Exploiting Reliability-Guided Aggregation for the Assessment of Curvilinear Structure Tortuosity

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Abstract. The study on tortuosity of curvilinear structures in medical images has been significant in support of the examination and diagnosis for a number of diseases. To avoid the bias that may arise from using one particular tortuosity measurement, the simultaneous use of multiple measurements may offer a promising approach to produce a more robust overall assessment. As such, this paper proposes a data-driven approach for the automated grading of curvilinear structures' tortuosity, where multiple morphological measurements are aggregated on the basis of reliability to form a robust overall assessment. The proposed pipeline starts dealing with the imprecision and uncertainty inherently embedded in empirical tortuosity grades, whereby a fuzzy clustering method is applied on each available measurement. The reliability of each measurement is then assessed following a nearest neighbour guided approach before the final aggregation is made. Experimental results on two corneal nerve and one retinal vessel data sets demonstrate the superior performance of the proposed method over those where measurements are used independently or aggregated using conventional averaging operators.

Keywords: Tortuosity assessment · Curvilinear structure · Fuzzy clustering · Reliability guided aggregation

1 Introduction

Tortuosity of curvilinear structures in ophthalmic images can be used as indicators to a number of diseases. For example, the tortuosity of corneal fibers shown in *in vivo* confocal microscopy images can be used to explain the nerve degeneration and subsequent regeneration [10], which is correlated with diabetic neuropathy, retinopathy of prematurity [9], and keratitis [11]. The assessment of curvilinear structures' tortuosity level could be utilised for early diseases prevention of further complications. In several studies, the tortuosity of curvilinear structures has been manually graded in the band of 3–5 levels [12] or ranked by ophthalmologists based on their clinical experiences. However, the imprecision and uncertainty inherently embedded in the subjective empirical assessment may lead to substantial inter-observer and intra-observer variability [2].

In the literature, the tortuosity grading may also be conducted using various measurements of curvilinear structures such as the angle [5], length [7], and curvature [8]. A fully automated pipeline on the basis of these measurements that takes raw images as inputs and outputs assessment results may be devised for tortuosity estimation. Typically, such automated methods employ segmentation algorithms to replace manual tracing of curvilinear structures. However, many of the existing tortuosity measurements are based on mathematical definitions, which are sensitive to pixel-level calculation. The jagged and inaccurate boundaries embedded in the automated segmentation, easily result in low performance of tortuosity estimates. On the other hand, hand-crafted tortuosity definitions only provide fixed models of subjective perception, which limits the generalisation ability of individual measurements across different tasks. The automated tortuosity assessment of curvilinear structures in ophthalmic images is therefore still a challenging problem.

As such, it is still prevalent to use different measurements of curvilinear structure to grade the tortuosity. To our best knowledge, there is no universal agreement as to which standard or measurement to apply. Recent studies suggest to simultaneously use multiple relevant measurements, in order to produce a robust overall assessment of tortuosity [2,14]. Indeed the use of multiple measurements may avoid the bias that may arise from using one particular tortuosity measurement. Inspired by this observation, This paper proposes a novel unsupervised pipeline for the automated grading of curvilinear structures' tortuosity, whereby multiple morphological measurements are aggregated on the basis of data-driven reliability to form a robust overall assessment. Experimental analysis on three data sets demonstrates the superior performance of the proposed method over those where measurements are used independently or aggregated using conventional averaging operators.

2 Method

2.1 Pipeline and Preprocessing of the Proposed Method

The proposed method is named Fuzzy Clustering and Measurement Reliability based Assessment of Tortuosity (FCMRAT). The working process starts by generating fuzzy clusters using fuzzy c-means algorithm [3] on each of the tortuosity measurements which are preselected (and predefined) by experts. The resultant fuzzy clusters (termed base clusters) can be associated with linguistic labels, which facilitate readability and validation against medical knowledge by clinicians. The reliability based aggregation operators are subsequently used to combine the base clusters that share the same linguistic label, resulting in the final fuzzy clusters of images. An illustrative flowchart of the proposed FCMRAT is shown in Fig. 1 with key operations detailed in the following subsections.

