Methods of Interpretation of a Non-stationary Fuzzy System for the Treatment of Breast Cancer

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Abstract—Recommending appropriate follow-up treatment options to patients after diagnosis and primary (usually surgical) treatment of breast cancer is a complex decision making problem. Often, the decision is reached by consensus from a multi-disciplinary team of oncologists, radiologists, surgeons and pathologists. Non-stationary fuzzy sets have been proposed as a mechanism to represent and reason with the knowledge of such multiple experts. In this paper, we briefly describe the creation of a non-stationary fuzzy inference system to provide decision support in this context, and examine a number of alternative methods for interpreting the output of such a non-stationary inference system. The alternative interpretation methodologies and the experiments carried out to compare these methods are detailed. Results are presented which show that using majority voting ensemble decision making from a non-stationary fuzzy system improves accuracy of the decision making. We conclude that non-stationary systems coupled with ensemble interpretation methods are worthy of further exploration.

I. INTRODUCTION

A trustworthy medical treatment decision can greatly improve the survival rate of patients with breast cancer following diagnosis and primary surgical treatment. Often in breast cancer decision making, multidisciplinary care involving a range of interdisciplinary expertise has shown its effectiveness in reaching recommendation for follow-up (adjuvant) therapy. Such a multidisciplinary team often consists of medical oncologists, radiologists, surgeons, pathologists and other specialist clinicians. In many countries, employing multidisciplinary care for breast cancer has become the standard recommended in clinical guidelines [1], [2].

Many computational intelligence techniques have been developed to assist in breast cancer diagnosis and decision making. For example, fuzzy sets have been used to represent the opinions of several radiologists in analysing two important features from the American College of Radiology Breast Imaging Lexicon [3]. Pena-Reyes and Slipper developed a fuzzy-genetic method to apply to the Wisconsin breast cancer diagnosis data, in which a genetic algorithm was utilised to generate a complete fuzzy inference system (including input variables, membership functions, rules, etc.) [4]. Abbass recently introduced an evolutionary artificial neural network method for breast cancer diagnosis [5]. Xiong et al. used data mining techniques using decision trees and association rules to discover unsuspected relationship within breast cancer data [6]. Zhou et al used particle swarm optimisation within a support vector machine for recommending treatments in breast cancer [7].

During the breast cancer diagnosis and treatment decision making process, the multidisciplinary panel often use uncertain and imprecise terms to describe the medical status of patients and when performing reasoning with such data and knowledge. Hence, using fuzzy methods would appear to be a natural way to transfer the opinions of such experts into clinically useful decision support systems. Because of the high degree of uncertainty in both data and knowledge, this application seems particularly suited to Zadeh’s ‘Computing With Words’ paradigm [8]. Both general type-2 fuzzy methods [9], [10] and interval type-2 fuzzy methods [11] may seem appropriate to adopt in this context, but type-2 fuzzy inference systems do not represent variability nor explicitly represent multiple opinions.

Recently, Garibaldi proposed non-stationary fuzzy sets which are able to exhibit the variability inherent in human decision making by randomly altering the parameters of the membership functions [12]. These were included in a fuzzy inference system run for a certain number of iterations, applied to umbilical acid-base assessments of an infant immediately after delivery [13]. The results showed that the intra- and inter-expert variability found in decision making can be modelled by a non-stationary fuzzy inference system featuring small variations in the membership functions. In previous studies of non-stationary fuzzy inference, the simple mean of multiple runs of inferencing was used [12]. In this paper, two new methods to process these iterative results are proposed and a breast cancer treatment decision making scenario is used to illustrate these proposed methods.

The rest of this paper is organised as follows. In Section II the breast cancer data used in this study is introduced, and in Section III the key concepts behind non-stationary fuzzy sets are summarised. A type-1 fuzzy system model based on the medical guidelines used by the multidisciplinary care team is described in Section IV. In Section V the normal method of processing and interpreting the output of non-stationary fuzzy inference systems is described, followed by the two newly proposed methods. The experiments which were carried out and their results are presented in Section VI, with discussion in Section VII. Finally, conclusions are drawn and possibilities for future work are highlighted.
II. DATA DESCRIPTION

The data involved in this study is a set of real clinical data concerning post-operative breast cancer treatment that was kindly provided by The Nottingham Breast Institute (within the Nottingham University Hospitals NHS Trust). This is a set of post-operative data collected from patients who had all undergone some form of breast cancer surgery. The follow-up treatment after surgery is called adjuvant therapy, and is used to reduce the chance of cancer reoccurrence. The adjuvant therapy treatment may include hormone therapy, radiotherapy, chemotherapy, biological therapy, further operation and follow up, or any combination of these. The data is comprised of a set of attributes examined on each patient’s post-operative visit and adjuvant therapy treatment decision. The attributes involved in the data include patient identification, date of birth, diagnosis date, size and grade of carcinoma, lymph node stage, estrogen and progesterone receptor status, and so on.

