2014 IEEE International Conference on Fuzzy Systems (FUZZ-IEEE)
July 6-11, 2014, Beijing, China

A General Type-II Similarity Based Model for Breast Cancer Grading with FTIR Spectral Data

Shabbar Naqvi, Simon Miller and Jonathan M. Garibaldi
School of Computer Science
University of Nottingham
United Kingdom
Email: {psxsn1, s.miller, jon.garibaldi@nottingham.ac.uk}

***Abstract*—Breast cancer is one of the most frequently occurring cancers among women throughout the world. In breast cancer prognosis, grading plays an important role. In this paper, we apply a novel method based on type-II fuzzy logic to Fourier Transform Infra-red Spectroscopy based breast cancer spectral data for the classification of breast cancer grade. A FTIR spectral data set consisting of 14 cases of breast cancer has been used. A zSlices based type-II fuzzy logic approach has been used to create prototype models for the classification of unseen breast cancer cases. The prototype models are used with a similarity measure to classify unseen cases of cancer. We have shown that the T-II similarity based model is a promising methodology for classification.**

***Index Terms*—Breast Cancer, FTIR, Type-II fuzzy logic, Similarity Measures**

I. INTRODUCTION

Breast cancer is one of the most common cancers among women throughout the world. According to the latest report by the Cancer Research, United Kingdom, it was the highest diagnosed cancer in the year 2013 [1]. After the diagnosis of cancer, monitoring its progress and re-occurrence of the disease (based on its complexity) for better prediction of survival of patients is very important [2]. This process is generally known as prognosis, which plays a vital role in predicting the survival of patients. In estimating long term survival, prognostic indices have shown good performance [3]. One of the most widely used indices is the Nottingham Prognostic Index (NPI), which considers tumour diameter, lymph node status and tumour grade as parameters for prognosis. Of these, grading is the most important parameter and is determined by the Nottingham Grading System (NGS).

Breast cancer is classified as either grade-1 (G-I), grade-2 (G-II) or grade-3 (G-III). G-I patients have more chance of long term survival where as G-III is the most severe and long term prognosis of such patients is poor. Classification of cancer grading involves a complicated procedure involving microscopic evaluation of cancer sample and different experts may disagree in predicting the grade. This complex manual method can result in variable prognosis and sub-optimal treatment [4]. In the literature, various efforts have been made using advanced computational methods for classification of breast cancer grade, but there is no universally accepted global method [5]. A relatively new technique is the use of Fourier Transform Infra-red Spectroscopy (FTIR) in combination with different machine learning methods for differentiating breast cancer cells from normal cells [6].

In this paper, we apply a newly developed Type-II (T-II) fuzzy logic model to a complex breast cancer FTIR spectral data set in order to help clinicians in the classification of breast cancer grade. The data set used consists of multiple cases of each grade. We consider two types of uncertainty, one within the spectra of a case of a grade (intra-case) and another when comparing with other cases of same grade (inter-case). Five features have been extracted from each case as interval data from features in the spectral region. The interval data of each case has been used to create type-I (T-I) fuzzy sets for each feature. After that these T-I fuzzy sets are combined to create zSlices based General Type-II fuzzy sets (zGT-II) for each grade. These zGT-II fuzzy sets are then used as prototypes with unseen cases of cancer for grade classification. T-I fuzzy sets are created for unseen spectral data and then compared against the benchmark prototype zGT-II fuzzy sets for each grade using a recently proposed similarity measure [7]. Based on these scores, unseen cases are assigned a grade. We have selected T-II fuzzy logic for this study as it has been shown to perform well when there are multiple layers of uncertainties in the data set [8]. To the best of our knowledge, this is first attempt to create zGT-II fuzzy sets from FTIR spectra, with interval valued data.

The rest of this paper provides a brief background of breast cancer grading, FTIR, fuzzy logic with a focus on T-II fuzzy logic, and the similarity measure used for this work. It is followed by a description of the data set, details of the proposed model, the results after applying the model and a discussion on the results.

II. BACKGROUND

A. Breast Cancer Grading

One of the most frequently used methods throughout the world for breast cancer grading is the NGS which is based on the microscopic evaluation of tumour cells by the histopathologist. The morphological variations found in the cells are considered including the form and shape of the cells for the classification of the grade [9], [10]. The grade is categorised as G-I (less aggressive appearance of tumour), G-II (intermediate appearance of tumour) or G-III (more aggressive appearance of tumour). As it is a very complex manual procedure, the chances of even an expert histopathologist making an error are high. Correct prediction of grade is vital in long term survival analysis and prognosis, and prescription of appropriate treatment of the disease [10]. There is a need to develop automated tools that can help clinicians in grade prediction in real clinical practice.

