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The application of MRI complexity analysis for pre-treatment prediction of brain tumor response to radiation therapy and radiosurgery- feasibility demonstration

Research Article

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Abbreviations: Magnetic resonance imaging, (MRI);

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Summary

Linguistic complexity is a methodology used for calculating the complexity of strings of data. It is based on the concept that the greater the vocabulary one uses, the more complex the data. Linguistic complexity is commonly applied to studying various human language texts. In biology it has been used for analyzing one-dimensional data such as genomic DNA and protein sequence analysis due to their similarity to spoken/artificial languages on one hand and their high repetitiveness on the other. We have recently shown that the basic definition can be extended to higher dimensions, allowing the linguistic complexity analysis of multi-dimensional data. In the current study we applied linguistic complexity analysis to conventional T2-weighted MRI and demonstrated the potential of this methodology to predict brain tumor response to therapy. Eighteen patients with twenty three malignant brain lesions undergoing conventional fractionated radiation therapy or high-dose single fraction radiosurgery were studied. Magnetic resonance images were acquired on a 0.5 T interventional MRI. Response to therapy was determined from changes in tumor volumes calculated from contrast-enhanced T1-weighted MRI, acquired before and 50 days on average after initiation of therapy. Linguistic complexity analysis was performed using the MRITA software and a homogeneity index, Hi, reflecting intensity homogeneity within the tumor, was calculated. The homogeneity index, Hi, for the pre-treatment tumors was found to correlate significantly with later tumor response or lack of response (r=0.57, p<0.004). This correlation implies that tumors with high pre-treatment Hi values, indicating tissue homogeneity, will respond better to therapy than tumors with low Hi values, indicating tissue heterogeneity. These results demonstrate the feasibility of applying complexity analysis of T2-weighted MRI for pre-treatment prediction of response to therapy in brain tumor patients undergoing radiation therapy and radiosurgery.

I. Introduction

Several magnetic resonance (MR) methods have been suggested recently as having potential for prediction of tumor response to treatment. Contrast-enhanced MRI has been shown to be able to reveal distinct tumor patterns that can serve as a predictor of response to chemotherapy in human breast cancer (Esserman et al, 2001). Dynamic contrast MRI has been shown to be useful in characterizing the microvasculature of tumors and has shown potential in predicting response to antiangiogenic treatments (Neeman et al, 2003). P-31 MR spectroscopy was shown in a preliminary study to be a feasible method in predicting response of head and neck cancers to radiation therapy (Shukla-Dave el al, 2002). This method, however, has a low sensitivity and is generally limited to large and superficial tumors. Recent diffusion-weighted MR studies suggested that the initial apparent diffusion coefficient could serve as a predictive parameter for primary rat mammary tumor sensitivity to chemotherapy (Lemaire et al, 1999) and chemoradiation/chemotherapy response (Dzik-Jurasz et al, 2002; Hein et al, 2003) in patients with rectal cancer. Our group has shown the feasibility of applying diffusion-weighted MRI for pre-treatment prediction of treatment outcome in brain tumor patients undergoing radiation therapy (Mardor et al, 2004).

Complexity is a multifaceted concept formally implemented in many disciplines. A need to numerically quantify it has arisen since complexity can categorize a system or data. The classical definitions of complexity (Shannon and Weaver, 1959; Kolmogorov, 1983) are broadly used, though these are not practical for multi-dimensional ensembles. Linguistic complexity introduced a decade ago (Trifonov, 1990), is a highly intuitive notion. The calculation of the complexity is an arithmetic procedure. It is based on the idea that the larger the vocabulary used in a text, the greater its complexity. The complexity of a sequence then is the product of vocabulary usage for each word length, or in other words, it measures the entire range of possible words. Many such calculations were successfully performed on human language texts and DNA sequences (Trifonov, 1991; Popov et al, 1996; Bolshoy et al, 1997). The limitation of the above definition is that it is restricted to one-dimensional data. We have recently shown (Gordon, 2003) that a simple extension of this definition to multi-dimensional data ensembles can be made. The extended methodology is based on representing a multi-dimensional ensemble as a linear array, thus returning to the initial one-dimensional definition, where vocabulary usage for each word size is defined in the same way.