The decisions regarding the recommended course of adjuvant treatment are normally made during multi-disciplinary team meetings. The clinical procedure employed for recording the data can be summarised by the following steps: i) the attribute information and additional comments related to each patient’s treatment are recorded on a form; ii) the forms are discussed during the multi-disciplinary meeting and a further course of action is agreed; and iii) after the meeting, the forms are collected and sent to a data analyst for entry.

Several challenges arise whilst using the dataset for this study due to the clinical procedures for recording the information. For example, the data has been collected over a period of twenty-five years by several different people and, because there is no standardised format for data entry, inconsistencies in data formats can occur. In addition, the treatment decisions are not separately identified in their own data field and are, instead, hidden within a free-text comment field. The processing of the data is further complicated by the fact that different treatment decisions may be identified through different notations or spellings. Furthermore, there can be missing values for some attributes. This affects the clarity of the data and complicates automatic classification.

In order to simplify the data, 1310 cases having full clinical records were chosen. The adjuvant therapy treatment decision was selected since the clinical guidelines give clear boundaries for different decision categories whereas, in practice, the boundaries may actually be less clear. Such an example is the interpretation of ‘age’. The clinical guidelines feature a n apparent crisp boundary for age at 40. In practice, this boundary is fuzzy. We utilised five attributes that were identified in the medical guidelines as inputs to our fuzzy system. These are: the Nottingham Prognostic Index (NPI), estrogen receptor status (ER), degree of vascular invasion (VI), patient age at diagnosis (age) and number of positive lymph nodes (LN). Both HER-2 status and ‘special type cancer’, which also feature in the guidelines, were neither available nor clearly described in the given data set, and so were not considered as inputs.

These guidelines include various treatment recommendations based on the results of the assessments of many patients (with the corresponding attributes described above). The clinical guideline for chemotherapy treatment as used in this paper are shown in Table I. The output of the fuzzy system is the recommendation for chemotherapy treatment, termed Chem to. It contains three categories: No (corresponding to a recommendation against chemotherapy), Maybe (corresponding to consider chemotherapy) and Yes (corresponding to a recommendation for chemotherapy). When the recommendation was ‘no adjuvant treatment’ or ‘recommend hormone therapy’, the decision was considered to be against chemotherapy. The output is the recommendation for the use of chemotherapy as an adjuvant treatment.

III. NON-STATIONARY FUZZY SETS AND SYSTEMS

The difference between non-stationary fuzzy sets and standard fuzzy sets is that the original static membership functions are replaced by membership functions that alter dynamically over time. Formally, if $A$ represents a non-stationary fuzzy set over a universe of discourse $X$, its membership function is $\mu_A(x, t)$, where $x \in X$, $\mu_A(x, t) \in [0, 1]$, and $t$ refers to the time at which the fuzzy set is instantiated. If $A$ denotes the underlying standard fuzzy set, and its associated membership function is $\mu_A(x)$, then every time $A$ is varied, it is termed an instantiation of $A$. Thus, the non-stationary fuzzy set $\hat{A}$ can be denoted by

$$\hat{A} = \int_{t \in T} \int_{x \in X} \mu_A(t, x) / t.$$  

Rather than the membership function being independent at each instantiation, however, we introduce a restriction relationship between the instantiations, as follows. We use $f(t)$ to characterise a perturbation function, which is utilised to vary the standard membership function $\mu_A(x)$. Before presenting the relationship between $f(t)$ and $\mu_A(x, t)$, we need to symbolise the parameters of $\mu_A(x)$ as $p_1, p_2, \ldots, p_m$.  

