

*Supporting medical diagnosis,
ovarian tumor, soft computing,
imprecise and incomplete data*

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OVAEXPERT: AN INTELLIGENT MEDICAL DIAGNOSIS SUPPORT SYSTEM FOR OVARIAN TUMOR

In this paper we present *OvaExpert*, an intelligent system for ovarian tumor diagnosis. We give an overview of its features and main design assumptions. As a theoretical framework the system uses fuzzy set theory and other soft computing techniques. This makes it possible to handle uncertainty and incompleteness of the data which is a unique feature of developed system. The main advantage of *OvaExpert* is its modular architecture which allows seamless extension of system capabilities. Two diagnostic modules are described in the paper along with examples. First module is based on aggregation of existing prognostic models for ovarian tumor. Second, on novel concept of Interval-Valued Fuzzy Classifier which is able to operate under data incompleteness and uncertainty.

1. INTRODUCTION

One of the most challenging current problems in gynaecology is the appropriate differentiation of adnexal masses. Identification of malignant ovarian tumors versus benign neoplasms and functional lesions is crucial, because it determines the necessity of surgery, the pre-operative work-up and adequate timing in the operation room [4]. It also has great importance for determining who should perform the surgery – a gynaecological oncologist or a general gynaecologist.

OvaExpert is an intelligent medical diagnosis support system for ovarian tumor. It is being developed by a scientists from two universities in Poland: Adam Mickiewicz University in Poznan and Poznan University of Medical Sciences. The problem of correct and early diagnosis of that kind of tumor is still a difficult task especially for inexperienced gynaecologists [4]. Moreover, small medical centres lack specialised equipment for advanced medical examinations. Such deficiency implies problems with collecting all the data by a physician during examinations and interpretation of the results. That, in turn, hinders making a final decision.

Gynaecologists around the world have developed many prognostic models, ultrasonographic morphological scales, and other risk of malignancy calculators that are used for differential diagnosis of ovarian tumors. The most common diagnostic models are based on scoring systems [1], [13] and logistic regressions [15]. However, the plurality of diagnostic models confirms their imperfections. Both the sensitivity and specificity of those models rarely exceeds 90% in

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external evaluation conducted by independent research centres [9], [17]. Their another limitation is that they cannot be applied when some of the patient data is missing which is a common problem resulted e.g. from technical limitations of the health care unit or high costs of medical examination.

Over 10 years ago, the International Ovarian Tumor Analysis (IOTA) Group started a project to improve our ability to differentiate between benign and malignant ovarian tumors. Several years of comprehensive and broad studies resulted in a number of predictive models. Among these, the most important are 2 models based on logistic regression (LR1 and LR2) [8] and the most recent IOTA model – ADNEX [16].

OvaExpert is meant to be an answer to the problem of effective diagnosis in a presence of low-quality (uncertain and incomplete) data. Its main aim is to equip a physician with a comfortable tool to

- gather and manage patient's data in a standardised format,
- reduce the impact of data quality on the final diagnosis,
- present the result in a way that gives maximum information to a doctor.

The system is easy to use and intuitive, yet it utilises recent methods mainly from the area of machine learning, soft computing and fuzzy sets theory [5].

In the following we describe the system in details, focusing on its modular architecture. We present main features and components of *OvaExpert*, namely diagnostic modules and some of their theoretical background.

2. FEATURES OF *OvaExpert*

OvaExpert is meant to integrate present knowledge about ovarian tumors (models, scoring systems, reasoning schemes, etc.) into a single computer-based system. It is a unique tool for many reasons. To the best of our knowledge it is the first time when incompleteness of data was taken into account and incorporated into a system for ovarian tumor diagnosis in a comprehensive way [10]

- at the stage of collecting data about the patient,
- at the stage of data processing,
- finally at the stage of presenting the diagnosis.

OvaExpert was build with the use of the modern software engineering tools and technologies such as Java, Spring, AngularJS and PostgreSQL. The system is available via web browser and it is based on RESTful webservice. The preliminary concept of the system, together with its architecture, was designed and presented in [5]. Currently *OvaExpert* is in prototype phase and its demo version is available at project website <http://ovaexpert.pl/en> to provide insight into all mentioned below functions of the system.

2.1. UNCERTAINTY MODELLING

Uncertainty has attracted increasing attention in health care practice and medical publications as an important problem. As studied in [6] there are multiple meanings and varieties of uncertainty in medicine, each of them having unique effects for diagnosis. Sorts of uncertainty can be distinguished according to its nature - whether it is objective (arises from a complex or probabilistic nature of a phenomenon), subjective (personal opinion or interpretation) or comes from low quality of information (incompleteness).