In this study we used the MRITA software package to analyze conventional, T2-weighted MR images with no contrast-enhancement, and to determine the homogeneity index of brain tumors. High values of the homogeneity index, Hi, imply homogenous tissue, while low Hi values imply heterogeneity. We studied the correlation between pre-treatment tumor homogeneity and later tumor response to therapy in patients with brain tumors undergoing radiation therapy and radiosurgery. The results suggest that complexity calculations may be used for non-invasive prediction of treatment outcome. This new information may be used clinically to optimize decisions concerning the appropriate treatment for individual patients, thereby preventing unnecessary toxicity or prolonged ineffective therapy in non-responding patients.

II. Materials and methods

A. Patients and treatment

Eighteen patients with twenty three brain lesions were included in the study. Four patients had gliomas (grades III-IV), one acoustic neuroma, one meningial sarcoma and twelve patients had brain metastasis (four breast, one renal, three melanoma and four lung cancer). Ten patients received conventional fractionated radiation therapy of 30-60 Gy. Eight patients underwent radiosurgery of 16-20 Gy. All patients underwent MR scans before treatment and at regular intervals thereafter.

B. Equipment and software

Data were acquired using a General Electric 0.5 T interventional MRI system (Signa SP/i (special proceeding/interventional)) at the Chaim Sheba Medical Center. The standard GE head-coil was used for data acquisition. Image analysis was performed using the MRITA, version 1.3, of Magnolia Medical Technologies, Ltd. Statistical analysis was preformed with InStat GraphPad version 3.05 software package.

C. Tissue complexity analysis method

Complexity is a multifaceted concept implemented in many disciplines. Linguistic complexity was first defined in a textual connotation and is based on the idea that the larger the vocabulary used in a text, the greater its complexity. The data set is composed of letters (e.g. Latin letters in text). Any combination of a specific number of letters is defined as a word (e.g. AB is a two-letter word). The complexity is measured by counting the number of different occurring words (of a given size), divided by the maximal possible different words (of the same size) within a data set. Thus the linguistic complexity is a number between 0.0 for the simplest data set and 1.0 for the most complex data set:

$$\textit{Linguistic Complexity} = \frac{(\text{\# of occurring words})}{(\text{maximum \# of possible words })} \quad \textbf{[1]}$$

Such calculations were successfully performed on DNA sequences and human language texts. The extension of the linguistic complexity calculation to a two-dimensional data set, such as a MR image, is carried out in the following way: The equivalent of an alphabet in an image is the color scale (e.g. 256 letters for gray scale) and the equivalent of a word is any specific combination of pixel intensities. An example is shown in **Figure 1**.

In order to perform a complexity calculation on any given data set, one has to determine two parameters: the word size (i.e. number of letters within the word) and the number of letters (i.e. the alphabet). The goals are to maximize the sensitivity of the complexity calculation and lower the required calculation power. The considerations for choosing the optimal parameters are discussed in the Appendix.

The linguistic complexity in most cases is proportional to the region of interest (ROI) size. This is not true in the extreme cases of completely homogenous ROIs, or in cases where the ROI is large in relation to the vocabulary size. Except for these extreme cases, linguistic complexity depends on the ROI size in the following manner:

$$\text{Linguistic Complexity} = 1.0 - Hi * ROI\_size \qquad [2]$$

Thus, large ROIs or high resolution ROIs (more pixels in a given ROI) will have smaller linguistic complexity than smaller or lower resolution ROIs. Hi, on the other hand, does not depend on the ROI size, and reflects the homogeneity of the ROI. Therefore, the output parameter of the complexity calculation was chosen to be the homogeneity index:

$$Hi = (1 - \text{Linguistic Complexity}) / ROI\_size \qquad [3]$$

where high values of Hi imply homogenous ROIs and low values of Hi imply heterogeneous ROIs.

