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Structural simplexity of the brain

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ABSTRACT

Simplexity is an emerging concept that expresses a possible complementary relationship between complexity and simplicity. The brain has been known as the most complex structure, and tremendous effort has been spent to study how it works. By understanding complex function of the brain, one can hope to unravel the mystery of its diseases and its biological systems. We propose herein an entropy-based framework for analysis of complexity with a particular application to the study of white matter changes of the human brain. In this analysis, the proposed approach takes into account both morphological structure and image intensity values of MRI scans to construct the complexity profiles of the brain. It has been realized that the quantity and spatial distribution of white matter changes play an important role in cognitive decline (i.e. dementia) and other neuropsychiatric disorders (i.e. multiple sclerosis, depression) as well as in other dementia disorders such as Alzheimers disease. Thus, the results can be utilized as a tool for automated quantification and comparison of various spatial distributions and orientations of age-related white matter changes where manual analysis is difficult and leads to different sensitivities for the respective MRI-based information of the brain.

1. Introduction

It has long been realized that the understanding how the brain works and its complex networks is a tremendous challenge in neuroscience (Bullmore et al., 2009). In fact, the brain has been thought to be the most complex piece of matter in the universe. To reduce the complexity of the brain problem, neuroscience is decomposed into smaller domains for systematic analysis. The levels of analysis in ascending order of brain complexity are known as molecular, cellular, systems, behavioral, and cognitive (Bear et al., 2001). At the molecular level of neuroscience, various molecules play various roles for the brain function including messengers for neuron communication, sentries for controling materials that enter or leave neurons, conductors for neuron growth, and archivists of past experiences. Cellular neuroscience is the study of molecules that work and interact with one another to provide the neuron its special properties. Systems level of neuroscience studies how different neural circuits analyze sensory information, perceive the external world, make decisions, and perform movements. Behavioral neuroscience studies neural systems working together to produce integrated behaviors to answer typical questions such as if different forms of memory accounted for by different systems, where in the brain dreams come from, and what is the normal contribution of neural systems to the regulation of mood and behavior. Cognitive neuroscience is considered to be the most daunting task of neuroscience as it aims to understand how the activity of the brain creates the mind by probing the neural mechanisms that are responsible for higher levels of mental activity such as self-awareness, mental imagery, and language.

We are particularly interested in the study of complexity applied to brain imaging which plays an essential role in neuroscience. The concept of complexity has various definitions. A popular mathematical approach for analysis of complexity is known as entropy. Since the introduction of the notion of entropy as an expression of information uncertainty by Shannon (Shannon, 1948; Shannon and Weaver, 1949); the term "entropy" has been used to refer to many different meanings depending the applications. Some common interpretations of the states of entropy are given in Table 1.

In medicine and biology, scientists have utilized the concepts of entropy, fractals and chaos to study shapes and functions of cells, eyes, the brain, the lung, the heart, and aging (Liebovitch, 1998; Goldberger et al., 2002). Although these methods can be helpful in the analysis of the data and the interpretation of the results, the models suffer from several simplified assumptions and restric-

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Table 1
States of entropy and typical interpretations (modified from Williams, 1997).

Low entropy	High entropy
Order	Disorder
Uneven distribution	Uniform distribution
Highly certain	Highly uncertain
Non-random	Random
Predictable	Unpredictable
Small diversity	Large diversity
Little or no surprise/information	Great surprise/information

tions, which make them far from distinguishing different complex patterns. For examples, straight-forward use of fractal dimensions in images or imprecise data may not give a clear interpretation of closely related entities because the computation assumes that image models are noise-free or objects of interest are manually extracted. These requirements hinder automated processes desired for the analysis of high-content data. An entropy-based measure of systems complexity known as approximate entropy (ApEn) (Pincus, 1991; Pincus and Goldberger, 1994; Pincus, 1995) and its extended family: sample entropy (SampEn) (Richman and Moorman, 2000) and multiscale entropy (MSE) (Costa et al., 2002, 2005) have been proposed to quantify the complexity of physiological and biological data. Effective applications of these methods are, however, subject to the good estimates of their control parameters, which are not always easy to determine, and also limit themselves to time-series data. Up to date, there have been rarely approaches which address the complexity in image data by taking into account both the geometry and pixel intensity. The quantification of the complexity of image patterns is helpful because it provides us an insight into the mechanism and characteristics of a particular complex system in order to advance our understanding or confirm our hypothesis of the problem under study. The ability to accurately distinguish or classify closely related objects is even more useful for practical purposes.