TABLE I  
CLINICAL GUIDELINES FOR ADJUVANT THERAPY FOLLOWING SURGERY

<table>
<thead>
<tr>
<th>NPI $&lt; 3.0$</th>
<th>No Adjuvant Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPI $3.1 - 3.4$</td>
<td>Recommend Hormone therapy</td>
</tr>
<tr>
<td>ER $+$ve</td>
<td>Recommend Chemotherapy if V1</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI $3.4 - 4.4$</td>
<td>Recommend Hormone therapy</td>
</tr>
<tr>
<td>ER $+$ve</td>
<td>Recommend Chemotherapy</td>
</tr>
<tr>
<td>NPI $&gt; 4.4$</td>
<td>Discuss Chemotherapy</td>
</tr>
<tr>
<td>ER $+$ve</td>
<td>Consider:</td>
</tr>
<tr>
<td></td>
<td>Recommending Chemotherapy:</td>
</tr>
<tr>
<td></td>
<td>Age $&lt; 40$</td>
</tr>
<tr>
<td></td>
<td>V1</td>
</tr>
<tr>
<td></td>
<td>HER-2 $+$ve</td>
</tr>
<tr>
<td></td>
<td>Weak ER ($&lt; 100/300$)</td>
</tr>
<tr>
<td></td>
<td>Recommending Against Chemotherapy:</td>
</tr>
<tr>
<td></td>
<td>Age $&gt; 60$</td>
</tr>
<tr>
<td></td>
<td>Only 1 LN positive</td>
</tr>
<tr>
<td>ER $-$ve</td>
<td>Special type cancer</td>
</tr>
</tbody>
</table>

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so if we express $\mu_A(t, x) = \mu_A(x, p_1(t), \ldots, p_m(t))$, then $p_i(t) = p_i + k_i f_i(t)$, where $i = 1, \ldots, m$. This means that at any time each parameter is varied by a perturbation function multiplied by a constant.

A fuzzy inference system (FIS) featuring any non-stationary fuzzy sets is termed a non-stationary fuzzy inference system (NSFIS). A diagram of a non-stationary FIS is shown in Figure 1. From the figure, it can be seen that a non-stationary FIS is a normal (type-1) FIS which is run $n$ times (i.e. $n$ instantiations of an ordinary FIS). For more details, including elementary theoretical properties of non-stationary fuzzy sets, see [12], [14], [15].

As an example of a non-stationary fuzzy set, consider Figure 2. Figure 2(a) illustrates an example membership function, for which the parameters are the left-point, centre-point and right-point of the triangle. This can be expressed as $\mu_{mf_1}(x, p_1, p_2, p_3) = \mu_{mf_1}(x, 2, 5, 8)$. The corresponding non-stationary membership of $mf_1$ is $\mu_{mf_1}(x, p_1(t), p_2(t), p_3(t))$, with parameters

\[
\begin{align*}
p_1(t) &= 2 + k_1 f_1(t) \\
p_2(t) &= 5 + k_2 f_2(t) \\
p_3(t) &= 8 + k_3 f_3(t)
\end{align*}
\]

where $[0, 10]$ is the universe of discourse. In order to shift the membership function left or right (rather than changing the shape of the triangle), we set the perturbation functions $f_1(t) = f_2(t) = f_3(t) = f(t)$ and $k_1 = k_2 = k_3 = k$. In Figure 2(b), $f(t)$ is following a Normal distribution with mean of zero and standard deviation $\sigma = 0.02$, $k = 1$ and $n$, the number of iterations, is 20.

IV. TYPE-1 FUZZY SYSTEM

There are four main interconnected components within a standard (type-1) fuzzy system, namely the fuzzifier, the rules, the inference engine and the defuzzifier. In this study, the input and output variables and the rules were produced based on the provided professional clinical guidelines from the Nottingham University Hospital NHS Breast Directorate.

The membership functions for each input were also based on the cut-offs which appear in the guidelines. For the NPI variable, for example, there are clearly four ranges: NPI < 3.0, NPI ∈ [3.1, 3.4], NPI ∈ [3.4, 4.4] and NPI > 4.4. We interpreted these ranges as fuzzy terms Low, Medium low, Medium high, and High, respectively. The universe of discourse of NPI was set to be $[0, 10]$. In this study, either triangular or trapezoidal membership functions were used for all the terms, since this made it more straight-forward to determine the points of intersection between membership functions. These intersection points were derived directly from the threshold values in the guidelines. Triangular membership functions are described by the notation $(l, m, r)$ corresponding to the left vertex, middle vertex and right vertex of the triangle, while trapezoidal membership functions are described by the notation $(a, b, c, d)$ corresponding to the left-base, left-top, right-top and right-base vertex, respectively. The membership functions of the input and output variables were as follows.