D. Data acquisition

Gadolinium contrast-enhanced spin-echo T1-weighted MR images and fast spin-echo T2-weighted MR images were used to monitor the patients before and at regular intervals following treatment. All images were acquired with 5 mm slices, 2 signal averages, and a 22x16.5 cm field of view. T2-weighted MR images were acquired with a 256x128 matrix, TR=3000 ms, and TE=95 ms. T1-weighted MR images were acquired with a 256x128 matrix, TR=500 ms, and TE=14.5 ms.

E. Assessment of tumor response

Tumor volumes were calculated from the contrast-enhanced T1-weighted images. A ROI was defined over the entire apparent tumor in each slice and the number of pixels was counted. Tumor volumes in cm^3 were calculated prior to treatment and 50 days on average post-treatment. The change in tumor volume was defined as the ratio between the final volume and the initial volume.

Responding tumors were defined as tumors which decreased to 50% or less of their original volume. The rest were defined as stable/non-responding tumors.

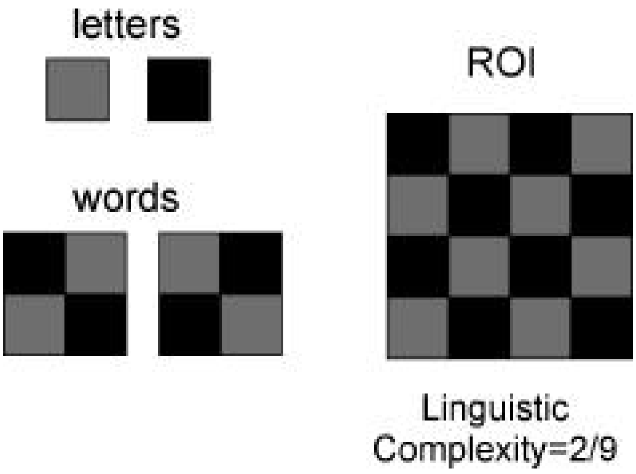

Figure 1. An example of a two-dimensional linguistic complexity calculation. The ROI image is composed of two letters (i.e. a binary image). Only two 2x2 words appear in the ROI. Since the ROI size is 4x4 pixels, the number of different possible words of size 2x2 is 9. Therefore, the linguistic complexity of this ROI is 2/9.

F. Tissue complexity analysis of data

ROIs were plotted on the contrast-enhanced T1-weighted images to define the area of the tumor. ROIs were then copied to the T2-weighted images, and a homogeneity index, Hi, was calculated for each slice of the lesion. These values were averaged over the slices to become the average homogeneity index, Hi, reflecting the intensity variation within the tumor in the T2-weighted MR images. Relative errors due to imaging noise were determined by calculating the ratio between the homogeneity index in a ROI chosen in the ventricles (the most homogenous/high-signal region in the image) and the homogeneity index of a totally homogeneous ROI of the same size ($Hi_{homogeneous}$ = #Letters^4 / ROI-size). The error in choosing the ROIs was determined by having three researchers choose ROIs for the same tumor independently. The standard deviation of the calculated Hi values was 4%. Since these errors are not correlated, the total relative error was defined as:

$$Err = \sqrt{\left(\frac{Hi_{ventricles}}{Hi_{homogenous}}\right)^2 + 4\,\%^2}$$

III. Results

A. Determination of complexity parameters

Linguistic complexity depends on interplay between ROI size, word size and alphabet size.

The grayscale in a T2-weighted MR image is divided into 256 shades (letters) ranging from 0 (black) to 255 (white). This number of letters is too large relative to the selected ROI sizes, resulting in a complexity value of 1.0. On the other hand, choosing an extremely small alphabet, for example a two color alphabet (black and white), will result in complexity values near 0. The optimal number of shades (letters) was found to be 12, i.e. instead of a grayscale of 256 shades, they were divided to 12 equal groups.

Since the linguistic complexity depends on the ROI size, the ROIs had to be limited to a certain range. The lower limit was determined by studying the correlation between linguistic complexity and ROI-size (**Figure 2**). The two parameters were linearly correlated down to a certain ROI size (ca 100 pixels). Below this ROI size, the combination of the chosen word size (2x2) and the number of letters (12 shades) resulted in the maximal value for the linguistic complexity, i.e. 1.

