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Characterising brain network topologies: A dynamic analysis approach using heat kernels

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ABSTRACT

Network theory provides a principled abstraction of the human brain: reducing a complex system into a simpler representation from which to investigate brain organisation. Recent advancement in the neuroimaging field is towards representing brain connectivity as a dynamic process in order to gain a deeper understanding of how the brain is organised for information transport. In this paper we propose a network modelling approach based on the heat kernel to capture the process of heat diffusion in complex networks. By applying the heat kernel to structural brain networks, we define new features which quantify change in heat propagation. Identifying suitable features which can classify networks between cohorts is useful towards understanding the effect of disease on brain architecture. We demonstrate the discriminative power of heat kernel features in both synthetic and clinical preterm data. By generating an extensive range of synthetic networks with varying density and randomisation, we investigate heat diffusion in relation to changes in network topology. We demonstrate that our proposed features provide a metric of network efficiency and may be indicative of organisational principles commonly associated with, for example, small-world architecture. In addition, we show the potential of these features to characterise and classify between network topologies. We further demonstrate our methodology in a clinical setting by applying it to a large cohort of preterm babies scanned at term equivalent age from which diffusion networks were computed. We show that our heat kernel features are able to successfully predict motor function measured at two years of age (sensitivity, specificity, F-score, accuracy = 75.0, 82.5, 78.6, and 82.3%, respectively).

Introduction

The human brain is a complex system of units (neurons) which interact with one another to process internal and external stimuli. In such complex systems, many features emerge due to their interaction and their global connections which can be analysed using graph theory. The application of graph theory for investigating brain function and connectivity has been readily adopted by the neuroimaging community (Bullmore and Sporns, 2009; Fornito et al., 2015). As a mathematical model capturing relationships between interacting objects, a graph (or network) provides a simple abstraction of neural connectivity; reducing a complex system into a collection of *nodes* (representing brain regions) which are connected by *edges* representative of their relation. In diffusion magnetic resonance imaging (MRI) based structural networks, edges between brain regions signify their connection via an anatomical pathway from white matter tracts inferred using tractography. Edges may be assigned a *weight* indicating the strength of the connection, such as the use of *fractional anisotropy* as a measure of the pathway's structural integrity (Fornito et al., 2013; Jones et al., 2013). In functional MRI based networks, edges represent a measure of association in blood-oxygen-level-dependent signals across time, which reflect neuronal activity. The strength of this association may be indicative of how functionally related two regions are and is thus assigned as an edge weight (Fornito et al., 2013). As a branch of mathematics, graph theory offers a wealth of tools to describe networks in a rich form, making it an attractive framework for investigating brain organisation. For example, topological principles such as *small-world* and *rich-club* organisation have been found in many natural complex systems, including the brain (Ball et al., 2014; Towlson et al., 2013; van den Heuvel et al., 2008). Networks with small-world architecture which may be characterised by both large clustering and short path lengths have been associated with efficient information transport (Watts and Strogatz, 1998). The rich-club can be seen as a highly inter-connected

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set of nodes which form a backbone of the network structure (van den Heuvel et al., 2012) and its network-theoretical importance has been shown with respect to nodal specialisation, functional integration and resilience to "attacks" (Colizza et al., 2006; Collin et al., 2014; McAuley et al., 2007). Several other graph-theoretical measures have been investigated to describe these topological properties of the underlying brain connectivity, however, there is no consensus on which set of measures can be used to completely characterise the brain (for a review of commonly used measures see Rubinov and Sporns (2010)).

The strength of a graph representation for brain characterisation lies in its simplicity. Graph topologies can be used to describe a number of *neural mechanisms* which shape neural responses to a disease and its propagation through brain architecture (Fornito et al., 2015). The highly interconnected brain enables disease propagation across the organ via its axonal pathways (Hirokawa et al., 2010; Perlson et al., 2010; Saxena and Caroni, 2011). Thus disorders can have a pervasive effect on function and structure that is not necessarily localised to the region of insult or pathological onset. For example, stroke patients exhibit functional over-activation across brain regions that are remote from the vicinity of the lesion (Rehme and Grefkes, 2013). Another example is widespread neurodegeneration alongside disease progression in degenerative disorders such as Huntington's and Parkinson's diseases which are believed to have focal onset (Goedert et al., 2013; Tabrizi et al., 2009). An example neural response is *dedifferentiation*, the recruitment of diffused, non-specific brain regions for task performance that is often observed in the ageing population (Sleimen-Malkoun et al., 2014) and schizophrenia (Honey et al., 2005). Another neural mechanism is *compensation*, where functional activity is increased following an insult or in the early stages of a neurodegenerative disease and is frequently reported in multiple sclerosis (Chiaravalloti et al., 2015) and Alzheimer's disease (Elman et al., 2014). As the spread and impact of these neural responses can be shaped by the underlying brain connectivity, network theory may provide quantitative descriptors of these mechanisms (Fornito et al., 2015; Schoonheim et al., 2015). Graph measures or features have thus been found to be associated with a number of neuropathologies (Lo et al., 2010; Odish et al., 2015; Pandit et al., 2014; Wang et al., 2009).