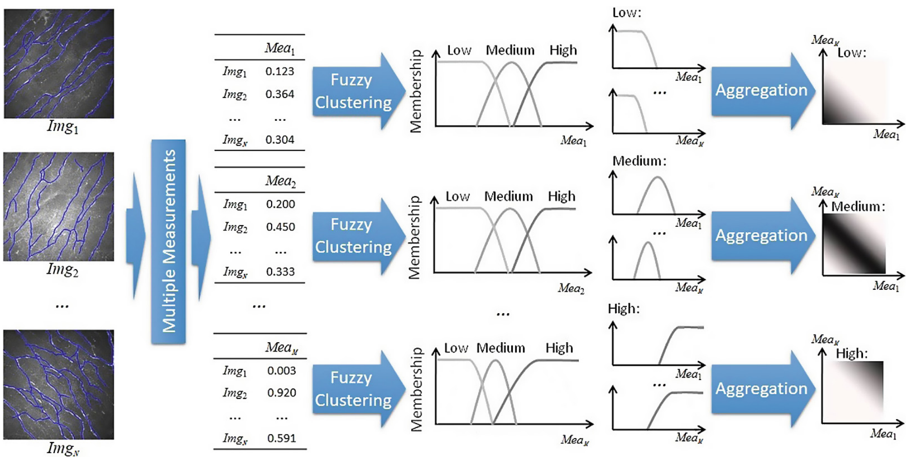

Fig. 1. Pipeline of FCMRAT. Firstly, the tortuosity of nerves in each image is evaluated by multiple measurements. Secondly, linguistic labelled fuzzy clusters are generated based on each measurement individually; Then, all the clusters are grouped by labels. Finally, an aggregation is applied on each group of fuzzy clusters with the same label.

Given a set of N images $\{Img_1, Img_2, \cdots, Img_N\}$ and M morphological measurements of tortuosity $mea_1, mea_2, \cdots, mea_M$, the curvilinear structures shown on $Img_i, i = 1, 2, \cdots, N$, can be traced and their tortuosity can be calculated by the M measurements. Typically, a measurement $mea_j, j = 1, 2, \cdots, M$, is deemed to be a mapping from the set of single curvilinear structures C to positive real-valued numbers $mea_j : C \rightarrow \mathbb{R}^+$, where large number indicates high tortuosity. An original image may contain a number of traced curvilinear structures. Therefore, an image-level tortuosity may be obtained by averaging all curvilinear structures traced in that image weighted by their length. Formally, given that H segments $c_h \in C, h = 1, 2, \cdots, H$ of curvilinear structures are traced in an image and the length of h-th structure is denoted as l_h, the image-level tortuosity can be defined as: $Mea_j(Img_i) = \sum_{h=1}^{H} l_h mea_j(c_h) / \sum_{h=1}^{H} l_h$ [2]. For images which contain only one single curvilinear structure c_1 (as in the RET-TORT [7]), $Mea_j(Img_i) = mea_j(c_1)$. Despite that the proposed FCMRAT is tested on segmentation results of curvilinear structures, both manually and automated segmentation can be embedded in the pipeline. However, it is worth noticing that in retina, certain diseases cause tortuosity alterations in portion of the eye, or just in capillaries. In such cases, the selection of curvilinear structures of interest is necessary in the preprocessing of images.

2.2 Generation of Fuzzy Clusters at Measurement Level

In case where there exists imprecision and vagueness that arise from the ophthalmologists' subjective empirical grading of tortuosity, fuzzy set theory is regarded as an effective means to dealing with vague concepts that are ubiquitous in natural languages and practical reasoning. It is a common practice to use fuzzification techniques to translate real-valued measurements into linguistic terms. In this paper, fuzzy clustering is employed for the fuzzification of each individual measurement. Suppose that $\{Img_1, Img_2, \cdots, Img_N\}$ are evaluated with regard to $Mea_1, Mea_2, \cdots, Mea_M$. For each measurement Mea_j, fuzzy c-means is utilised to form S base clusters $\widetilde{F}_1^j, \widetilde{F}_2^j, \cdots, \widetilde{F}_S^j$ on the set of images with respect to $\{Mea_j(Img_i)|i = 1, 2, \cdots, N\}$, with $\widetilde{F}_s^j(Img_i) \in [0, 1]$ representing the degree of Img_i belonging to an individual base cluster $\widetilde{F}_s^j, s = 1, 2, \cdots, S$, which satisfies $\sum_{s=1}^{S} \widetilde{F}_s^j(Img_i) = 1$ for all $j = 1, 2, \cdots, M$.