Following these considerations, tumor ROIs were limited to a size range of above 100 pixels.

The word size was chosen to be a 2x2 pixel combination. Due to the sizes of the ROIs, this is the only logical choice, because choosing a smaller size (e.g. a word of only one pixel) would not have given a proper indication of the complexity, but only the statistical variation of the intensity. Choosing a larger word size (e.g. 3x3 pixel combinations) would have produced a complexity of 1.0 for all tumors.

Figure 3 shows examples of linguistic complexity maps of homogenous and complex tumors. Low complexity regions appear dark and high complexity regions appear bright.

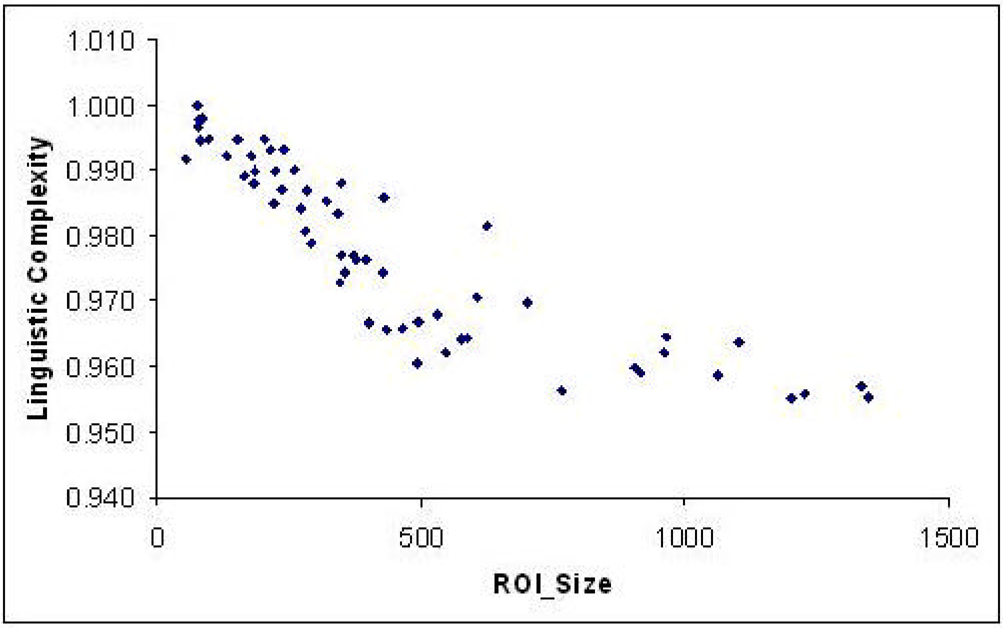

Figure 2: Linguistic complexity as a function of ROI size (in pixels). The two parameters are linearly correlated down to a certain ROI size (ca 100 pixels). Below this ROI size, the combination of the chosen word size (2x2) and the number of letters (12 shades) become too large relative to such a small ROI size, resulting in saturation of the complexity value.

