciences and, at the same time, head of the University Clinic of Gastroenterology and Hepatology) and the IBM information scientist W. Spindelberger started to use a computer for medical diagnosis in the late 1960's. This was followed by intensive collaboration between physicians and mathematicians, and engineers constructed a first *c*omputer-*a*ssisted *diag*nostic system basing on two-value logic in 1968 [15]. One year later Gangl, Grabner, and Bauer published their first experiences with this system in the differential diagnostics of hepatic diseases [16].

When Klaus-Peter Adlassnig came to the Vienna Institute in 1976, the second generation of the system was developed on the basis of three-valued logic. Here, in addition to symptoms and diagnoses being considered to be 'present' or 'absent', 'not examined' or 'not investigated' symptoms and 'possible' diagnoses are also included. For this system known as CADIAG-I (*C*omputer-*A*ssisted *DIAG*nostic), the following relationships between symptom (S_i) and disease (D_j) have been defined:

- OP: S_i is *obligatory occurring and proving* for D_j.
- E: S_i forces *obligatory exclusion* of D_j.
- FP: S_i is *facultative occurring and proving* for D_j.
- ON: S_i is *obligatory occurring and not proving* for D_j.
- FN: S_i is *facultative occurring and not proving* for D_j.
- NK: A specific relationship between the symptom and the disease is *not known*.

With three-valued logic these relationships could be expressed in the form of three-valued logic operators: the symptom's values could be *present* (1), *absent* (0), or *not investigated* (½), whereas the possible diagnoses' values could be *present* (1), *absent* (0), or *possible* (½).

As an example we show here the three-valued logic truth table of the relationship OP (S_i is *obligatory and proving*. S_i must be present for D_j and S_i proves D_j; $S_i \Leftrightarrow D_j$.)

D_j / S_i	**0**	**½**	**1**
0	1	½	0
½	½	½	½
1	0	½	1

Figure 3: Three-valued logic truth table of OP: $S_i \Leftrightarrow D_j$.

Adlassnig was aware of the theory of fuzzy sets and the fact that it had been used in computer-aided diagnosis. In his first paper together with Grabner, *The Viennese Computer-Assisted Diagnostic System. Its Principles and Values* in 1980 [17], he referred to the medical diagnostic systems using the concept of fuzzy sets by Tautu and Wagner [18] and by Moon et al. [19]. He now proposed to integrate this concept into a more suitable version of the system CADIAG: "Fuzzy set theory with its capability of defining inexact medical entities as fuzzy sets, with its linguistic approach providing an excellent approximation to medical texts as well as its power of approximate reasoning, seems to be perfectly appropriate for designing and developing computer-assisted diagnostic, prognostic and treatment recommendation systems" ([20], p. 205).

This new fuzzy version of the computer-assisted diagnostic system, CADIAG-II, appeared in 1980. In Adlassnig's *fuzzy logical model of computer-assisted medical diagnosis* [20], all symptoms $S_i \in \Sigma$ are considered to be fuzzy sets of different universes of discourse X with membership functions $\mu_{S_i}(x)$, for all $x \in X$, indicating the strength of x's affiliation in S_i, while all diagnoses $D_j \in \Delta$ are considered to be fuzzy sets in the set Π of all patients under consideration, with $\mu_{D_i}(p)$ assigning the patient p's membership to be subject to D_j.

To describe 'medical knowledge' as the relationship between symptom S_i and disease D_j Adlassnig found two fuzzy relationships, namely *occurrence* (How often does S_i occur with D_j ?) and *confirmability* (How strongly does S_i confirm D_j?) ([21], p. 225). These functions could be determined by

- linguistic documentation by medical experts and
- medical database evaluation by statistical means or a combination of both.

In both ways to determine these fuzzy relationships between symptoms and diagnoses, *occurrence* and *confirmation*, they have been defined as fuzzy sets. When physicians had to specify these relationships by only giving answers like *always*, *almost always*, *very often*, *often*, *unspecific*, *seldom*, *very seldom*, *almost never*, and *never*, they choose fuzzy sets which have been defined by Adlassnig's determination of their membership functions. In the case of medical databases, the membership functions' values of *occurrence* and *confirmability* could be defined as relative frequencies.

