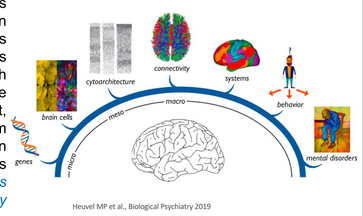
Automated Development of Novel Functional Interactomes Across Brain Scale

DALJIT TAKHER[1], Shreyank Kadadi[1], Artin Allahverdian[2], Sharmila Venugopal[3]

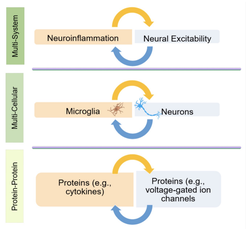
[1]Computational and Systems Biology Undergraduate Program, [2]Human Biology, Society & Genetics Program, Division of Life Sciences, [3]Dept. of Neurology, David Geffen School of Medicine, University of California Los Angeles, CA 90095

Introduction

In Systems and Computational Neuroscience, integration of knowledge across biological scales is an ongoing effort and has its own challenges. Additionally, dynamic diseases such as neurodegeneration which threaten the body's homeostatic machinery are intractable to tackle with traditional spatiotemporal modeling approaches. We need a novel quantitative perspective to this effort, and here we propose linking various nervous system functions through functional interactomes which can offer a scale free solution. For example, this approach will answer questions such as '*how does the neuroinflammatory subsystem functionally interact with neural excitability subsystem?*'

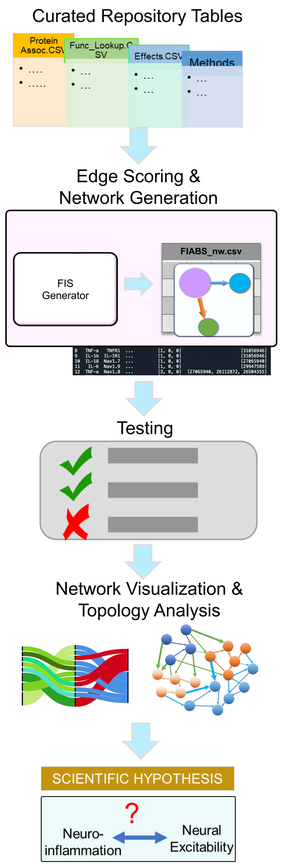


Heuvel MP et al., Biological Psychiatry 2019



As proof-of-concept, we compiled evidence-based functional associations between neuroinflammation and neural excitability at molecular and cellular scales. We defined a novel functional interaction score (FIS) to assign as edge weights between nodes (e.g., proteins) and developed molecular interaction networks called Functional Interactomes Across Brain Scales (FIABS). Here we present the automation of FIABS network generation and systematic testing to simulate creation of known types of biological motifs such as cascades, feed forward and feedback loops. Topology analysis of these networks should divulge causal functional pathways of multi-system interactions and bodily homeostasis.

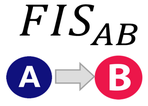
Methodology & Workflow



- We used a compilation of causal functional associations (CFAs) from >150 published studies curated in the NCBI (PubMed) database. The CFAs were sorted into tables with pairwise molecular interactors, effect direction and functional modification types.
- We developed innovative Functional Interaction Score (FIS) as edge weights between pairwise interactors and automated the computation of FIS using Python libraries (NumPy, pandas).
- Using NetworkX, we automated the generation of directed network graphs with edge weights reflecting the magnitude of the FIS.
- We generated systematic test cases to simulate a comprehensive set of network architectures and edge weight choices to validate automation.
- The Python libraries, NetworkX, Matplotlib, and Seaborn were utilized to visualize causal relationships and network topology.
- Ongoing work is developing a motif search algorithm to identify modules of multi-system crosstalk (e.g., neuroinflammation and neural excitability).

Results

1. Novel approach to quantitate causal protein associations as Function Interaction Scores, $FIS_{A\rightarrow B}$

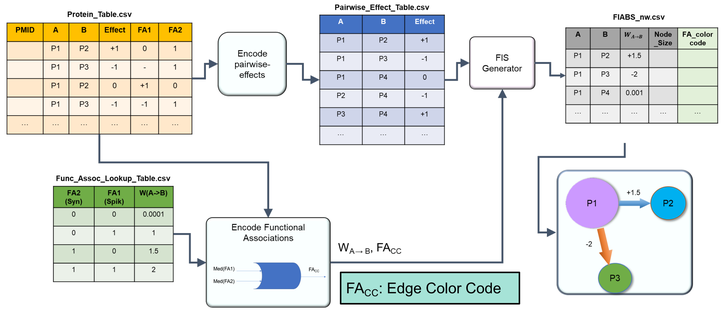


$$FIS_{A\rightarrow B} = D_M \times W_{A\rightarrow B}$$

D_M: Median value of the pairwise effect direction from $A \rightarrow B$, evidenced across N studies