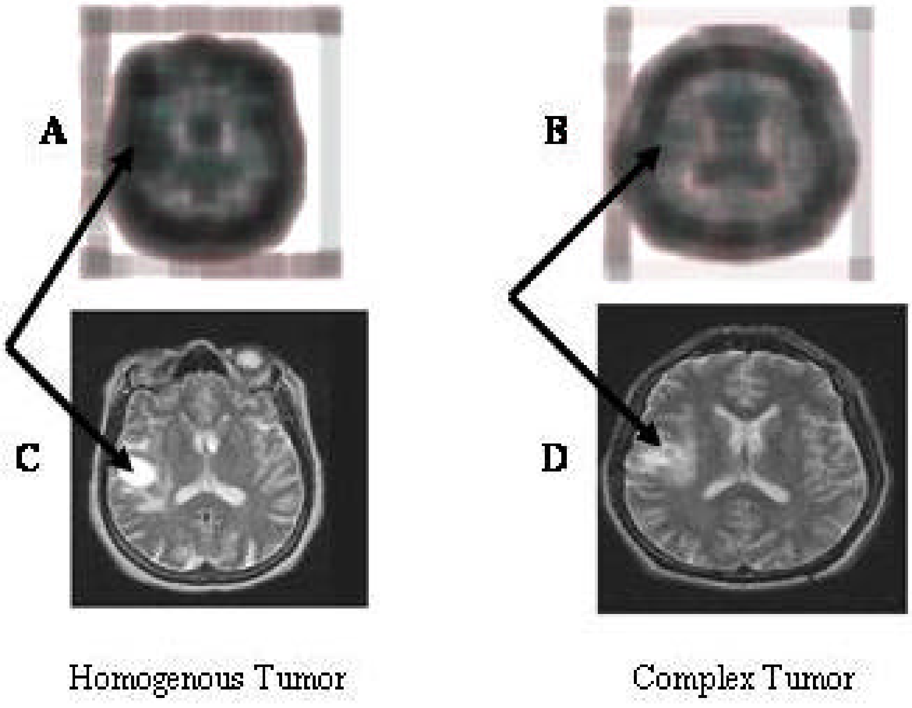

Figure 3. Examples of Complexity maps calculated from T2-weighted MRI. (**A**) and (**B**) are the linguistic complexity maps of (**C**) and (**D**), respectively. Note that the homogenous tumor (**C**) has low complexity, appearing dark in (**A**). In contrast, the complex tumor (**D**), appears brighter in (**B**).

B. Correlation between complexity parameters and later tumor response

The tumors included in the study covered a wide range in tumor response (post-treatment/pre-treatment volumes: 0.11-1.60). The pre-treatment values of the homogeneity index, Hi, as well as the changes in tumor volumes 50 days on average after initiation of treatment, are listed in **Table 1** for all 23 tumors.

The feasibility of using pre-treatment complexity parameters for predicting tumor response to therapy was studied by correlating the tumor heterogeneity index, Hi, measured prior to initiation of treatment, with the change in tumor volume, measured on average 50 days after initiation of treatment.

The positive correlation between pre-treatment values of Hi and later tumor response was found to be significant ($p<0.004$, $r=0.57$, Pearson correlation), as presented in **Figure 4**.

A comparison between the homogeneity index values of responding and stable/non-responding tumors using a one-tail unpaired t-test resulted in $p<0.026$ for Hi, considered significant.

IV. Discussion

The radiological parameters of brain tumors vary significantly within any group of brain tumors, including well defined cancer phenotypes. Moreover, the radiological parameters of a single brain tumor may change dramatically in a short time scale. It has been suggested (Esserman et al, 2001; Shukla-Dave et al, 2002; Mardor et al, 2004; Roth et al, 2004) that the response pattern of brain tumors depend significantly on specific radiological parameters at a given time and not necessarily on their disease group.

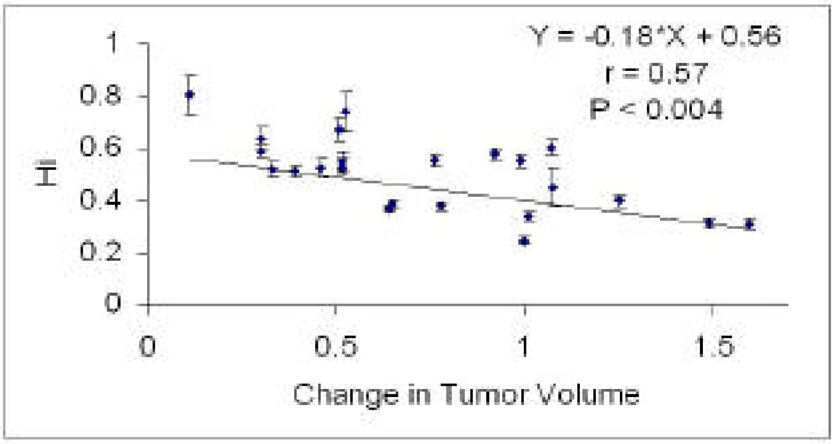

Figure 4. The correlation between the pre-treatment values of the homogeneity index, Hi, as calculated from T2-weighted MR images, and later tumor response for the 23 lesions included in the study.