1) **NPI**: Universe of discourse: $[0, 10]$
   - Low: $(0, 0, 2.8, 3.2)$
   - Medium low: $(2.8, 3.2, 3.6)$
   - Medium high: $(3.9, 3.9, 4.9)$
   - High: $(3.9, 4.9, 10, 10)$

2) **ER**: Universe of discourse: $[0, 300]$
   - Negative: $(0, 0, 40)$
   - Weak: $(0, 40, 160)$
   - Positive: $(40, 160, 300, 300)$

3) **Age**: Universe of discourse: $[0, 90]$
   - Young: $(0, 0, 30, 50)$
   - Middle age: $(30, 50, 70)$
   - Old: $(50, 70, 90, 90)$

4) **VI**: Universe of discourse: $[1, 3]$
   - No: $(1, 1, 3)$
   - Maybe: $(0.75, 2, 3.25)$
   - Yes: $(1, 3, 3)$

5) **LN**: Universe of discourse: $[0, 1]$

From the clinical data, it was noticed that the range of positive lymph nodes found could vary substantially, from 1 out of 1 lymph node sample, to 1 positive out of 36 nodes sampled. Obviously these results all satisfy the condition ‘only one lymph node positive’, but it was thought that the interpretation of whether the lymph nodes have been affected may be fuzzy. In order to represent this, the ratio of the number of positive lymph nodes to the number of lymph nodes taken was used as the input for the LN variable. Two membership functions were:

- Negative: $(0, 0, 0.04)$
- Positive: $(0, 0.2, 1, 1)$
6) *Chemo*: The universe of discourse was \([0, 100]\) (arbitrarily). From observation of actual recommendation decision in the database, it was found that there were fewer cases in the *Maybe* category than the other two groups. By manually tuning the parameters, the range of *Maybe* that was found to achieve the best results was around \([55, 57]\). Based on these findings, the three membership functions were set to be:

- *No*: \((0, 0, 54, 56)\)
- *Maybe*: \((55, 55, 57)\)
- *Yes*: \((55, 57, 100, 100)\)

Table II shows the fuzzy rules derived directly from the clinical guidelines. The fuzzy inference system was implemented using conventional Mamdani style inference. The usual min and max operators were used for conjunction and disjunction, respectively, and also for implication and aggregation, respectively. Centroid (centre-of-gravity) defuzzification was used to obtain the crisp output of fuzzy inference.

The last step of the inference process was to convert the crisp defuzzified value into a categorical agreement in the set \(\{\text{no, maybe, yes}\}\). This was implemented by assigning the crisp value into different *Chemo* recommendation groups based on the intersection points of its three membership functions described above, where *No* \(\in [0, 55]\), *Maybe* \(\in [55, 56]\) and *Yes* \(\in (56, 100]\). After all 1310 cases had been defuzzified through this process, an agreement confusion matrix showing the number of agreements in each classification group, cross-tabulating the actual clinical decision (as indicated on the patient database) with that assigned by the fuzzy inference system. The confusion matrix obtained from the original type-1 fuzzy system is shown in Figure 3.

**V. NON-STATIONARY FUZZY INFERENCE SYSTEM OUTPUT PROCESSING**

The type-1 fuzzy system was converted into a non-stationary fuzzy inference system by the incorporation of non-stationary fuzzy sets based directly on the type-1 fuzzy sets described above. A Normally distributed random perturbation function with mean zero and a range of standard deviation varying from 0.01 to 0.1 (of the universe of discourse) was applied over 30 iterations. In order to investigate different ways to interpret the results from the non-stationary fuzzy system, three post-processing methods (including two newly proposed methods) were compared.

**A. Existing Approach to Output Interpretation**

In the existing approach to output processing in non-stationary fuzzy systems, the output was calculated by taking the defuzzified crisp result obtained for each case, averaged over the specified number of iterations. This is named the *ns-avg* method, and is illustrated in Figure 4, where each case represents the defuzzified crisp output value resulting from the specific perturbations for that instantiation. After running all 1310 cases on all instantiations, the mean defuzzified values were calculated and assigned into the different decision recommendation groups \{no, maybe, yes\}, based on the thresholds specified in Section IV-6. Finally, the total *agreement* for the single resultant confusion matrix was computed.

**B. Two Proposed Output Processing Methods**

In the first new approach, each instantiation of the NSFIS is considered independently. In each instantiation, the defuzzification results are assigned as \{no, maybe, yes\}, from all 1310 cases. Then the *agreement* is calculated from each confusion matrix (one for each instantiation), and then the final *agreement* is calculated as the mean over the instantiations. This is named the *sum-avg* method, as illustrated in Figure 5.