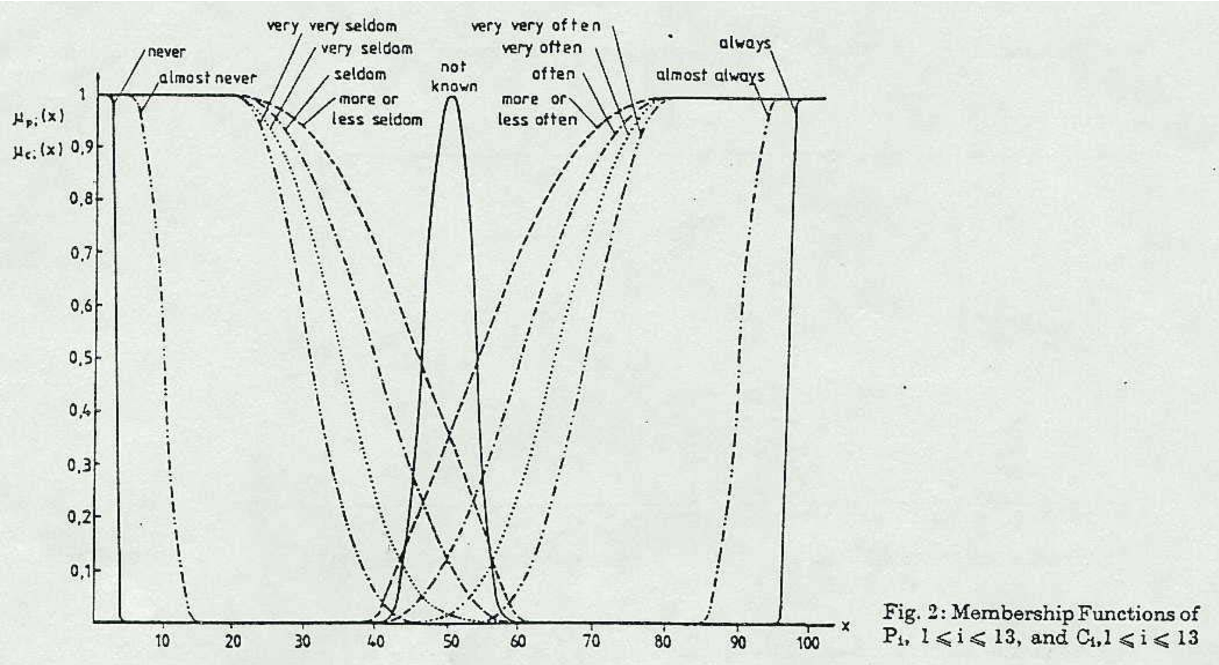

Figure 4: Membership functions of the fuzzy sets *occurrence o (former presence p)* and *confirmability (former conclusiveness c)* ([6], p. 145)

Thus, in CADIAG-II, the fuzzy relationships between symptoms (or symptom combinations) and diseases are given in the form of rules with associated fuzzy relationship tupels (*frequency of occurrence o*, *strength of confirmation c*); their general formulation is ([22], p. 262):

- IF antecedent THEN consequent WITH (o, c)

In particular, the following fuzzy relationships exist ([22], p. 262; K = set of symptom combinations SC_i):

- S_i, D_j (occurrence relationship) $R^o_{SD} \subset \Sigma \times \Delta$
- S_i, D_j (confirmation relationship) $R^c_{SD} \subset \Sigma \times \Delta$
- SC_i, D_j (occurrence relationship) $R^o_{SCD} \subset K \times \Delta$
- SC_i, D_j (confirmation relationship) $R^c_{SCD} \subset K \times \Delta$
- S_i, S_j (occurrence relationship) $R^o_{SS} \subset \Sigma \times \Sigma$
- S_i, S_j (confirmation relationship) $R^c_{SS} \subset \Sigma \times \Sigma$
- D_i, D_j (occurrence relationship) $R^o_{DD} \subset \Delta \times \Delta$
- D_i, D_j (confirmation relationship) $R^c_{DD} \subset \Delta \times \Delta$

To deduce diseases $D_j \in \Delta$ suffered by patient $P_k \in \Pi$ from the observed symptoms $S_i \in \Pi$ in CADIAG-II we use three max-min-compositions as inference rules:

- hypotheses and confirmation $R^1_{PD} = R_{PS} \circ R^c_{SD}$ defined by

$$\mu_{R^1_{PD}}(P_k, D_j) = \max_{S_i} \min\{\mu_{R_{PS}}(P_k, S_i); \mu_{R^c_{SD}}(S_i, D_j)\}$$

- exclusion (by present symptoms) $R^2_{PD} = R_{PS} \circ (1 - R^c_{SD})$ defined by

$$\mu_{R^2_{PD}}(P_k, D_j) = \max_{S_i} \min\left\{\mu_{R_{PS}}(P_k, S_i); 1 - \mu_{R^c_{SD}}(S_i, D_j)\right\}$$

- exclusion (by absent symptoms) $R^3_{PD} = (1 - R_{PS}) \circ R^o_{SD}$ defined by

$$\mu_{R^3_{PD}}(P_k, D_j) = \max_{S_i} \min\left\{1 - \mu_{R_{PS}}(P_k, S_i); \mu_{R^o_{SD}}(S_i, D_j)\right\}$$

CADIAG-II was very successful in partial tests, e.g., in a study of 400 patients with rheumatic diseases, CADIAG-II elicited the correct diagnosis in 94.5 % ([22], p. 264). More results can be found in [21, 22].