In neuroscience, advanced brain imaging allows medical researchers to observe details and to match morphological changes in the physical structure of the brain to changes in cognitive performance over time. For example, it has been known that the deterioration as well as the activity of various brain regions can be detected using magnetic resonance imaging (MRI) or positron emission tomography (PET) scans of the brain. These scans can reveal particular areas of the brain that are believed to play a key role in cognitive decline with age (Glei et al., 2005; Carstensen, 2007). As another example, it has been reported that structural brain abnormalities and neuropsychological impairments is well established in schizophrenia (Davidson and Heinrichs, 2003), and there is interest in answering the question if the pattern of correlations between brain structure and function in patients also deviates from normal (Toulopoulou et al., 2004).

Other studies reported changes in the brain such as subcortical lesions of the white matter that can be observed on the MRI of the brain of healthy older individuals and in patients with neurodegenerative diseases (Scheltens et al., 1992; de Leeuw et al., 2001). An investigation on the relationship of cognitive functions and white matter lesions (WMLs) reported that WMLs are often related to other morphological changes detectable by brain imaging such as lacunar infarctions (van Swieten et al., 1996). The combined appearance of WMLs and lacunar infarctions is conceptualized as cerebral small-vessel disease (Erkinjuntti, 2002). Recent clinical studies in hospitalized patients with acute stroke due to lacunar infarctions found that the WMLs appear to be mostly associated with executive dysfunction (Jokinen et al., 2006). Although consequences of WMLs and lacunar infarctions have been examined in several studies, it is still unclear if their impact on cognitive performance differs between their single and combined occurrence in an elderly individual (Baune et al., 2009).

Furthermore, clinical significance of WML is not fully understood and still to be investigated to validate associations between WML and other factors such as cerebro-vascular risk, age, and cognitive impairment factors. Understanding complex patterns of white matter changes may contribute to answering the questions if it is possible to affect the evolution of white matter changes with pharmacological treatment, and if the rate of change would have any impact on cognitive performance or other tasks that require more complex cerebral processing, such as coordinated movement (Wahlund et al., 2001). However, rating of white matter lesions, which are defined as areas with high signal intensities on MRI, requires skill and knowledge of experts who read the MRI scans independently, discuss any differences and agree a final standard rating for each case (Fazekas et al., 1993; Wahlund et al., 2001).

In this paper we adopt the framework of GeoEntropy (Pham, 2010) for studying the complexity of MRI scans showing age-related white matter changes. The interpretation of GeoEntropy is analogous to that of approximate entropy and sample entropy as GeoEntropy is built on the mathematical principle of this entropy family. In light of this analysis, we will then be able to establish simple decision rules for automated classification or rating of white matter lesions in an accurate and detailed way, where current methods are subject to manual and different sensitivities (Wahlund et al., 2001). The rest of this paper is organized as follows. Section 2 describes approximate entropy, sample entropy, and multiscale entropy methods, which lead to the development of GeoEntropy, and also presents a mathematical formulation of differential redundancy based on GeoEntropy. Analysis of brain imaging subject to white matter changes is presented in Section 3. Section 4 concludes the finding of this study.

2. Methods

Given a finite sequence $X_N = [x_1, x_2, \ldots, x_N]$, m and r; the quantification of time-series signal complexity using approximate entropy (ApEn) is determined as follows:

1. Construct vectors of length m, X_1 to X_{N-m+1}, defined as

$$X_i = (x_i, x_{i+1}, \ldots, x_{i+m-1}), \quad 1 \le i \le N - m + 1$$

2. Compute distance between X_i and X_j, denoted by $d(X_i, X_j)$, as

$$d(X_i, X_j) = \max_{0 \le k \le m-1}(|x_{i+k} - x_{j+k}|)$$

3. For $i = 1, N - m + 1$, calculate the probability that any vector X_j which are similar to X_i within r as

$$C_i(m, r) = \frac{n_i(m, r)}{N - m + 1}$$

where $n_i(m, r)$ is the number of vectors X_j that are similar to X_i subject to the criterion of similarity $d(X_i, X_j) \le r$.

4. Calculate

$$\phi(m, r) = \frac{1}{N - m + 1} \sum_{i=1}^{N-m+1} \ln[C_i(m, r)]$$

5. Set $m = m + 1$ and repeat steps 1–4.
6. Calculate the approximate entropy of X_N as

$$ApEn(X_N, m, r) = \phi(m, r) - \phi(m + 1, r)$$