B. FTIR

FTIR is a technique based on the principle that when an infrared (IR) beam is passed through a sample, the functional groups within the sample absorb the IR radiation and the rest of the radiation passes through. The resulting spectrum creates a molecular fingerprint of a sample, no two unique molecular structures produce the same infra-red spectrum [6].

C. T-II Fuzzy Logic

Classical or Type-I (T-I) fuzzy sets were introduced by Zadeh in 1965 [11]. General Type-II fuzzy sets (GT-II) were then introduced by Zadeh as a generalisation of T-I fuzzy sets [8], [12]. By generalisation, it means that instead of using a single point membership grade on the domain x, the membership grade itself is a T-I fuzzy set. For our proposed model, we use the zSlices approach in which a GT-II fuzzy set is represented by slicing it in the third dimension (z) at a level z_i to create a zSlices based type-II fuzzy set (zGT-II) [13]. The result of this process is a set of zSlices which are Interval Type-II (IT-II) fuzzy sets with a secondary membership grade of z_i, in contrast to the regular IT-II fuzzy sets whose secondary membership grade is always one. Thus, each zSlice can be written as:

$$\tilde{Z}_i = \int_{x\in X} \int_{u\in J_{i_x}} z_i/(x,u_i) \tag{1}$$

Then fuzzy set $\tilde{F}$ is represented as a collection of zSlices:

$$\tilde{F} = \sum_{i=1}^{I} \tilde{Z}_i \tag{2}$$

where I represents the number of zSlices. Increasing the number of zSlices to represent a T-II fuzzy set increases the resolution of the representation [14], achieving an ever closer approximation to the original GT-II set.

D. Similarity Measures

Similarity measures are used to describe how similar fuzzy sets are. For the current model, we have used a new similarity measure introduced by McCulloch et al [7]. In our model, this measure is used to calculate the similarity between a zGT-II fuzzy set and a T-I fuzzy set. Each zSlice is weighted and the weighted average of Jaccard's similarity for IT-II fuzzy sets is computed for each zSlice. The method can be summarized by the following equation:

$$S(\tilde{P},U) = \frac{\sum_{i\in L} z_i S_\lambda(\tilde{P}_{z_i},U)}{\sum_{i\in L} z_i} \tag{3}$$

where S is a similarity function for the zGT-II fuzzy set $\tilde{P}$ and an unseen T-I fuzzy set U. S_λ is a similarity function applied to the IT-II fuzzy set at zLevel i shown as $\tilde{P}_{z_i}$ and the unseen T-I fuzzy set U. L is the set of zLevels used in $\tilde{P}$, and z_i represents a particular zLevel (secondary degree of membership). A value of 0 indicates disjoint sets where as a value of 1 means the sets are identical.

E. T-II Medical Applications

A recent review by Melin and Castillo [15] has shown that applications of T-II fuzzy sets in classification and pattern recognition are increasing. Researchers are increasingly inclining towards the use of T-II fuzzy logic in complex scenarios and problems where more and more uncertainty is involved, such as face recognition [16]. In the medical sciences, Chumklin and Auephanwiriyakul [17] developed a system based on GT-II fuzzy sets for the detection of microcalcification in Mammograms for breast cancer with 89.47% correct results. The use of T-II fuzzy sets for breast cancer grade classification with spectral data sets is a relatively new area of research and it is a motivation behind our work.

III. Data Set Description

The data set used for initial experiments has been obtained from the University of Illinois at Urbana Champaign, USA [18]. There are two cases of G-I, 26 cases of G-II and six cases of G-III. Instead of using whole spectral range for the experiments, we have selected the spectral region between 1000-1800 cm^{-1} for our experiments, on the basis that the area around this region has been found to provide valuable information about the data [6]. Data from the selected spectral region was pre-processed by a process of standard base line correction and normalisation to remove abnormalities found in spectra. For this initial study, we have used two cases of G-I, six cases of G-II and six cases of G-III. In this way we have a complex data set with multiple numbers of cases for each grade with a high level of uncertainty involved making it an ideal problem for the application of T-II fuzzy logic.

IV. Model Structure

The model used for this work creates T-I and zGT-II fuzzy sets based on interval data extracted from spectral features which are used as a prototype for grade classification of unseen cancer cases. A block diagram of the model is shown in Fig. 1. Now we describe the stages for the model.

A. Feature Extraction

In the first stage, five features were selected for the experiments. The region 1000-1800 cm^{-1} was divided into three sections in line with Chiu et al's [19] division of the region.