Working under information uncertainty is an everyday experience in medical practice and it is impossible to eliminate it completely. However, many tools that support gynaecologists,

like before mentioned diagnostic models, neglect that problem and shift the responsibility for good-quality data to a doctor. A different approach is proposed in *OvaExpert* system.

OvaExpert introduces a completely new approach to the uncertainty related to the incompleteness and lack of data [5], [18]. The aim of the system is therefore to deal with the uncertainty of received information as good as it is possible and to present the resultant diagnosis retaining the information about the level of uncertainty. For example, in addition to the precise examination results, uncertain values can be also handled. This can occur if the physician is not sure of the result or results are ambiguous. For example, if the tumor thickness in ultrasound examination is between 30 and 50mm, such values can be stored and handled in the system. The presentation of uncertain results also depends on the type of a given attribute. In the case of integers or decimals, the result is an interval, for boolean attributes one may indicate that both values are possible. For attributes with a list of possible values (enums) one may indicate several possible examination outcomes.

2.2. MEDICAL DATA GATHERING

One of the main objectives of the *OvaExpert* system is to provide a simple, convenient and efficient way of collecting patient data and a final diagnoses. Currently, due to a lack of general data format there are limitations to cooperation between physicians from different centres. The potential loss of some data may also occur when translating one data format to another. So far, data was collected by individual doctors using traditional methods, like spreadsheet or notebook, without paying sufficient attention to the quality and format. Created system by providing standardised data schema developed on the basis of the recommendations of the IOTA group, allows to collect data in a common database. Thanks to that we initialised building a knowledge base about different medical cases. This also enables quality assessment of the diagnostic decisions taken by the system, performed by specialists from different medical centres, and a collection of data for further scientific research.

The personal data (especially medical records) are sensitive information, which are legally protected. In order to conduct research on data collected by the system it must be anonymised. *OvaExpert* has the ability to automatically anonymise medical data in such a way that sensitive data are never sent to the server, but doctors can still access it.

2.3. SIMPLE AND INTUITIVE INTERFACE

The design of the interface was carefully consulted with gynaecologists to meet the need for ease of use in all conditions, also on mobile devices, especially on smartphones. At any time, the attending physician can be provided with the history and the visualisation of the patient's diagnostic process. During the whole process a gynaecologist is accompanied by a system that supports him or her by identifying further examinations, the execution of which may increase the likelihood of giving accurate diagnosis. Such solution is a great help for inexperienced gynaecologists and, moreover, allows to avoid unnecessary examinations and costs related to them.

2.4. VARIOUS POPULAR DIAGNOSTIC MODELS

OvaExpert implements known prognostic models, including models of IOTA group, namely: SM scale [13], Alcazar scale [1], IOTA LR1 model [15], IOTA LR2 model [15], Timmerman model [14] and Risk of Malignancy Index (RMI) [7]. Many gynaecologists are familiar with

those methods and trust their results.

2.5. BIPOLAR DIAGNOSIS

OvaExpert presents the result of a diagnostic process in a bipolar way [10], giving the possibility of diagnosis towards malignant and towards benign together with a degree of impossibility of determining the nature of malignancy. Such presentation informs a physician about the reliability and completeness of a diagnosis. A classical approach to medical diagnostic process involves identifying the most adequate diagnosis. However, it is also possible to follow the criteria that exclude certain diagnoses. It is apparent that in case of doubts regarding the diagnosis, such bipolar - positive and negative - perspective is valuable and carries more information for a doctor.

OvaExpert uses an approach based on Atanassov's intuitionistic fuzzy sets [2], [19] to model bipolarity in the diagnostic process. This concept is innovative in medicine, its use in the diagnosis having only been indicated as a possibility [3], [12]. It is coherent with a basic premise of *OvaExpert* system that is to accept and to cope with uncertainty. On the one hand, the patient's condition is described by a degree that indicate a tumor being malignant, and on the other - being benign. Those two degrees need not sum to 100% and the system may suggest further examination to increase the reliability and completeness of a diagnosis.

3. DIAGNOSTIC MODULES IN *OvaExpert*

The main advantage of the system is the modular architecture, which will be discussed in this section. All existing and new methods for supporting the diagnosis of ovarian tumors can be integrated into the system as modules. Currently, two top level diagnostic modules are implemented: *based on diagnostic models* and *based on Interval-Valued Fuzzy Classifier*. With the aforementioned architecture, the system gives the option to add further modules that provide a diagnosis using techniques completely different from those currently used.