Linguistic terms are often used by clinicians in practice to describe the grading of curvilinear structure tortuosity in the ophthalmic images. A preference ordering relation is usually defined to describe the grading of tortuosity on a set of linguistic terms such as $Low \prec Medium \prec High$. In FCMRAT, labelling base clusters is not only helpful for ophthalmologists to investigate the relative tortuosity reflected in objective measurements, it also plays a significant role in organising base clusters into groups for subsequent aggregation process. Since the resulting clusters for a certain tortuosity measurement Mea_j on the set of images are totally ordered, the cluster centers $\widetilde{F}_1^j, \widetilde{F}_2^j, \cdots, \widetilde{F}_S^j$ can be employed to signify the overall relative tortuosity. Thus, given a set of S pre-defined linguistic terms $\mathbb{L} = \{L_1, L_2, \cdots, L_S\}$ which satisfy that $L_1 \prec L_2 \prec \cdots \prec L_S$, the fuzzy clusters $\widetilde{F}_1^j, \widetilde{F}_2^j, \cdots, \widetilde{F}_S^j$ can be readily sorted in ascending order with regard to their cluster centers and labelled with $L_1, L_2, \cdots, L_S$, respectively. From this, the notation $\widetilde{F}_{L_s}^j$ represents the base cluster generated by tortuosity measurement Mea_j and labelled with linguistic term $L_s, s = 1, 2, \cdots, S$.

2.3 Consensus of Base Clusters Guided by Reliability

Having gone through the fuzzification process as described in the preceding subsection, a total number of $M \times S$ fuzzy clusters are generated and labelled. They can be groupted into S sets of fuzzy sets $\mathbb{F}_{L_s}, s = 1, 2, \cdots, S$, where $\mathbb{F}_{L_s} = \{\widetilde{F}_{L_s}^j | j = 1, 2, \cdots, M\}$ consists of all the base clusters with label L_s. The base clusters in each group $\mathbb{F}_{L_s}$ is further aggregated to generate a final fuzzy cluster of images (denoted as $\widetilde{F}_{L_s}^*$) with their tortuosity graded into level L_s. The membership of an image Img_i to $\widetilde{F}_{L_s}^*$ can be computed by

$\widetilde{F}^*_{L_s}(Img_i) = \frac{Agg(\widetilde{F}^1_{L_s}(Img_i), \widetilde{F}^2_{L_s}(Img_i), \cdots, \widetilde{F}^M_{L_s}(Img_i))}{\sum_{t=1}^{S} Agg(\widetilde{F}^1_{L_t}(Img_i), \widetilde{F}^2_{L_t}(Img_i), \cdots, \widetilde{F}^M_{L_t}(Img_i))}$ where $Agg : \mathbb{R}^M \rightarrow \mathbb{R}$ is an aggregation operator.

As the effectiveness of certain measurements varies on different tasks, weighting all available tortuosity measurements equally may not reflect the deviations in the contribution made by individual measurements and therefore limit the quality of overall assessment. In addition, it is practically difficult and time-consuming for ophthalmologists to use empirical knowledge to agree on proper weights for different tortuosity measurements. In order to automate this complicated aggregation task, this paper employs the concept of K-Nearest-Neighbour guided Dependent Ordered Weighted Averaging (KNNDOWA) [4,15], in which an argument (such as a measurement in this case) whose value is similar to its neighbours is deemed reliable and can be highly weighted. In contrast, an argument that is largely different from its neighbours is discriminated as an unreliable member. Formally, the reliability of an argument a_j, $j = 1, 2, \cdots, M$, in KNNDOWA is defined as: $R_j^K = 1 - \frac{\sum_{k=1}^{K} d(a_j, n_k^{a_j})/K}{\max\limits_{t,t' \in \{1,2,\cdots,M\}} d(a_t, a_{t'})}$. where $n_k^{a_j} \in \{a_1, 2, \cdots, a_M\}/\{a_j\}$ is the value of k-th nearest neighbour ($k = 1, 2, \cdots, K$ and $K < M$) of the argument a_j, and the distance matric is $d(a_t, a_{t'}) = |a_t - a_{t'}|$ for $t, t' \in \{1, 2, \cdots, M\}$. Note that the distance metric is also used to perform neighbour-searching. Having obtained the reliability values of all arguments concerned, they are normalised to form the weighing vectors in KNNDOWA. Given the reliability value R_j^K of each argument $a_j, j = 1, 2, \cdots, M$, the corresponding aggregation operator Agg^K can be specified by $Agg^K(a_1, a_2, \cdots, a_M) = \sum_{j=1}^{M} R_j^K a_j / \sum_{j=1}^{M} R_j^K$.