3.3 Fuzzy Control in Medicine

Fuzzy control techniques have recently been applied in various medical processes, such as pain control [23] and blood pressure control [24]. Fuzzy control compared to classical control theory (PID control), which is a fuzzy logic approach to control, offers the following advantages [25, 26]:

- It can be used in systems which cannot be easily modeled mathematically. In particular, systems with non-linear responses that are difficult to analyze may respond to a fuzzy control approach.
- As a rule-based approach to control, fuzzy control can be used to efficiently represent an expert's knowledge about a problem.
- Continuous variables may be represented by linguistic constructs that are easier to understand, making the controller easier to implement and modify. For instance, instead of using numeric values, temperature may be characterized as "cold, cool, warm, or hot".
- Fuzzy controllers may be less susceptible to system noise and parameter changes; in other words, they will be more robust.
- Complex processes can be controlled by relatively few logical rules, permitting an easily comprehensible controller design and faster computation for real-time applications.

In other words, fuzzy control can be best applied to production tasks that heavily rely on human experience and intuition, and which therefore rule out the application conventional control methods. The use of *Patient Data Management Systems* (PDMS) in *Intensive Care Units* (ICU) since 1992 has made it possible to apply fuzzy control applications in real-time in this medical field.

Mechanical ventilation is such an example. One purpose of mechanical ventilation is to achieve optimal values of arterial O_2-partial pressure (pO_2) and arterial CO_2-partial pressure (pCO_2) while ensuring careful handling of the lung.

Careful handling of the lung:

- $FiO_2 < 60$ (else oxygen toxicity)
- low inspiratory pressures $P_I < 35$ (else barotrauma)
- small shear forces equivalent to small tidal volumes (else volume trauma)
- prevent atelectasis formation (else shear forces at reopening)

In addition, the patient has to be carefully handled in order to avoid cardiac failure and respiratory muscle fatigue. Both of these conditions have to be observed if the heart rate or the respiratory rate increases. The value pO_2 states whether the oxygenation is sufficient. pO_2 is not continuously available because it would entail taking a blood sample. O_2 saturation (SpO_2) provided by pulsoximetry is more convenient because SpO_2 is permanently available. pCO_2 states whether alveolar ventilation is sufficient. Similarly, the end-tidal CO_2 ($EtCO_2$) is permanently available, but at the disadvantage of being an indirect measure of pCO_2. Thus, the main physiological input parameters of the weaning system are SpO_2 and $EtCO_2$.

For instance, the *Biphasic Positive Airway Pressure* (BIPAP) controlled mode is an integrated mode of ventilation of Evita ventilators (Evita, Dräger, Lübeck, Germany). This mode allows spontaneous inspiration during the whole respiratory cycle and thus permits a very smooth and gradual transition from controlled to spontaneous breathing. Ventilatory adjustments are based on two pressure levels: inspiratory pressure (P_I or P_{high}) and expiratory pressure (P_E, or P_{low}); on two durations, inspiration time (t_I) and expiration time (t_E), as well as on the fraction of inspired O_2 (F_IO_2). Within this mode, five parameters can be adjusted (see figure 5).