3.1. MODULE BASED ON DIAGNOSTIC MODELS

The number of different diagnostic models is large and it is not commonly accepted which one should be used in a particular situation. Moreover, original models had not been prepared to handle incomplete data, while the incompleteness is common in medical practice. Thus, the biggest challenge was to support a physician in making an effective final diagnosis under incomplete information.

One of the proposed approaches is to take advantage of the diversity of diagnostic models and to aggregate their results to benefit from synergy effect.

The evaluation conducted on set of 268 patients proved that fuzzy aggregation is a powerful method to improve the quality of diagnosis as well as to minimise the impact of the lack of data and uncertainty [21]. As can be seen in Fig. 1, approach based on Ordered Weighted Average aggregation (OWA, see [20]), marked on figure as *OvaExpert*, achieved efficacy which exceeded individual diagnostic models despite missing data. More details concerning our approach, its evaluation and results can be found in original paper. In the following we will give an basic example of operation of this diagnostic module.

For sake of simplicity in this example we assume that patient is described only by two attributes, namely patient's age and one cancer antigen test. We define the domains of those attributes as $D_1 = [0, 100]$ and $D_2 = [0, 1500]$. Consider following two patients $\mathbf{p}^A = (35, 100)$

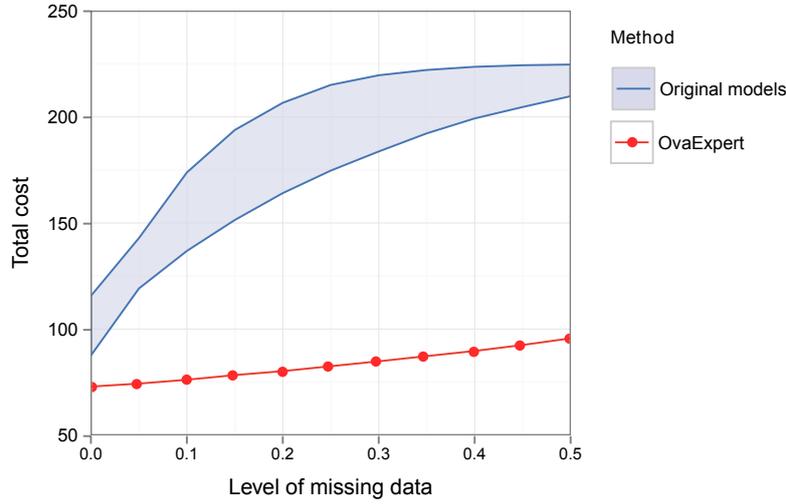


Fig. 1. A comparison of total costs between the original diagnostic models and the selected aggregation strategy. The shaded area indicates bounds of the total cost of the original models. All models are evaluated on the same patient data. Total cost was obtained with following cost matrix: TP=TN=0, FP=2.5, FN=5, lack of diagnosis: 1 (benign) and 2 (malignant).

and $\mathbf{p}^B = (60, 1200)$. Let m_1 be a simple example diagnostic model defined by

$$m_1(\mathbf{p}) = 0.0025p_1 + 0.0005p_2, \quad (1)$$

where the values above 0.5 indicate diagnosis towards malignancy. Now we can easily see that according to diagnostic model m_1 patient A should be diagnosed as benign ($m_1(\mathbf{p}^A) = 0.138$) while patient B as malignant ($m_1(\mathbf{p}^A) = 0.75$).

Now suppose that some patient data is missing: $\mathbf{p}^A = (35, NA)$ and $\mathbf{p}^B = (NA, 1200)$. In our approach we define new interval representation of patients

$$\hat{\mathbf{p}}^A = ([35, 35], [0, 1500]), \quad \hat{\mathbf{p}}^B = ([0, 100], [1200, 1200]) \quad (2)$$

and compute diagnoses from *uncertaintified* models using following formula

$$\hat{m}(\hat{\mathbf{p}}) = \{m(\mathbf{p}) : \mathbf{p} \text{ is such that } \forall_{1 \leq i \leq n} p_i \in \hat{p}_i\}. \quad (3)$$

This results in following

$$\hat{m}_1(\hat{\mathbf{p}}^A) = \{m_1(p_1, p_2) : p_1 = 35, p_2 \in [0, 1500]\} = [0.088, 0.838] \quad (4)$$

and analogously $\hat{m}_1(\hat{\mathbf{p}}^B) = [0.6, 0.85]$. It is easy to see that for first patient it is hard to make diagnosis while for second one, despite missing data, we can still say with high confidence that it is malignant tumor.

