

Evaluation Report by Gary Zhang

Thesis Title: Computational models of brain tumours using network science and connectomics

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Overview

This thesis addresses an exciting, highly current and impactful topic of the modelling brain tumours and their surroundings computationally as a complex network, leveraging network science and imaging-derived connectomics. It is also a very strong thesis that consists of three original and distinctive contributions that form a coherent whole. These three original contributions are reported in Chapters 1, 2, and 3 of the thesis, covering respectively, the exploitation of quantum computing for identifying the existence of community structure within brain networks, the assessment of functional and structural reorganisation of brain tumours and their surroundings, and the application of brain tumour connectomics for the survival modelling of the most aggressive brain tumour (glioblastoma).

The originality, rigour and significance of these contributions have been eminently demonstrated by their publications in leading international journals. Chapter 2 was the first contribution to be published, in 2024 in *Communication Biology*, a highly respected journal within the Nature Portfolio, and has already accumulated 28 citations, demonstrating its significant impact on the community. Chapter 3 was the second contribution to be published, in 2026 in *Neuro-oncology*, one of the best journals in clinical neurology, with an impact factor > 10 . Chapter 1 was under review at the time of the writing of the thesis but has now also been published in *IEEE Transactions on Network Science and Engineering*, a highly respected technical journal in this field.

On this assessment, I want to congratulate the candidate for this outstanding thesis and declare that, in my opinion, *the doctoral dissertation meets the conditions set out in Art. 187 of the Act of July 20, 2018 Law on Higher Education and Science (Journal of Laws of 2021, items 478, 619, 1630)*. Below, I will provide the specific comments that I have for each chapter of the thesis.

Introduction

This chapter sets out the overall context and motivation for the thesis as a whole, presents the research questions, and summarises the key contributions. A particular strength of this chapter is its presentation style, specifically with the use of questions to engage its audience, which has certainly

succeeded in piquing my interest. With that said, I do feel that the choice and the sequencing of the questions can be improved. The first question posed was “Why is the brain a network?”. It is a very worthy question to ask but it requires the premise that the brain is in fact a network, which at this stage of the narrative has not yet established. In fact, the next question posed, logically, should arguably come first, namely “If the brain is a network, what exactly is this network?”.

This second question, additionally, has its own logical challenges. On one hand, as explained above, it has not yet been established that the brain is a network. On the other hand, depending on the definition of what constitutes a network, the question may not make any logical sense. If the definition of a network requires one to identify the network of the brain in the first place, knowing exactly what network is the brain is exactly equivalent to answer the question if the brain is a network in the first place.

This leads to my final critique regarding this, namely at this stage, no definition of a network has been given. Given the nature of discourse the candidate is pursuing, it is, in my view, important to provide an operational definition by which a network is defined. In the first paragraph of this chapter, the interaction between the earth and the sun was mentioned as an example of interactions. Possessing interactions between the elements of a system alone is not enough to define a system as a network; one would hardly find any scientific publications that refer to the system of the earth and the sun as a network. The presence of interactions between the elements of a system is the necessary condition for treating them as a system that is interesting to be studied together but this does not make such a system a network.

Specific points:

Pg 2 “*One of the research fields where network science and connectomics might play a fundamental role is, surprisingly enough, neuro-oncology.*”: what makes this surprising?

Pg 3 “*From these insights, three central research questions emerge:*”: It is not very clear what you are referring to by “these insights”.

Pg 3 “*..., what is the contribution of MRI-derived signals originating from intramural and peritumoral areas?*”: It is not very clear the said contribution is to what.

Chapter 1

This chapter presents the first original contribution of the thesis on the use of quantum computing for identifying the existence of community structure within brain networks. The task has been formulated

as an optimisation problem known to be NP-hard, which makes it a target application that may benefit from quantum computing, in particular quantum annealing. However, the mapping of this task onto a formulation amenable to quantum computing turns out to be non-trivial. Existing approaches had to resort to hybrid quantum-classical implementation which severely limits the algorithmic transparency. The key contribution of this chapter is the reformulation of the task as a recursive and hierarchical clustering problem, a formulation that is amenable to a pure quantum implementation. Experimental evaluation against both pure classical and hybrid solvers shows that the proposed approach performs on par with the alternatives.

This chapter can benefit from a dedicated section describing the hardware and software used for hybrid and pure quantum computing. For example, Figure 1.1 (b) does not appear to have been referred to anywhere in the text. An overview on the D-Wave platform, its Chimera Graph and Chimera embedding would be very beneficial in deed.