Five features have been selected from these three regions. The location and the area covered by each region is shown in Fig. 2. For each feature, two absorbance values are used from each spectrum to create an interval. Maximum peak height and minimum absorbance values are used to create an interval. For example, for feature 1, minimum absorbance

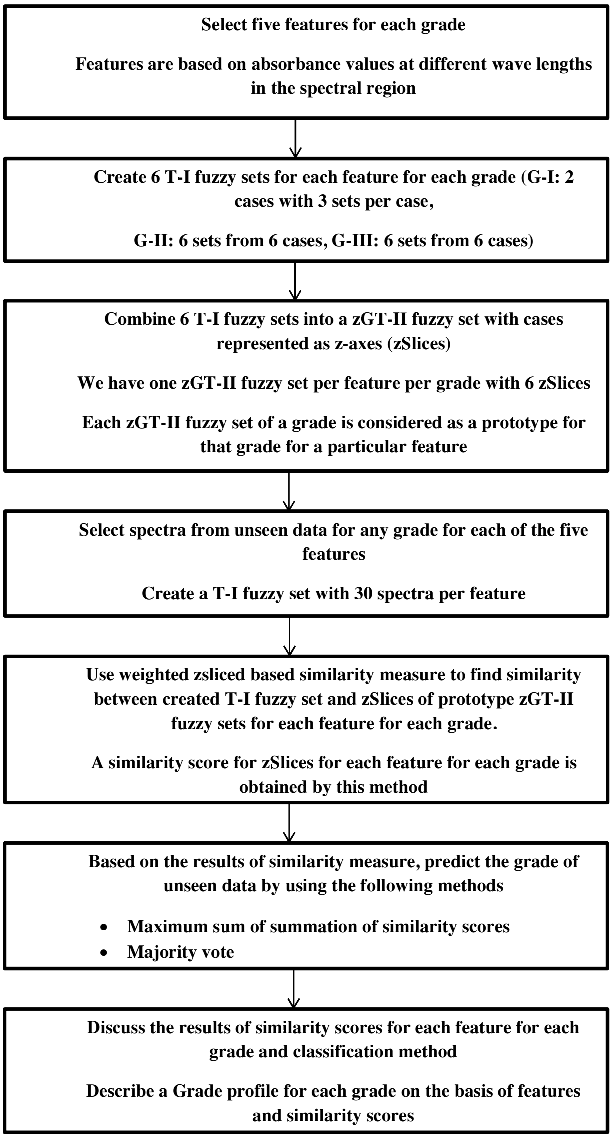


Fig. 1. Block diagram of the model structure

value A and maximum absorbance value B are combined to create an interval (A, B) as shown in Fig. 2. For feature 5, two distinct peak heights have been used to create an interval. Every spectrum used has a set of five interval values each for a feature.

B. T-I Fuzzy Set Creation

For the second stage, T-I fuzzy sets have been created from the interval data. We have initially selected 30 spectra to create a T-I fuzzy set. As there are 30 values for each set, the primary membership domain is divided into 30 sections ranging from 1/30 to 30/30. As we have two cases from G-I, 26 cases from G-II and six cases of G-III, we have decided to create six T-I fuzzy sets for each grade per feature from these cases. For G-I, three regions from two cases have been selected making

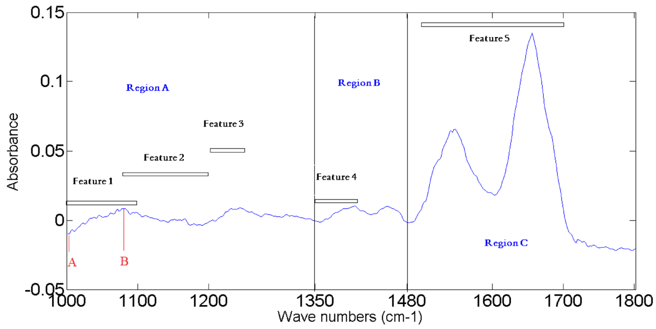


Fig. 2. Regions and approximate locations of selected features

it six sets in accordance with other grades. For G-II, we have selected six cases out of 26 and for G-III, spectra from all six cases have been included. We have six sets of 30 spectra from each grade per feature. In total we have 90 T-I fuzzy sets for all features for all grades. The T-I fuzzy sets are created with the help of the following Equation for interval data as described by Miller et al [20]:

$$\begin{aligned}\mu(A) &= y_1 / \bigcup_{i^1=1}^{N} \bar{A}_{i^1} \\ &+ y_2 / \left(\bigcup_{i^1=1}^{N-1} \bigcup_{i^2=i^1+1}^{N-1} (\bar{A}_{i^1} \cap \bar{A}_{i^2}) \right) \\ &+ y_3 / \left(\bigcup_{i^1=1}^{N-2} \bigcup_{i^2=i^1+1}^{N-1} \bigcup_{i^3=i^2+1}^{N} (\bar{A}_{i^1} \cap \bar{A}_{i^2} \cap \bar{A}_{i^3}) \right) \\ &+ \dots \\ &+ y_n / \left(\bigcup_{i^1=1}^{1} \dots \bigcup_{i^N=N}^{N} (\bar{A}_{i^1} \cap \dots \cap \bar{A}_{i^N}) \right),\end{aligned} \tag{4}$$