To illustrate next step assume that there is new blood marker ($D_3 = [0, 100]$) and it is used in new diagnostic model

$$m_2(\mathbf{p}) = 0.0025p_1 + 0.0075p_3. \quad (5)$$

New marker results were assessed for both patients with following results $\mathbf{p}^A = (35, NA, 5)$ and $\mathbf{p}^B = (NA, 1200, 90)$. New diagnostic model (after *uncertaintification*) yields $\hat{m}_2(\hat{\mathbf{p}}^A) = [0.125, 0.125]$ and $\hat{m}_2(\hat{\mathbf{p}}^B) = [0.675, 0.925]$.

Having two different pieces of information we can try to merge them into one which will be more reliable. What we know about first patient is that diagnostic models yielded $[0.088, 0.838]$ and $[0.125, 0.125]$ as a suggested diagnosis. The most simple method of aggregation uses mean calculated with the use of interval arithmetic. Calculation leads to following results

$$\hat{A}gg(\hat{m}_1(\hat{\mathbf{p}}^A), \hat{m}_2(\hat{\mathbf{p}}^A)) = \left[\frac{0.088 + 0.125}{2}, \frac{0.838 + 0.125}{2} \right] = [0.107, 0.482] \quad (6)$$

and

$$\hat{A}gg(\hat{m}_1(\hat{\mathbf{p}}^B), \hat{m}_2(\hat{\mathbf{p}}^B)) = \left[\frac{0.6 + 0.675}{2}, \frac{0.85 + 0.925}{2} \right] = [0.638, 0.888]. \quad (7)$$

Thanks to the use of aggregation we obtained new diagnoses which are less uncertain and make it easier to take final decision.

3.2. MODULE BASED ON INTERVAL-VALUED FUZZY CLASSIFIER

As a separate module, *OvaExpert* implements a novel concept of an Interval-Valued Fuzzy Classifier based on the uncertainty-aware similarity measure [11]. The main idea is to preserve full information – including the uncertainty factor – about data during the classification process. The classifier is designed to deal with situations in which both the classified objects as well as the classes themselves are imprecise, subjective and/or incomplete. In such cases, the resulting classification would also be imprecise or incomplete.

There are two ways to divide patients into classes. A basic, binary classification, discriminates two kinds of tumor: malignant and benign. A multi-class classification allows more sophisticated discrimination into histopathological types of tumor. For each class, one prototype vector which represents the entire class is constructed. We assume that class prototypes as well as objects to be classified (patients) are coded as interval-valued fuzzy sets (IVFS, see [22], [19]) and that their attributes are normalised to interval $[0, 1]$. Then, the assignment of patient p_i to classes can be stated as follows:

$$\tilde{A}_{p_i} = \sum_{c \in \mathcal{C}} \hat{sim}(\tilde{iv}(c), \tilde{iv}(p_i)) / c \quad (8)$$

where \hat{sim} is a uncertainty aware similarity measure and $\tilde{iv}(c)$ as well as $\tilde{iv}(p_i)$ denotes interval-valued fuzzy set representation of particular class and patient, respectively. This approach was discussed in details in [11].

The crucial issue for this approach is the method of constructing prototypes. Prototypes can be formed from data, for example by using clustering algorithms such as k -means, or can result from the application of expert knowledge. Thus the proposed method gives the valuable opportunity to integrate knowledge taken from data and from expert in one tool.

In the following we illustrate the use of Interval-Valued Fuzzy Classifier as a diagnostic module in *OvaExpert*. The objective is to assign the best matching histopathological profile of a tumor using the data available before an operation. Both patient and histopathological profiles are coded as IVFSs. For the purpose of the example, we will present only four histopathological types. Two of them were benign – *Endometrioid cyst* and *Mucinous cystadenoma* – and two malignant – *Serous adenocarcinoma* and *Undifferentiated carcinoma* – referred to further as HP 1, HP 6, HP 21 and HP 25 respectively. Let choose five arbitrary patient attributes: age, size of papillary projections (PAP), blood serum levels of CA-125 and HE4 tumor markers, and resistive index (RI). These attributes may be more or less subjective or imprecise. Moreover, some data may be not available at all. A patient's age is known precisely, while blood serum levels of tumor markers are subject to some uncertainties. Resistive index and size of papillary projections are subjective attributes, thus their value is uncertain. Moreover, values of the last three attributes may be not known for technical, medical or financial reasons. Example histopathological profiles and patient data is presented in Tables 1 and 2. Note that patients' missing attributes were replaced with the unit interval $[0, 1]$.