Specific points:

Pg 7. “ d_c is the sum of the degrees of those nodes”: degree is not defined.

Pg 13. Eqn (1.12) shows that k indexing from 1 but the line above having k starting from 0. Is this disparity intended?

Pg 15. §1.2.5 “... *in practice, reaching maxQ once is enough*”: but in practice, one does not know if maxQ is ever reached.

Pg 21. §1.3.1 The use of Zachary karate club network is not motivated in the methods section.

Chapter 2

This chapter presents three novel approaches to the assessment of functional and structural brain reorganisation in the presence of brain tumours. First, a method for assessing functional brain reorganisation is described. This involves the use of resting-state fMRI. A key novelty is the analysis of the fMRI signals within brain tumours. A new metric, Dynamic Alteration Score (DAS), is proposed to provide a single scalar summary measure to reveal the difference between fMRI signals, which are time series. One key idea here is that the comparison is not made directly on the time series but on their power spectra. It is shown that the proposed metric can reveal differences that is invisible to the direct comparison between time series.

Second, a method for assessing structural brain reorganisation is described. This involves the use of diffusion MRI. A key novelty is adopting two different strategies of deriving structural connections for healthy tissue and brain tumour tissue. This is motivated by the observation of overdamped diffusion MRI within brain tumour. While there is no ground truth, visual inspection seems to suggest improvement.

Third, a method for predicting post-surgical structural brain networks from pre-surgical structural brain networks is described. This builds on the second method and leverages machine learning to make the prediction. A key novelty is the of anatomical priors built from healthy subjects in a Bayesian framework. The evaluation of the proposed method is done against a null model and a basic outlier-robust regression model. It would benefit from the inclusion of an ablation analysis, namely as model otherwise identical to the proposed one but without the inclusion of the anatomical priors. This would help shed light on the specific role of these priors. Another weakness is that it is in the description of the problem. It would benefit from a clear statement of the problem that specifies precisely what information is the input. In fact, I note that the published journal paper has a very misleading title, in particular the bit that reads “*a machine learning approach using desynchronized functional oscillations*”. But unless I have misunderstood it, the machine learning is only used in the context described in this paragraph, involving pre-operative structural brain networks which are derived from diffusion MRI data, not from fMRI signals.

Specific points:

Pg 50. “*We simplify the notation and refer to pre-surgery connectomes as ...*”: this is an example of unclear definition of input/output of the problem. The choice of notation, in particular, for healthy connectomes, itself is insufficient to inform a reader if it is an input or an output.

Pg 51. Eqn (2.10): the r.h.s. does not directly follow the Bayes theorem and requires additional derivations. In fact, the sentence that follows this reads “For Eq 2.10 to hold, ...” directly supports this argument, as if that equation follows immediately from the Bayes theorem, there would be no need to specify any additional condition.

Pg 58. “*However, validation of any fiber tracking pipeline is difficult due to the lack of a unique ground truth.*”: Incorrect phrasing. There exists a unique ground truth but one we do not know *a priori* in practice.

Chapter 3

This chapter presents a novel approach to predict survival rates in patients with glioblastoma from diffusion MRI. The key novelty is the proposal of a new non-local metric called lesion tract density index (L-TDI), a metric inspired by the well-known tract density index (TDI) but formulated to allow the modelling of the interactions between brain tumours and their surroundings. This is computed by using a normative structural tractogram constructed from a large cohort of healthy subjects and patient-specific connections extracted by selecting only the connections that intersect with the tumour mask of each patient. This is compared against computing TDI within the brain tumours. Therefore, L-TDI emphasises how the brain tumours connect with its surroundings, which can be reasonably approximated by structural tractogram derived from healthy individuals. In contrast TDI emphasises the connection properties within a tumour, which can not be realistically approximated by healthy structural tractogram. Evaluation with data acquired from two large cohorts of glioblastoma patients show that lower L-TDI is consistently associated with better survival. In contrast TDI does not show a consistent association with survival. Additional analysis reveals the underlying mechanism behind the advantage of L-TDI and supports the need to understand a glioblastoma from its interactions with its surrounding white matter connections. Finally, L-TDI is shown to improve the prediction of survival probability over TDI.

There is no doubt that this is a very strong and important contribution but it is a bit unfortunate that the novel method developed in Chapter 2 for producing a patient-specific tractogram was not exploited in this chapter. It would be nice to see the preliminary data from the UCSF cohort to be included.

Signed by:


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