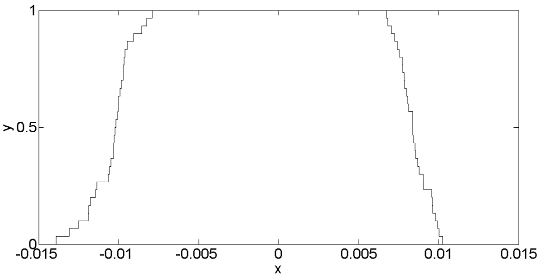
where

$$y_i = \frac{i}{N},$$

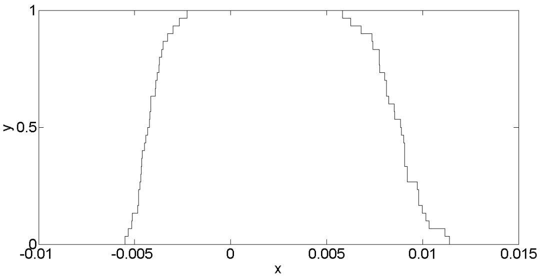
and y is the degree of membership over the domain x. It represents the number of intervals overlapping at a certain point. If $\tilde{A}_n$ is a series of intervals where $i \in \{1....N\}$ and N is the number of the intervals, then the T-I fuzzy set A is defined by the membership function $\mu(A)$. In Equation 4, the '/' sign refers to degree of membership and is not a division sign and the addition symbol represents the union. The T-I fuzzy set is created by taking the union of all the intervals which are associated with a membership of y_1, the union of all possible two tuple intersections of intervals are associated with y_2 and so on. Fig. 3 shows examples of created T-I fuzzy sets for various features for all three grades. These sets aim to cover the intra-case uncertainty found within spectra of a single case.

C. zGT-II Fuzzy Sets Creation

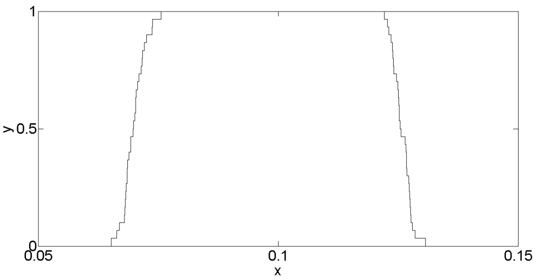
In the next stage, zGT-II fuzzy sets have been created by combining six T-I fuzzy sets using the method described by



(a) Feature-1 of G-I

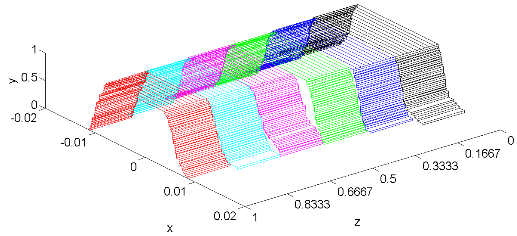


(b) Feature-2 of G-II

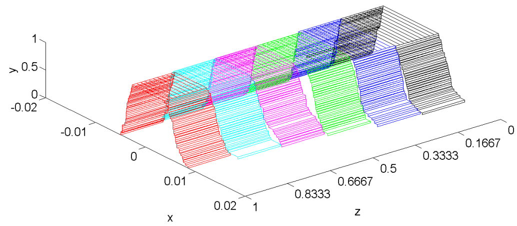


(c) Feature-5 of G-III

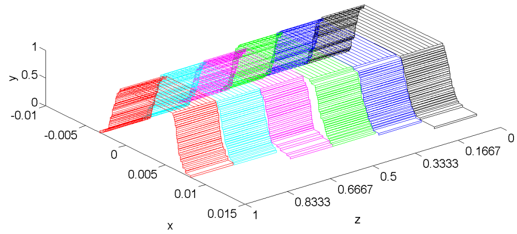
Fig. 3. Examples of T-I fuzzy sets for various features for different grades