In FCMRAT, KNNDOWA is adopted to aggregate the memberships of images with respect to base clusters in each labelled group. Computationally speaking, alternative aggregation operators can also be fitted into the FCMRAT pipeline. The advantages of selecting KNNDOWA out of alternatives are: 1) the weights used in the aggregation are purely data-driven, which are automatically learned from the memberships $\widetilde{F}^j_{L_s}(Img_i)$, and 2) the weight assigned to each argument $w(a_j) = R_j^K / \sum_{t=1}^{M} R_t^K, j = 1, 2, \cdots, M$, represents the reliability of a_j, which can be utilised as a meaningful indicator to ophthalmologists for further interpreting the effectiveness of the underlying tortuosity measurements.

2.4 Tortuosity Assessment Based on Aggregated Fuzzy Clusters

The final step of the proposed FCMRAT is to assess the tortuosity based on the aggregated fuzzy clusters. Consider an example where the set of pre-defined linguistic terms $\mathbb{L}$ is $\{Low, Medium, High\}$ with the preference ordering relation $Low \prec Medium \prec High$, the memberships of an image Img_i to the final fuzzy clusters is represented as a vector such as $(\widetilde{F}^*_{Low}(Img_i), \widetilde{F}^*_{Medium}(Img_i), \widetilde{F}^*_{High}(Img_i)) = (0.2, 0.5, 0.3)$, it is straightforward to defuzzify the assessment result by assigning Img_i to the linguistic label associated with the final fuzzy cluster that possesses the maximum membership degree among others. The final grade of Img_i is computed as $\arg\max_{L_s \in \mathbb{L}} \widetilde{F}^*_{L_s}(Img_i)$, i.e., the tortuosity of Img_i is graded to $Medium$ in this example.

To utilise all available information, an alternative method is to assign a significance score to each of the linguistic terms and then, to sort the images with respect to the weighted sum of the scores and memberships to the final fuzzy clusters. In this paper, the significance score of L_s is set to s. Then, the ranking over a set of images can be obtained by sorting the images in a descending/ascending order, according to a ranking index: $\sum_{s=1}^{S} s\widetilde{F}^*_{L_s}(Img_i)$. In the previous example, the ranking index of Img_i is 2.1.

3 Experimental Analysis

The FCMRAT is tested on two public data sets: the NERVE TORTUOSITY (NT1) in which 30 images are graded into 3 levels [6] and the RET-TORT [7] in which the images of arteries (Art.) and veins (Vei.) are ranked and used independently. An in-house conrneal nerve data set (NT2) is also employed, in which 242 images are taken in the resolution of 384×384 pixels and are graded into 4 levels of tortuosity based on a protocol [12]. Five tortuosity measurements including the arc Length over Chord length ratio (LC), Total Curvature (TC), Total Squared Curvature (TSC), Inflection Count Metric (ICM) [1], and Absolute Direction Angle Change (DCI) [13] are employed for generating the base clusters of FCMRAT. An segmentation algorithm proposed in [17] is adopted on the NT1 and NT2 data sets to trace the curvilinear structures. Depending on whether the segmentation of curvilinear structures is implemented by automated algorithm or by manual annotation, a suffix -A or -M is used for annotation. The Spearman's coefficients between individual measurements and the ground truth of each data set are reported in Table 1, where the highest values are highlighted in boldface. The average and median values of the coefficients on each data set are provided as baselines.

Table 1. Spearman's coefficients of individual measurements

Dataset	Lc	Tc	Tsc	ICM	DCI	Average	Median
NT1-A	0.5990	0.7547	0.7924	0.4339	**0.8160**	0.6792	0.7547
NT1-M	**0.8254**	0.8018	0.7830	0.6226	0.7028	0.7471	0.7830
NT2-A	**0.6316**	0.6112	0.6013	0.3184	0.5210	0.5367	0.6013
Art.	0.8194	0.8945	**0.9017**	0.8269	0.7161	0.8317	0.8269
Vei.	0.6130	0.8143	**0.8346**	0.6397	0.7378	0.7279	0.7378

The Spearman's coefficients between ranks generated by the FCMRAT ranking index (the number of final clusters S is set to 5) and the ground truth are reported in Table 2. In addition to the KNNDOWA, four aggregation operators namely: Andness-OWA (an OWA operator with weighting vector $(0.300, 0.233,$

$0.167, 0.100, 0.033)$), Mean, Orness-OWA (an OWA operator with weighting vector $(0.033, 0.100, 0.167, 0.233, 0.300)$), and Dependent OWA [16] are also implemented under the FCMRAT pipeline for the consensus of base clusters to support systematic comparisons. Since there are five measurements to be aggregated, the number of nearest neighbours K in KNNDOWA is set to 2, which indicates the reliability of each measurement is estimated by half (2 out of 4) of its neighbours. The fuzzy c-means algorithm starts with random initialisation of memberships and each reported FCMRAT result is an average of 30 runs. The standard deviation of all the results are smaller than 0.0075. The performance for the NT1 and NT2 data set is also evaluated based on the weighted accuracy (wAcc) [2] through defuzzifying final fuzzy clusters. In order to generate the grade-based result, the number of final clusters (i.e., the number of base clusters for each measurements) S in this experiments is set to the number of grades in the ground truth (3 and 4 for NT1 and NT2, respectively).