Table 1. Pre-treatment homogeneity and later tumor response for the 23 lesions included in the study.

	Change in Tumor Volume*	Homogeneity Index (Hi)	Error	ROI Size(pixels#)
1	0.33	0.52	0.03	344
2	0.52	0.74	0.08	357
3	0.11	0.81	0.08	412
4	1.07	0.60	0.03	429
5	0.30	0.64	0.05	340
6	1.01	0.34	0.02	1133
7	1.08	0.45	0.07	392
8	0.52	0.55	0.03	180
9	0.52	0.53	0.03	100
10	0.51	0.67	0.04	163
11	0.99	0.55	0.03	675
12	1.00	0.25	0.02	2108
13	0.76	0.56	0.02	492
14	0.39	0.52	0.02	285
15	0.65	0.39	0.02	260
16	0.30	0.59	0.02	133
17	0.46	0.53	0.03	843
18	1.25	0.40	0.03	220
19	1.60	0.31	0.02	196
20	1.49	0.32	0.02	214
21	0.92	0.58	0.02	506
22	0.78	0.38	0.02	284
23	0.64	0.37	0.02	1144

*changes in tumor volumes 50 days on average after initiation of treatment

Therefore, in order to demonstrate the ability of the complexity methodology to predict response, it is necessary to study a radiologically heterogeneous group of tumors. The tumors included in this study covered a wide range in tissue heterogeneity and in tumor response enabling us to study the correlation between pre-treatment values of the homogeneity index and treatment outcome over a wide range of tumors.

On the other hand it is our experience (Roth et al, accepted for publication, 2004) that the radiological prediction pattern does depend on the treatment type. The data sample presented in this study includes tumors treated by radiation therapy or radiosurgery. It is not large enough to study each treatment type separately. This study is ongoing, and once the data base will be large enough, the tumors will be divided to subgroups according to the treatment type.

A. Complexity parameters

The choice of the color scale can strongly affect the sensitivity to tissue characterization within the tumor. On one hand, too large a color scale will be too sensitive to noise and will not represent the true complexity of the tumor itself. On the other hand, a small color scale will include too little information about the tumor and will produce a misleading complexity index. The choice of a 12-color alphabet was found to be optimal for these types of images. For higher resolution images and a better filtering technology (i.e. reduced noise in the images) a different color scale may be more adequate.

The ROI size may also affect the results. Too small ROIs have too little information in them to correctly categorize them according to their complexity. According to Figure 2, the minimal ROI size was determined to be 100 pixels.

Using higher magnetic field MR systems will enable the acquisition of high resolution (more pixels) images without compromising the signal to noise ratio. As a result the number of pixels in the chosen ROIs will be larger, enabling both higher sensitivity of the complexity calculation to fine tissue inhomogeneities as well as inclusion of smaller tumors in the study.

B. MR acquisition sequence

In the presented study we demonstrate the application of complexity analysis to T2-weighted MR images. Applying this methodology to other types of sequences may be beneficial as well. We preferred not to perform this study on contrast-enhanced images, since absolute intensities of contrast-enhancement in T1-weighted images are not reliably reproducible. They vary with time post injection and may depend on other variables as well. Non-contrast-enhanced T1-weighted images do not confer significant tissue contrast. T2-weighted MR images, on the other hand, convey significant tissue contrast as well as good signal to noise ratio and were therefore our first choice for complexity analysis. We hope that in the future higher field MR systems, will enable sufficient signal to noise ratio for other tissue sensitive sequences as well, such as T2 FLAIR and diffusion-weighted MRI. Applying the complexity analysis to these types of images may add prediction power to the methodology demonstrated in this study.