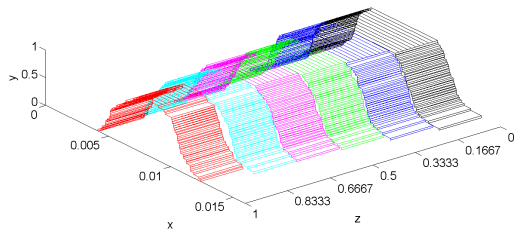
(a) Feature-1



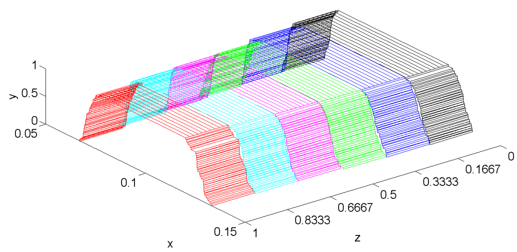
(b) Feature-2



(c) Feature-3



(d) Feature-4



(e) Feature-5

Fig. 4. 3D plots for zGT-II fuzzy sets for features 1-5 for G-I

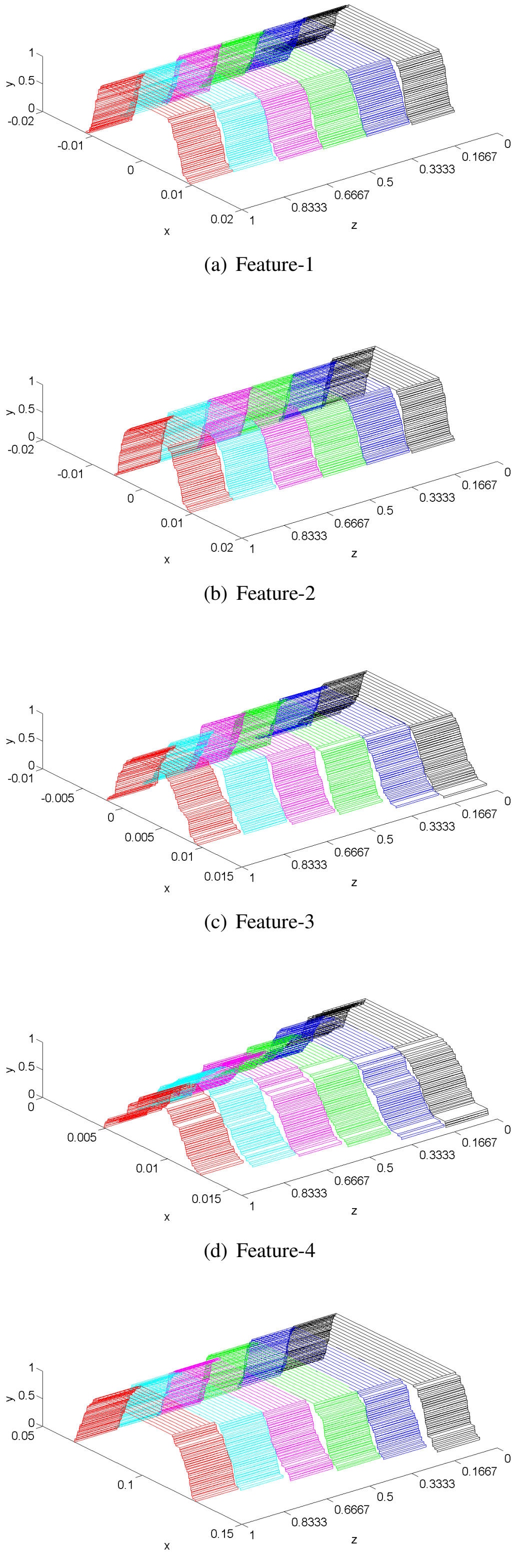
Wagner et al [21].

For our data set, for each feature, we create a zGT-II fuzzy set. Each zGT-II fuzzy set has six zSlices. For each grade, we have five zGT-II fuzzy sets. There are 15 benchmark zGT-II fuzzy sets to be used for classification of unseen spectral data.

The created zGT-II fuzzy sets for the features of G-I, G-II and G-III are shown in Figs. 4, 5 and 6 respectively. Each zGT-II fuzzy set has been created by combining the six T-I fuzzy sets for each feature. The z-axis shows the six zSlices. It can be observed from the figures that these zSlices aim to cover both the intra-case and inter-case uncertainties in the interval data taken from spectra of the same case and from different cases of the same grade. The created zGT-II fuzzy sets serve as benchmark prototypes for the unseen spectral data to be classified.

D. Model Testing with a Similarity Measure

In the next stage, we aim to classify the unseen spectra for each grade. For this purpose, two sets of unseen spectral data are selected from the two cases of G-I, six sets from the six G-II cases and six sets from the six cases of G-III.