A classification using the Interval-Valued Fuzzy Classifier can be computed. By definition, the patient's classification is following:

$$\tilde{A}_{o_1} = \hat{sim}(\tilde{iv}(o_1), \tilde{iv}(hp_1)) / hp_1 + \hat{sim}(\tilde{iv}(o_1), \tilde{iv}(hp_6)) / hp_6 + \hat{sim}(\tilde{iv}(o_1), \tilde{iv}(hp_{21})) / hp_{21} + \hat{sim}(\tilde{iv}(o_1), \tilde{iv}(hp_{25})) / hp_{25}. \quad (9)$$

HP type	AGE	PAP	CA125	HE4	RI
HP 1	[0.27, 0.64]	[0.00, 0.27]	[0.00, 0.04]	[0.00, 0.03]	[0.49, 0.78]
HP 6	[0.29, 0.72]	[0.00, 0.14]	[0.00, 0.18]	[0.01, 0.06]	[0.22, 0.83]
HP 21	[0.47, 0.76]	[0.00, 0.52]	[0.30, 1.00]	[0.12, 0.90]	[0.23, 0.56]
HP 25	[0.39, 0.77]	[0.00, 0.58]	[0.15, 0.98]	[0.04, 0.62]	[0.27, 0.45]

Table 1. Profiles of ovarian tumor histopathological type coded as IVFS.

Postoperative diagnosis	AGE	PAP	CA125	HE4	RI
HP 21	[0.62, 0.62]	[0.00, 0.25]	[0.95, 1.00]	[0.95, 1.00]	[0.00, 1.00]

Table 2. Patient profile coded as IVFS.

We use the classical Jaccard index

$$sim(A, B) = \frac{|A \cap B|}{|A \cup B|} = \frac{\sum_i \min(A(x_i), B(x_i))}{\sum_i \max(A(x_i), B(x_i))} \quad (10)$$

to build uncertainty aware similarity measure

$$s\hat{im}(\tilde{A}, \tilde{B}) = \left[\begin{array}{cc} \min_{\substack{\underline{A}(x_i) \leq A(x_i) \leq \bar{A}(x_i) \\ \underline{B}(x_i) \leq B(x_i) \leq \bar{B}(x_i)}} sim(A, B), & \max_{\substack{\underline{A}(x_i) \leq A(x_i) \leq \bar{A}(x_i) \\ \underline{B}(x_i) \leq B(x_i) \leq \bar{B}(x_i)}} sim(A, B) \end{array} \right]. \quad (11)$$

The interval membership to HP 1 class is calculated as a minimum and a maximum of

$$\frac{\sum_i \min(a_i, b_i)}{\sum_i \max(a_i, b_i)}. \quad (12)$$

where a_i , and b_i satisfy following restrictions: $0.62 \leq a_1 \leq 0.62$, $0.0 \leq a_2 \leq 0.25$, $0.95 \leq a_3 \leq 1.0$, $0.95 \leq a_4 \leq 1.0$, $0.0 \leq a_5 \leq 1.0$ and $0.27 \leq b_1 \leq 0.64$, $0.0 \leq b_2 \leq 0.27$, $0.0 \leq b_3 \leq 0.04$, $0.0 \leq b_4 \leq 0.3$, $0.49 \leq b_5 \leq 0.78$. The final classification is as follows:

$$\tilde{A} = [0.07, 0.48]_{/hp1} + [0.08, 0.52]_{/hp6} + [0.21, 0.99]_{/hp21} + [0.13, 0.90]_{/hp25}. \quad (13)$$

The interval-valued score towards class HP 1 is [0.07, 0.48], which is a low. By contrast, the score for class HP 21 is [0.21, 0.99].

4. CONCLUSIONS AND FURTHER WORK

OvaExpert is an innovative system based on machine learning techniques and computational intelligence. It addresses the need for a tool that not only supports a gynaecologist in the final diagnosis, but also assists him or her during the whole diagnostic process, beginning with collecting data about the patient.

The primary advantages of the system are the built-in possibility of representation and processing of subjective, imprecise and uncertain information and modular architecture that allows to extend system capabilities with new diagnostic methods. The system was designed to support less experienced gynaecologists and it allows a continuous improvement of the quality of diagnosis. Moreover, we believe that *OvaExpert* can connect the medical community in the exchange of experience and verification of knowledge.

We are currently working on creating two new diagnostic modules based on Fuzzy Control and Deep Neural Networks. Fuzzy Control module will allow seamless integration of knowledge both from experts and the data. Deep Neural Networks based module will enable us to use

high-level abstractions in data and therefore to obtain new meta-attributes describing patient. In addition, we are planning to improve the diagnostic examination recommendation module.

The project is currently in prototype phase and despite fact that prototype is fully functional piece of software, there is still many problems that need to be solved. The most important of them concern legal issues dealing with processing of personal data and medical records.

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