Table 2. Results of FCMRAT with different aggregation operators

	Spearman's coefficient					wAcc		
	NT1-A	NT1-M	NT2-A	Art.	Vei.	NT1-A	NT1-M	NT2-A
FCMRAT+And	0.7309	0.8160	0.6156	**0.9132**	0.7972	0.8222	0.7333	0.5809
FCMRAT+Mean	0.7314	0.8242	0.6132	0.9119	0.7949	0.8222	0.7333	0.5831
FCMRAT+Or	0.7294	**0.8279**	0.6115	0.9052	0.7835	0.8222	0.7333	**0.5834**
FCMRAT+DOWA	0.7283	0.8174	0.6166	0.9119	0.8019	0.8222	0.7333	0.5828
FCMRAT+2NN	**0.7558**	0.8018	**0.6167**	0.9026	**0.8112**	0.8222	0.7333	0.5786

It can be seen from Table 1 that the most relevant single measurement, i.e., the one with highest Spearman's coefficient with the ground truth (in boldface) varies on different data sets, which supports the observation that there is no agreement as to which measurement to apply universally. As it is shown in Table 2, by applying the proposed FCMRAT pipeline, the aggregation based results are better than those obtained by averaging individual measurements across all the data sets. The FCMRAT based results are better than the median value of individual measurements for four out of five data sets. These observations show the effectiveness of the fuzzy clustering based aggregation of multiple measurements for tortuosity assessment. It is also worth noticing that the FCMRAT based aggregations can achieve results which are better than the best result achieved by individual measurements on the NT1-M and Art. data sets. This further demonstrates that the proposed aggregation of multiple measurements is effective in the tortuosity assessment for curvilinear structures. Furthermore, the weighted accuracies of all FCMRAT based aggregations on the NT1 data set are the same, which indicates the insensitivity and robustness of FCMRAT in the selection of aggregation operators. The performance of the proposed method on the in-house data set is lower than that on the public data sets, which is mainly attributed to the low performances achieved at the level of individual measurements, possibly resulting from the inaccurate segmentation of curvilinear structures and inconsistent grading in the ground truth.

Amongst all the tested aggregation operators, the KNNDOWA based FCMRAT is the only one which achieves results better than the medians of individual measurements across all the tested data sets. In addition to the superior and stable performance of KNNDOWA in providing overall tortuosity assessment, the linguistic term labelled base clusters and the data-driven generated reliabilities during aggregation operation provide a supportive tool for ophthalmologists to interpret and fine-tune the assessment model. For each measurement Mea_j, its overall reliability can be evaluated by the mean of its weights in all the aggregations as $\sum_{i=1}^{N}\sum_{s=1}^{S} w(\widetilde{F}^j_{L_s}(Img_i))/(NS)$. Take the NT1-A data set as an example with the number of final clusters is set to 3, the overall reliability of the Lc, Tc, Tsc, ICM, and DCI is 0.1969, 0.2182, 0.2238, 0.1646, and 0.1965, respectively, with Tc and Tsc being considered more reliable than the other three measurements in the FCMRAT.

It is worth noticing that in practice, the 3-level (low, medium, high) or 4-level tortuosity grades may be more common in nerve fiber studies. In retinal studies, 5-level grading may be used. Theoretically, the clustering granularity can be defined as fine as possible by allowing a large number of clusters and associated linguistic labels. In practice, this is not encouraged, especially in cases where clearly divided stages for tortuosity grading may not exist, or for psychological reasons in order to linguistically interpret the labelled clusters to clinicians.

4 Conclusion and Future Work

This paper proposes a novel pipeline for the assessment of curvilinear structure tortuosity based on fuzzy clustering and reliability-guided aggregation of morphological measurements. The proposed work is verified on three real-world data sets with superior and stable results achieved over those at the level of individual tortuosity measurements, demonstrating the efficacy and effectiveness of the proposed method. Whist promising, the proposed pipeline could be naturally extended to cope with a broader range of medical imaging tasks such as investigation of unsupervised methods in automated tortuosity assessment systems.

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