(a) Feature-1

(b) Feature-2

(c) Feature-3

(d) Feature-4

(e) Feature-5

Fig. 5. 3D plots for zGT-II fuzzy sets for features 1-5 for G-II

TABLE I
SIMILARITY SCORES FOR G-I WITH TEST DATA FOR CASE 1

Feature	G-I	G-II	G-III
1	**0.9264**	0.8397	0.8235
2	**0.8938**	0.8035	0.7905
3	0.8122	0.8452	**0.8790**
4	**0.6407**	0.5194	0.5347
5	**0.9001**	0.8391	0.8719
Sum	**4.1732**	3.8469	3.8996
Majority Vote	**W**	L	L

TABLE II
SUMMARY OF RESULTS WITH TEST CASES BY THE SUMMATION AND MAJORITY VOTE METHOD

Type	Test Cases	Correct Classification Summation	Incorrect Classification Summation	Correct Classification Majority Vote	Incorrect Classification Majority Vote
G-I	2	2	0	2	0
G-II	6	1	5	2	3 (1 Tie)
G-III	6	6	0	3	1 (2 Tie)

All of these T-I fuzzy sets are compared against the prototype zGT-II fuzzy sets for each feature of each grade using the method described in Equation 3 that uses a weighted similarity criteria. A similarity score is obtained for each comparison. For the grade classification of the unseen data, we have used two methods.

1) Summation over similarities
2) Majority vote

In the first method, we record a similarity value for each feature of each grade and then compute the sum of all feature similarities for each grade and report the grade with the maximum value as the predicted grade. In the second method we take the grade with the maximum value for each feature as a vote. The grade with maximum number of votes is reported as the classified grade.

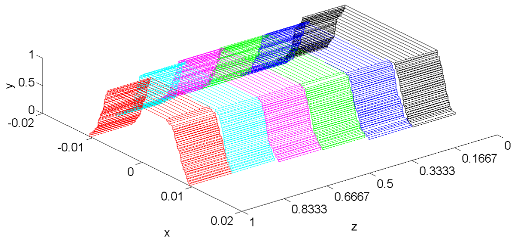
V. RESULTS

Table I shows an example of the similarity scores obtained after testing with case 1 of G-I with both classification methods for all grades. **W** in the table indicates a winner in the majority vote and **L** indicates a failure. A tie occurs if two features have equal votes. It can be seen that except feature 3, all features are able to classify the test case of G-I correctly, and both the majority vote and summations methods classify correctly. Following this, all test cases were compared in the same way.

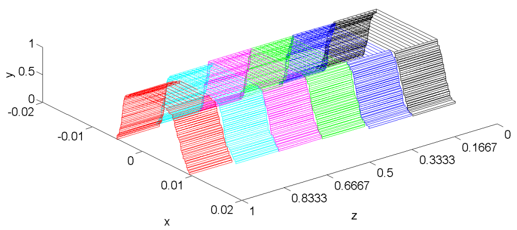
Table II shows a summary of the results including the correct / incorrect classifications made with the summation and majority vote methods. It can be seen that summation method correctly classifies all cases of G-I and G-III and 17% of G-II cases. The majority vote method correctly classifies all of G-I, 33% of G-II and 50% of G-III cases. Neither method achieved better than could be expected with random classification (33%) on G-II.

VI. DISCUSSION

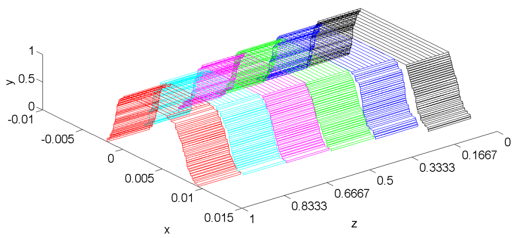
Fig. 7 shows a grade profile for two cases of G-I testing data, plotting similarity scores for features as described in previous