C. Biological model

The biological explanation for the correlation between the pre-treatment homogeneity index and treatment outcome has not yet been determined. It may be related to the fact that cancer cells near necrotic regions may experience hypoxic conditions and therefore are less sensitive to treatment. Necrosis spread over several regions in the tumor increases its heterogeneity and will have a larger surface area than a single necrotic core. The larger surface area will consist of a larger number of slow metabolizing cells. Therefore complex tumors might be less sensitive to treatment. Another explanation might be due to the fact that the outcome of anti-cancer therapies such as radiation is determined by the most resistant clones which survive and repopulate if they are not destroyed. The heterogeneity observed in the T2-weighted images may reflect diversity of clones which may be correlated with higher probability for the existence of clones resistant to treatment (Suit et al, 1992; Brown, 2002; Knisely and Rockwell, 2002).

The correlation between the pre-treatment homogeneity index and later tumor response to therapy indicates that the complexity information may be used prior to initiation of treatment, to non-invasively predict the outcome of certain anti-tumor therapies, thus enabling optimization of the treatment plan.

In summary, this study presents for the first time the possibility of applying two-dimensional linguistic complexity calculations for medical use. This preliminary study demonstrates the feasibility of applying the complexity calculation for pre-treatment prediction of response to radiation therapy and radiosurgery in brain tumor patients. We are currently extending this study to a larger group of patients and to images acquired with higher magnetic field MR systems in order to asses the application of this method for clinical use.

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Appendix

Tissue complexity analysis method

Complexity is a multifaceted concept implemented in many disciplines. Linguistic complexity was first defined in a textual connotation and is based on the idea that the larger the vocabulary used in a text, the greater its complexity. The data set is composed of letters (e.g. Latin letters in text). Any combination of a specific number of letters is defined as a word (e.g. AB is a two-letter word). The complexity is measured by counting the number of different occurring words (of a given size), divided by the maximal possible different words (of the same size) within a data set. Thus the linguistic complexity numerical result is between 0.0 for the simplest data set and 1.0 for the most complex data set:

$$\textit{Linguistic Complexity} = \frac{\textit{(\# of occurring words)}}{\textit{(maximum \# of possible words)}}$$

For example, the string ABABA in Latin alphabet has a vocabulary of two different two-letter words (AB and BA) while the maximal possible vocabulary for the string of that size would be four words (AB, BA, AA and BB), resulting in a linguistic complexity of 2/4=0.5. For the string AAAAAA, there is only one two-letter word (AA), thus the complexity is 1/5=0.2. Theoretically, for an infinite string of a repeating word, the complexity will approach 0.

Such calculations were successfully performed on DNA sequences and human language texts. The extension of the linguistic complexity calculation to a two-dimensional data set, such as a MR image, is carried out in the following way: A letter in an image is the color scale (e.g. 256 letters for gray scale) and a word is any specific combination of pixels intensities. For example a four pixel word is defined as a 2x2 array of pixels. To calculate the two-dimensional linguistic complexity of an image, one has to count the number of different 2x2 pixel intensity combinations and divide it by the maximal number of different 2x2 pixel intensity combinations possible in the given image. **Figure 1** shows an example of a binary image linguistic complexity calculation.

In order to calculate the complexity of any given data set, one has to determine two parameters: the word size (i.e. number of letters within the word) and the number of letters. In the case of two dimensional images, the letters are the color shades (256 letters in the gray scale images) and the words are combinations of pixels, such as the 2x2 words in **Figure 1**. The goals are to maximize the sensitivity of the complexity calculation and lower the required calculation power. This can be obtained by optimizing the limiting factors of the maximal possible words. Thus we will gain the maximal variance of words possible within the given data size.

The considerations for choosing the optimal word size are the following: Assume a given data set with a fixed (alphabet) number of letters. If the chosen word size is too small, only a few letters, there will only be few possible words and the probability that all of them will appear within the data set will be high, resulting in complexity 1.0.

Similar considerations should apply for choosing the optimal number of letters: If the number of letters used is too large, the number of different occurring words consisting of these letters will be large, as well as the number of possible such words, resulting in complexity 1.0

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