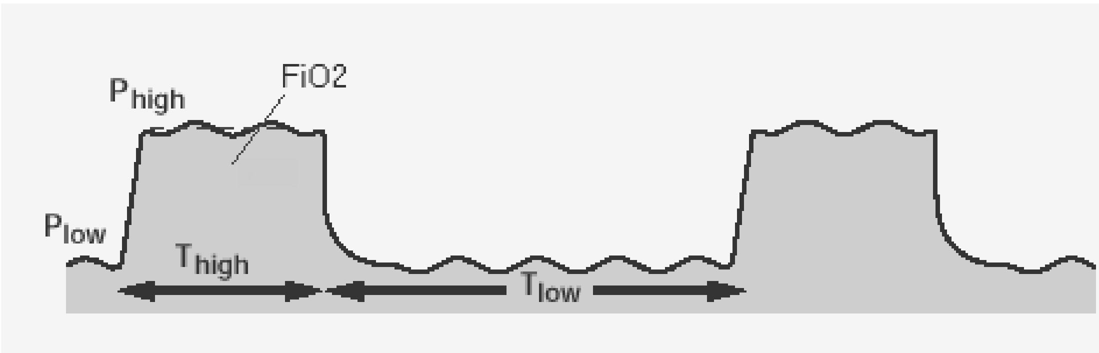

Figure 5: BIPAP ventilation mode

Some recent examples are: VentPlan, a ventilator management advisor that interprets patients' physiological data to predict the effect of proposed ventilator changes [27]; ESTER, a program which assesses the patient's pathophysiological state using modified APACHE-II criteria, then offers suggestions for weaning from intermittent mandatory ventilation [28]; NEOGANESH, a program for automated control of assisted ventilation in ICUs [29]; KUSIVAR, a program which describes a comprehensive system for respiratory management during all phases of pulmonary disease [30]; and FuzzyKBWean, a fuzzy knowledge-based control system that proposes stepwise changes in ventilator settings during the entire period of artificial ventilation at the bedside in real time [31]. Although many such expert systems have been described, only a few have been tested in clinical patient care. For example, studies of computer-controlled optimization of positive end-expiratory pressure and computerized protocols for the management of adult respiratory distress syndrome were explored by East and Bohm [32]. A computerized ventilator weaning system for postoperative patients was tested by Strickland and Hasson [33] and Schuh et al. [31].

The procedure for weaning a patient with respiratory insufficiency from mechanical ventilation is a complex control task and requires expertise based on long-standing clinical practice. Fuzzy knowledge-based weaning (FuzzyKBWean) is a fuzzy knowledge-based control system that proposes stepwise changes in ventilator settings during the entire period of artificial ventilation at the bedside in real time. Information is obtained from a PDMS operating at the ICU with a time resolution of one minute. The system is used for postoperative cardiac patients at the Vienna General Hospital. A large part of the explicitly given and implicitly available medical knowledge of an experienced intensive care specialist could be transferred to the fuzzy control system. Periods of deviation from the target are shorter with FuzzyKBWean.

4 Conclusion

In medicine, two fields of fuzzy applications were developed in the nineteen-seventies: computer assisted diagnostic systems and intelligent patient monitoring systems. Both developments of Zadeh's "rule of max-min composition", namely fuzzy relations and fuzzy control, have been applied in these areas.

For obvious reasons, the available body of medical data (on patients, laboratory test results, symptoms, and diagnoses) will expand in the future. As mentioned earlier, computer-assisted systems using fuzzy methods will be better able to manage the complex control tasks of physicians than common tools. Using current web technology, integrated systems of both types of fuzzy systems described above can be easily implemented as internet or intranet applications.

The actual successor of the systems CADIAG and CADIAG-II, developed at our department, is MedFrame/CADIAG-IV. In contrast to its predecessors, which were developed for an IBM-host-based system, Medframe/CADIAG-IV will be part of the client/server-based medical expert system shell MedFrame, which has as a core component "an object model for storing domain knowledge in various representation formalisms" … "including lookup tables, rules (if-then rules, certainty factor rules, fuzzy control rules, ...), crisp and fuzzy automatons, crisp and fuzzy decision graphs, and fuzzy-neuro systems. In addition, the object model has been extended by a set of classes for storing patients' administrative and examination data" ([33], p. 55). Medframe/CADIAG-IV will include

- a class library for modeling and storing electronic medical and patient data records and "medical knowledge" applying fuzzy sets and fuzzy relations, and
- a set of tools for implementing client/server-based expert systems.

MedFrame/CADIAG-IV, which is currently being developed, will be a huge step towards decision-making support and computer-based automation of sub-fields of medical practice having internet capabilities, which will be available for patients as well as physicians.

Most control applications in the hospital setting have to be performed within critical deadlines. Decisions have to be made locally and promptly. This is a setting that requires a local hospital intranet rather than the possibilities of the world-wide internet.

An intranet is simply a set of applications that employs internet technology for internal use. The advantages of an intranet include the following: efficient access for remote users, universal access, and system-independent clients. All this is achieved in a safe intranet environment. The greatest benefit of a hospital intranet is its universal access. In the case of FuzzyKBWean, for instance, the attending physician may not be at the patient's bed but can retrieve information about the patient more or less simultaneously via the intranet. A wireless intranet access with webpads is likely to be the next step for monitoring patients in such an environment.

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