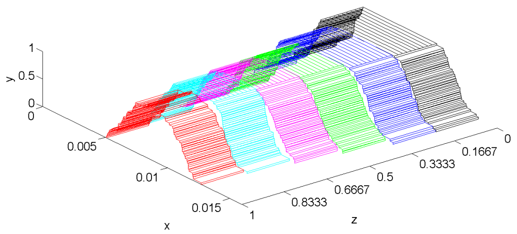
(a) Feature-1



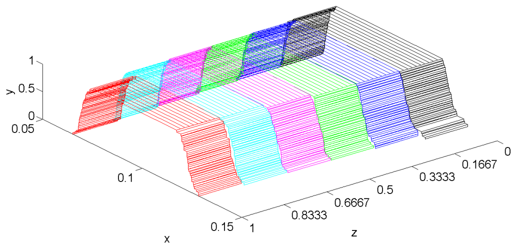
(b) Feature-2



(c) Feature-3

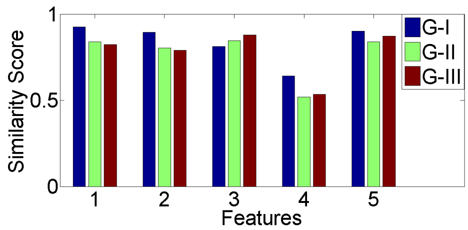


(d) Feature-4

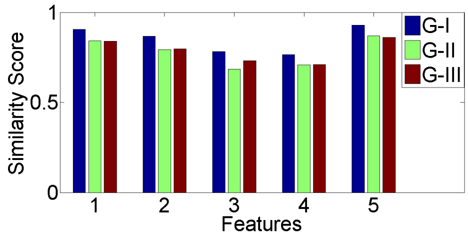


(e) Feature-5

Fig. 6. 3D plots for zGT-II fuzzy sets for features 1-5 for G-III



(a) Case-1

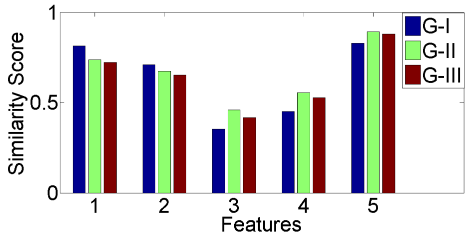


(b) Case-2

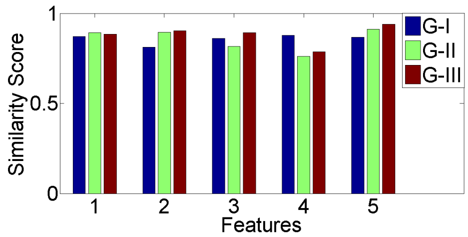
Fig. 7. Grade profile for two cases of G-I

section. For each feature, the similarity scores for each grade have been shown as a group of vertical bars with similarity score values ranging from 0 to 1. It can be seen that features 1, 2 and 5 provide high scores for the correct grade in both cases and although feature 4 provides the lowest similarity scores, it still gives the highest score to the correct grade. Feature 3 is a more inconsistent feature as it classifies case 2 correctly but classifies case 1 as G-III. It can also be observed that there are significant differences between G-I similarity scores compared to G-II and G-III for all features where G-I was chosen. That is why both maximum sum of similarity and majority vote performed well for G-I. Another observation is that scores for G-II and G-III remained very close to each other in more features. We conclude that features 1, 2 and 5 are the most useful as benchmark features to distinguish G-I from other grades.

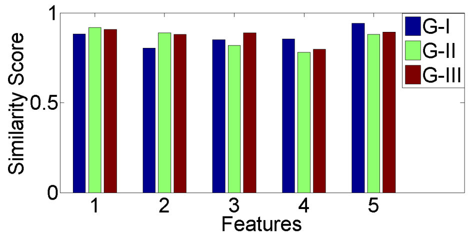
Fig. 8 shows grade profiles for six test cases of G-II. Previously we have seen that both classification methods perform poorly suggesting that G-II is not clearly distinguishable from other grades. However, there are some interesting observations that we can make by looking at Fig. 8. Feature 1 is able to classify the correct grade for cases 2, 3, 4 and 6 and case 5 is narrowly mistaken as G-III. Feature 2 correctly classified the grade for cases 3 and 6 where as for cases 2, 4 and 5 it was very close to classifying the correct grade. Feature 5 only classified correctly for case 1. In the majority of the cases where G-II was not classified correctly, it was classified as G-III. This is generally the case in real world scenarios, as G-II and G-III are considered very close to each other and chances of false classification remain high. We conclude that only feature 1 is able to classify the correct for majority of the G-II cases (4 out of 6) while the other features are inconsistent, this suggests that feature 1 is useful as a benchmark feature for identifying G-II from other grades.