A main objective in neuroimaging studies is to elucidate how a specific disease affects the underlying network topology; gaining such an understanding then allows discrimination between patients and healthy controls. Identifying biomarkers of a disease would thus be useful for advanced diagnostic or predictive applications. The power of network-derived features for describing the human brain is evident by their increasing use in classification of neuroimaging data. Network classification involves categorising a network as belonging to a control or a disease population, or even to a subcategory in the case of spectrum disorders. Network classification requires the extraction of graph-based *features* which are typically used as predictors in statistical classifiers. Studies have explored the discriminative power of network edges, revealing their promise in classifying a range of pathologies (Arbabshirani et al., 2013; Prasad et al., 2015; Richiardi et al., 2012; Rosa et al., 2015; Shen et al., 2010; Zalesky et al., 2010). Comparisons of graph metrics which characterise local and global topology as well as network principles have also been employed for classification purposes in major depressive disorder (Sacchet et al., 2015), Alzheimer's disease (Prasad et al., 2015) and pre-school versus adolescent children (Meskaldji et al., 2015).

The mechanisms by which neural impulses, or *information*, propagate through the human brain network are limited by the finite propagation speed of the electro-chemical signals. Some network measures, such as shortest characteristic path length, do not incorporate the idea of information transport directly, but describe the structural (and static) connectivity profile while using shortest path lengths. However, given the propagative neural mechanisms discussed earlier, we hypothesise that capturing *energy transfer* through a network over 'time' could provide useful features for classification purposes. In this work, we propose the *heat kernel* for capturing energy transfer in a network. A heat kernel summarises the effect of applying a source of heat to a network and observing its diffusion process over 'time'. It encodes the distribution of heat over a network and characterises the underlying topological structure of the graph. This diffusion process, from which the heat kernel is the fundamental solution to, was widely used in image analysis for smoothing purposes (Babaud et al., 1986; Perona and Malik, 1990). This idea was later extended by applying the heat kernel on a graph representation of the image (Zhang and Hancock, 2008). In the context of brain network analysis, a few studies using heat kernels have been reported. They include an application on structural networks to investigate disease progression in Alzheimer's in which the eigenmodes of the heat kernel showed spatial similarity to the measured atrophy patterns from the grey matter volume (Raj et al., 2012). Heat kernels have also been utilised to investigate the relationship between structural and functional networks (Abdelnour et al., 2014). In these cases, analyses are performed with respect to a single heat kernel calculated with its time parameter fixed to a single value. In contrast, we propose an alternative approach where we make use of a time-series of heat kernels computed over a range of the time parameter. From this time-series, we derive features representative of energy transport which appear to capture salient network properties that can be used to discriminate between different network topologies. It should be noted that there are similar works which capture information propagation through a brain network such as the modelling of spreading patterns to characterise global interactions between regions (Mišić et al., 2015), or random walkers for community detection (Betzel et al., 2013).

Furthermore to our proposed heat kernel features, we present a framework for generating a baseline of synthetic networks to simulate brain networks of varying network densities and randomisation levels. With these synthetic networks, we investigate the changes in our heat kernel features with graph topology and demonstrate an association with small-world architecture. Subsequently, using linear discriminant analysis we show the ability of our heat kernel measures to classify between specific topologies. In addition, we apply our methodology to the problem of early detection of adverse neurological outcome that is common in children born very preterm (born at 32 weeks gestation or younger) (Delobel-Ayoub et al., 2009; Edwards et al., 2011). Surviving preterm infants are susceptible to significant deficits in cognitive, behavioural and sensory development as well as long-term motor dysfunction with a high risk of cerebral palsy (Back and Miller, 2014; Marlow et al., 2007). Associations between cognitive outcome and diffusion tractography features computed at term from premature neonates have been reported (Ball et al., 2015; Duerden et al., 2015; van Kooij et al., 2012), demonstrating the advantage of imaging predictors for early diagnosis. The development of brain architectural features such as those proposed in our work may contribute towards understanding the neural mechanisms characteristic of functional deficits linked with prematurity. Obtaining predictors which are sensitive to neurodevelopmental outcome is also invaluable for early intervention and treatment planning to mitigate the impact of preterm birth. Thus we test the efficacy of heat kernel features computed from structural networks to be predictors of motor dysfunction in a cohort of preterms. By dividing the cohort into two groups depending on their mobility score, we demonstrate that our heat kernel features can predict the motor outcome of preterm babies scanned at term.

The rest of the paper takes the following format: in the Material and methods section, we first detail our heat kernel methodology and synthetic network framework. This is followed by experimental settings for the synthetic networks and the clinical application on a premature cohort. Results of the experiments are next presented and lastly the paper closes with the Discussion section.