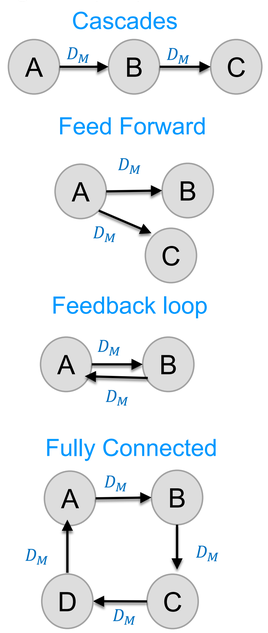
$W_{A\rightarrow B}$: Weighted functional association, generated using a custom look-up table

2. Design of automated FIS Calculator: Flow diagram shows the various stages in FIS generation



3. Testing simulation of key network motifs

A. Validated sample network motifs for positive (green) and negative (red) values of effect direction, D_M.

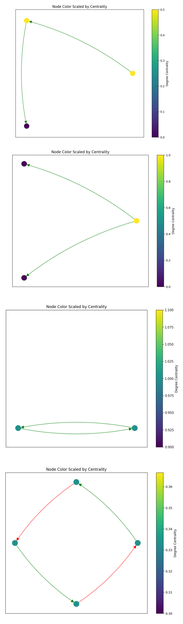


D_M	A	B	C
A	0	1	0
B	0	0	1
C	0	0	0

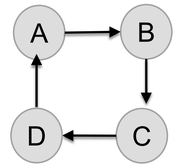
D_M	A	B	C
A	0	1	0
B	0	0	1
C	0	0	0

D_M	A	B
A	0	1
B	1	0

D_M	A	B	C	D
A	0	1	0	0
B	0	0	1	0
C	0	0	0	-1
D	-1	0	0	0

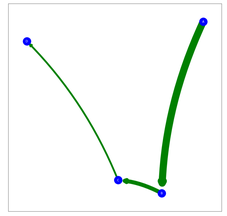


B. Testing network generation with $FIS_{A\rightarrow B}$ edge weights

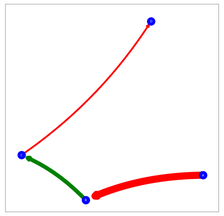


Pairwise effect	FA2 (Syn)	FA1 (Spik)	W(A->B)
A→B	1	1	2
B→C	1	0	1.5
C→D	0	1	1
D→A	0	0	0.001

All positive D_M values

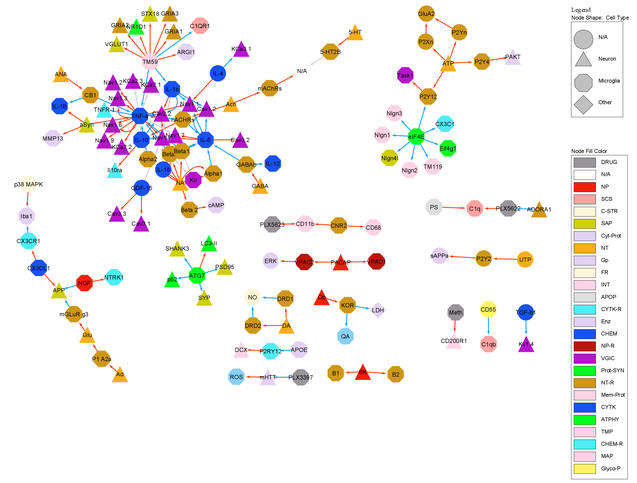


Mixed positive and negative D_M values



In both networks it can be seen no edge is drawn from D→A, since FIS score = 0.001.

4. The FIS network topology can then be analyzed to reveal biological motifs of multisystem crosstalk



Conclusions

- Through systematic consolidation of causal empirical evidence of protein interactions between brain cells, we created novel FIS's to quantitate interaction strengths.
- We employed motif patterns as a testing framework to rigorously assess the network model's performance, ensuring its suitability for biological networks.
- We demonstrated preliminary motif analysis of the FIS network graph, which will be automated in the next steps of this study.
- The FIS network can be used to test hypothesis on multi-system interactions. For example, to determine the most influential cytokine-ion channel protein interactions that can alter the functional homeostasis of neural excitability.

Acknowledgements

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