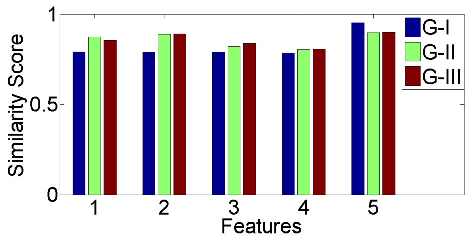
(a) Case-1



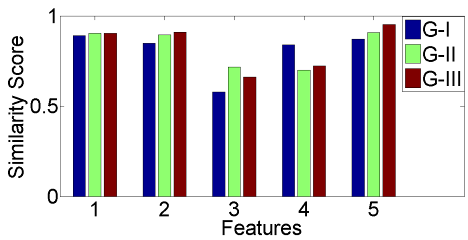
(b) Case-2



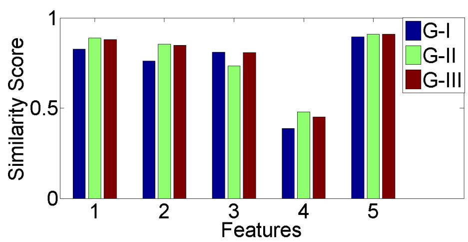
(c) Case-3



(d) Case-4

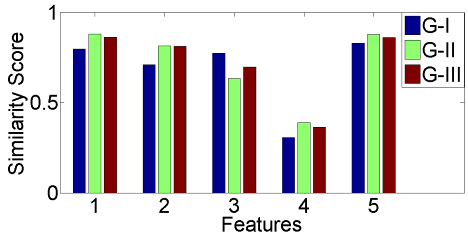


(e) Case-5

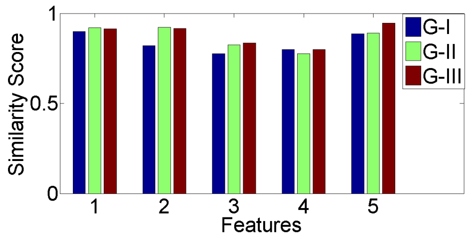


(f) Case-6

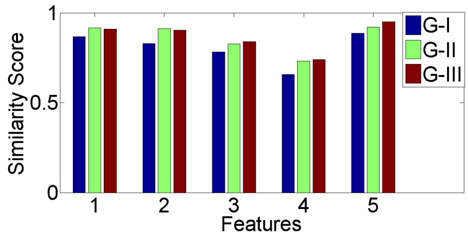
Fig. 8. Grade profile for six cases of G-II



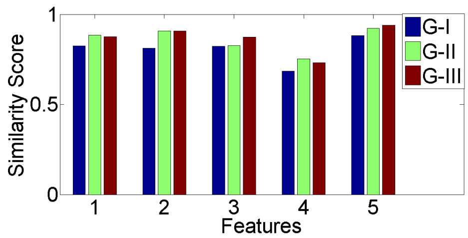
(a) Case-1



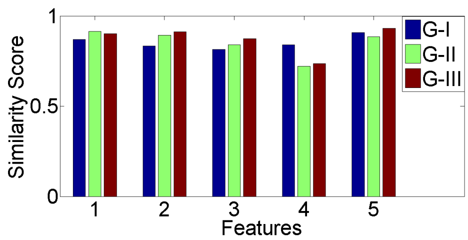
(b) Case-2



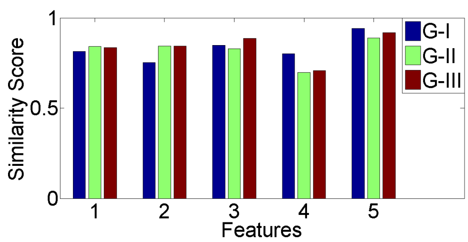
(c) Case-3



(d) Case-4



(e) Case-5



(f) Case-6

Fig. 9. Grade profile for six cases of G-III

TABLE III
SUMMARY OF GRADE PROFILES (CORRECTLY CLASSIFIED / TOTAL TEST CASES)

Grades	Feature 1	Feature 2	Feature 3	Feature 4	Feature 5
I	2/2	2/2	1/2	2/2	2/2
II	4/6	2/6	2/6	2/6	2/6
III	0/6	3/6	5/6	1/6	4/6

Fig. 9 shows grade profiles for six test cases of G-III with their similarity scores for each feature of each grade. It can be seen that feature 3 always classifies correctly except for case 1. Feature 5 also classified the correct grade for 4 out of 6 cases (cases 2, 3, 4, and 5). In the case of features 1 and 2, G-III scores were slightly less than G-II where as in case of feature 4, G-III is falsely classified as G-I for cases 2, 5 and 6. We conclude that features 3 and 5 are best suited for classifying G-III correctly for the majority of the cases and may be used as benchmark features for G-III classification.

Table III shows a summary of the features with correctly classified cases for each grade. The results indicate that features performed differently for the three grades. Feature 3 is only significant in G-III classification and did not perform well for any other grade. Similarly, feature 2 only performed well for G-I and incorrectly classified all other grades. Our results indicate that various features based on different regions of the same spectra provide different information, and some are more useful for cancer grade classification than others. zGT-II fuzzy sets based on interval data from spectral regions have been shown to be useful in extracting important information regarding cancer grade from FTIR data. The zGT-II fuzzy sets can be useful in classification problems where both inter and intra variabilities among spectra are involved.

VII. CONCLUSION

In this paper, we have shown that T-II fuzzy sets can be used to represent valuable information from spectral data sets in which high levels of uncertainties are involved. In particular, we use the different dimensions of the GT-II sets can be used to simultaneously represent the variation found in the single feature from a number of regions within a single case (intra-case variation) and the variation found between different cases of the same class (inter-case variation).

We have created zGT-II fuzzy sets with interval data extracted from features from various spectral regions within FTIR data in the context of breast cancer grading. These zGT-II sets have been used in a novel model that utilises a similarity-based approach for classification applications. We have used a breast cancer grading as a case study to test the method with a real-world complex data set. While not statistically significant, the results are very promising and they demonstrate that this is an important area of research.

In future, we will test the proposed model on a number of different case studies to evaluate its robustness and generalisability. We will also conduct extended experiments on this breast cancer data set using all of the cases available.

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