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Review of the PhD dissertation 'Computational models of brain tumours using network science and connectomics' by Joan Falcó-Roget

This doctoral dissertation presents interdisciplinary research at the interface of network science, computer science and neuro-oncology. It addresses important scientific problems using modern computational techniques and methodologies. In my opinion, the dissertation fully meets the requirements for a doctoral dissertation.

I begin this review with a brief formal description of the dissertation.

The dissertation was written under the supervision of Prof. Alberto Cacciola and the co-supervision of Dr. Jan K. Argasiński.

The dissertation consists of 207 pages, including the front matter, the main text, references, and four appendices containing supplementary methodological details, additional results, tables, and figures. The main body of the dissertation extends from Chapter 'Introduction' through three research chapters to Chapter 'Conclusions', followed by a list of References (20 pages) and Appendices (80 pages).

The dissertation addresses three principal research questions:

- Can quantum computing be effectively applied to connectomics and network neuroscience?
- How do brain tumours alter structural and functional brain connectivity?
- How do connectomic representations of gliomas relate to clinical outcomes and patient prognosis?

which are extensively discussed in three research chapters:

Chapter 1 develops a framework for community detection in brain networks based on modularity maximization, QUBO formulations, and quantum annealing.

Chapter 2 investigates structural and functional brain networks in patients with meningioma and low-grade glioma using multimodal MRI, tractography, and machine-learning techniques.

Chapter 3 studies neuron-glioma interactions in glioblastoma and proposes connectomics-based biomarkers for prognosis and survival prediction using statistical and machine-learning models.

The dissertation is based in part on the Candidate's previously published research. According to Appendix A, it is primarily based on three peer-reviewed publications and is complemented by several conference contributions.

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The Candidate has an impressive scientific record, as illustrated by the extensive list of peer-reviewed publications, conference contributions, preprints, research grants, and reviewing activities presented in Appendix A.

The topic of the dissertation is very important and timely. It lies at the intersection of many rapidly developing fields in computer science, neuro-oncology, and diagnostics based on advanced physical and numerical methods, which increasingly utilize advanced computer tools, including machine learning and artificial intelligence, and potentially quantum computing as these technologies continue to mature.

The first chapter investigates the potential application of a quantum annealer for the problem of community detection, which, as discussed in the dissertation, has potential applications in brain science. This aspect is studied in Chapter 1, where the Candidate formulates the modularity maximization problem as a Quadratic Unconstrained Binary Optimization (QUBO) problem and demonstrates how hierarchical community detection can be implemented using quantum annealing techniques. This work represents an original application of emerging quantum-computing methodologies to connectomics.

Among other important scientific contributions of the dissertation, it is worth mentioning:

- Development of computational methods for analyzing structural and functional brain networks in patients with brain tumours.
- Introduction of a framework for reconstructing postoperative structural brain networks using artificial intelligence;
- Development of connectomics-inspired biomarkers for glioblastoma prognosis based on novel indices describing tumour–brain interactions;
- Integration of modern computational methodologies within a clinically relevant framework by combining methods from graph theory, connectomics, machine learning, survival analysis, and neuroimaging into a coherent framework that addresses clinically important questions in neuro-oncology.

In my opinion, the strongest point of the dissertation is the successful integration of advanced computational methods with clinically relevant neuro-imaging data into a coherent framework for studying brain tumours from a connectomics perspective. Overall, the work clearly demonstrates the Candidate's ability to conduct independent interdisciplinary research at a high scientific level.

The dissertation is very well written. The manuscript is well organized, the objectives are clearly stated, and the scientific narrative is easy to follow despite the interdisciplinary nature of the subject.

I found no major weaknesses in the dissertation. If I were to mention aspects that could be improved, they would mainly concern the presentation rather than the scientific content. In my opinion, some parts, particularly Appendix B, could have been presented more concisely without reducing the scientific value of the work. The text is clear and free of

editorial errors, with only a few typos: for example, on page 12, the assignment constraint is written as $\sum_{i,u} x_{iu} = 1$ rather than $\forall i \sum_u x_{iu} = 1$. The recurrence relations on page 130 appear to be inconsistent and could benefit from clarification. Of course, this in no way affects my high rating of the work.

The dissertation is ambitious, interdisciplinary, and addresses several important scientific questions. It naturally gives rise to further topics worthy of discussion. The following questions are, therefore, not intended as criticisms of the work but rather as an invitation for the Candidate to elaborate on several methodological choices, discuss possible alternative approaches, and share his broader perspective on the research presented in the dissertation.

- Since modularity constitutes the central objective function throughout the dissertation, it would be useful to hear the Candidate's broader perspective on its role in community detection. While modularity has become the standard approach in network science, does the Candidate consider it to be the most appropriate criterion for identifying community structure?
- The hierarchical optimization strategy is one of the central methodological ideas of the dissertation. It would be interesting if the Candidate could elaborate further on its theoretical motivation and discuss whether alternative formulations, such as direct multi-state optimization, were considered during the development of the method.
- Another aspect that may be interesting to discuss during the defense concerns the choice of the resolution parameter γ . Since different values of γ may reveal community structures at different scales, it would be interesting to hear the Candidate's perspective on possible strategies for selecting this parameter in practical applications. I would be particularly interested to hear whether the Candidate believes that there exists a general principle guiding the choice of the resolution parameter, or whether its selection remains largely application dependent.

Overall, my assessment of the dissertation is very positive. In my opinion, it fulfills the requirements of a doctoral dissertation and demonstrates the Candidate's ability to conduct independent scientific research. Therefore, I recommend that the dissertation be approved and that the Candidate be admitted to the public defense of the PhD degree.

Additionally, I recommend that the dissertation be awarded distinction, *summa cum laude*, in recognition of its ambitious and interdisciplinary research programme, which aims to integrate advanced computational, data-driven, and diagnostic techniques into a coherent framework supporting the diagnosis of brain tumours.



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