The second new approach is named the *majority* method. This is initially similar to the *sum-avg* method just described, but rather than calculating the *agreement* straight after grouping the results, instead it finds the majority of the categorical results in each case, over all instantiations. After determining all the majority decisions for all 1310 cases, the final *agreement* is computed as the ultimate result of this system. This is illustrated in Figure 6.

**VI. EXPERIMENTAL RESULTS**

The results of the three methods of output processing on the designed non-stationary fuzzy system are presented and compared. Figure 7 shows the number of agreements over a range of variation for the three output processing methods. From this Figure, it can be seen that within the 30 instantiations, the *majority* and *ns-avg* approaches obtained the highest and the lowest number of agreements, respectively, especially when
The variation \( \sigma \) increases. At \( \sigma = 0.05 \), both the majority and ns-avg methods achieved their highest number of agreements, while the sum-avg method obtained its highest number of agreements at \( \sigma = 0.06 \). In order to further compare these three methods, the confusion matrices at the variability where each method obtained the highest number of agreements were generated, and are shown in Figure 8.

VII. DISCUSSION

From the diagram shown in Figure 7, it can be observed that in the sum-avg approach, the number of agreements decreases after the variation reaches 0.06. However, for the ns-avg and majority approaches, the number of agreements continues to rise, reaching a maximum at \( \sigma = 0.06 \).

This observation may be due to the way the agreement is obtained in these three methods. In the sum-avg approach, the agreement is calculated after grouping the defuzzification results in each iteration on all 1310 cases. Thus, it reflects the system accuracy corresponding to each instantiation of perturbation functions separately. The trend observed in Figure 7 indicates that after \( \sigma = 0.06 \), the instantiations in which large perturbations are generated result in very poor agreement, which leads to a decrease in the overall accuracy of the system.

On the other hand, for the ns-avg approach, the defuzzification results are averaged over all iterations for each case, before the overall agreement is calculated. This means that this can reduce the impact on the overall agreement of a ‘bad’ perturbation within an individual instantiation. Similarly, the majority approach, by taking the majority view before calculating the overall agreement, the poor agreements obtained from a single rare, ‘bad’ perturbation can be filtered out. The
agreements start to decrease after $\sigma = 0.08$ for both the $ns$-avg and majority approaches. This may be the consequence of the detrimental impact of huge perturbation as the variation gets large — in effect, the ability of these methods to ‘balance’ the results is reduced for large variations.

From the confusion matrices shown in Figure 8 (a-c), it can be seen that the sum-avg approach not only has less accuracy but also appears to have more false negative and false positive than the other two methods. The $ns$-avg and majority approaches have similar agreements for the no decision, but for yes decision, the majority approach shows more advantage than $ns$-avg. It also can be clearly seen that for the maybe decision there is no case identified using the majority method. This is because the membership function setting of maybe is very narrow, since in this given breast cancer treatment recommendation data, there are fewer maybe cases than the rest of the decisions. Therefore the maybe output is very rare, and so will be ‘filtered-out’ by the majority approach.

It should be noted that the sum-avg method averages over the set of all cases on the data set and so would not be applicable in situations where only a single case is observed. Neither the $ns$-avg nor the majority approaches suffer the same problem. The algorithms presented in the paper are for the purposes of reaching an overall decision based on a (possibly large) number of decisions formed by a non-stationary fuzzy inference system. All three consensus algorithms run after the repeated non-stationary inference process is completed, and take very little time in comparison with the inference process itself. As an example, 30 repeats of non-stationary inference performed on all 1310 cases (40,000 individual inferences) took approximately 50 seconds, while in comparison it took less than one second to perform the calculations for all three methods of interpretation.

Finally, the confusion matrix from the original membership function setting (see Figure 3) can be compared with the three confusion matrices obtained by non-stationary systems. The original has the least agreements for the no decision and least false negative rate, but has the largest agreement for the yes decision and the largest false positive rate.

**VIII. CONCLUSIONS**

In this paper, we have presented two new methods for interpreting the results of non-stationary fuzzy inference. We have presented the results obtained when using these methods on a real decision making problem in the context of breast cancer. We have shown that taking a majority approach to decision making can improve the accuracy of results for a non-stationary system. This is a promising area of research which warrants further investigation.

**REFERENCES**