Combining function and structure in a single macro-scale connectivity model of the human brain

A Preprint

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Abstract

Combining the macro-scale functional and structural connectivity matrices of the human brain could provide useful information on how various diseases and conditions affect the brain. However, it is not a simple task to combine such information as they are derived usually in very different ways with functional information typically gathered using fMRI, EEG, or MEG whereas structural information relies on robust diffusion-weighted MRI tractography methods. This work proposes a solution to this problem using an analogy to an electric circuit with the functional information being the voltage sources and the structural information resistance of the elements in the circuit. The voltage sources and resistances can be used to solve the current in the circuit using Modified Nodal Analysis, for example. In the proposed analogy, the solved electric current represents how the functional information flows in the structural brain network. This work demonstrates a connection-specific example of such analysis

as well as whole-brain analysis using data from the Human Connectome Project. How this is achieved is explained in the method sections which has a complimentary Python function that can readily be applied to any project that has both functional and structural connectivity data. The main motivation for the proposed analysis method is that it could provide new information on various conditions and diseases such as Alzheimer's or multiple sclerosis that affect the human brain. In a sense, the proposed approach is a macro-scale version of the classical Hodkin-Huxley model.

Keywords brain connectivity · structure · function · diffusion MRI · resting-state fMRI · conductance

1 Introduction

Understanding the human brain and its macro-scale connections or 'the brain connectome' (Sporns et al., 2005) is a challenge with likely far-reaching benefits in brain sciences and medicine. This challenge is often divided into two parts that either study the brain function or the brain structure. While both parts alone are readily difficult to study, it seems that linking them is an even more elusive task (Damoiseaux and Greicius, 2009; Greicius et al., 2009; Hermundstad et al., 2013; Huang and Ding, 2016; Sporns, 2013; Suárez et al., 2020). However, it is reasonable to assume that such a link must exist as the brain could not support functions without the structure.

The functional connectome or functional networks can be derived from statistical patterns (Rubinov and Sporns, 2010) detected in the brain using functional magnetic resonance imaging (fMRI) time series, electroencephalography (EEG), or magnetoencephalography (MEG), for example. (Sporns, 2013). The derived functional connectome depicts only the correlations between activities in different brain regions which means that this information alone cannot be used to imply causal relationships (Smith et al., 2011). Yet, functional connectome has provided insights into the behavior, aging, and how various diseases and conditions can affect the human brain.

The structural connectome of the living human brain is derived using diffusion-weighted magnetic resonance imaging (dMRI) and tractography (Basser et al., 1994; Behrens and Sporns, 2012; Johansen-Berg and Rushworth, 2009; Le Bihan et al., 2001). The derived connectome depicts pathways in which water molecules can travel in the brain and is often assumed to remain relatively stable during short time periods. These pathways are often referred to as tractography streamlines. While streamlines do not directly imply that there would be a white matter tract or fiber, many studies have demonstrated that streamlines indeed can be used to infer orientations and trajectories of white matter bundles. (Sporns, 2013) However, tractography has a tendency to produce many false positive streamlines (Maier-Hein et al., 2016) due to e.g., noise, measurement methods, and processing (Sairanen and Andersson, 2023) which complicate deductions from the results. Despite these complications, the structural connectome has provided new insights into the organization of the human brain in various conditions.

Combining the functional and structural connectomes is a difficult task as both techniques depend heavily on the chosen data acquisition and processing methods which can set various limitations on how data could be merged. In many cases, functional correlations may be found between two brain regions that do not share a direct structural connection (Damoiseaux and Greicius, 2009). In such cases, finding the optimal indirect connection between regions can be challenging. Especially, with the dMRI tractography providing large numbers of false positive streamlines (Maier-Hein et al., 2016).

An interesting proposal to join these two connectomes is to use an electrical circuit as an analogy for the human brain on the macro scale. Recent studies (Chung et al., 2017; Frau-Pascual et al., 2021, 2019) used voxel-wise structural model to derive the analogue for electric conductance from the structural information and then used a fixed current of one ampere to solve the voltage from the partial differential equations related to electrical circuit laws. The authors showed that the ensuing voltage matrix correlated well with the functional connectivity matrices obtained using fMRI.

In this study, we take the electrical circuit analogy a step further. Instead of using a fixed current, we propose that the analogy could be defined as the structural connectome being the resistance (or conductance) and the functional connectome being the potential (or voltage sources) in the electrical circuit. In this formulation, the current would be the unknown element of interest, and it can be readily solved following Ohm's and Kirchhoff's laws using the modified nodal analysis (MNA) (Ho et al., 1975; Wedepohl and Jackson, 2002).

In the proposed analogy, the current depicts how the functional information flows through the brain structures similar to how electrical current flows through elements of resistance in an electric circuit. The proposed analogy provides a way to naturally combine the two brain connectomes while taking into account direct and indirect structural connections simultaneously. The ensuing novel connectivity matrix depicts the functio-structural current (FSC) in the brain which hopefully can be used to deepen the understanding of the living brain.

Showing in which kind of clinical or research cases, or if at all, the proposed method is applicable or capable of providing useful information is beyond this technical report. To facilitate fast implementations of the proposed approach, a Python function that calculates FSC matrix from a given functional and structural connectome is provided in GitHub [add link]. As this FSC is a matrix, many existing network analysis tools can be readily applied to study it further (Sporns, 2013). Additionally, FSC could be used to prune the false positive findings of the tractography by merging it to tractography filtering (Sairanen et al., 2021). Streamlines or bundles that carry only minimal currents could be deemed as false positives, for example.

2 Results

Functional and structural connectivity matrices from the Human Connectome Project (Van Essen et al., 2012) were used to demonstrate the proposed functio-structural current analysis. These connectivity matrices were obtained using the ENIGMA TOOLBOX (Larivière et al., 2021).

The figure 1 demonstrates how an indirect functional connection could be facilitated by the structural network. This example starts with a functional connection between the source at the left middle temporal gyrus (L_MTG) and the target at the right middle temporal gyrus (R_MTG). The structural connectivity matrix does not show a direct link between the source and the target therefore this functional connection is likely established via an indirect link or links. By applying the proposed FSC analysis, a current flowing from L_MTG to the right inferior temporal gyrus (R_ITG) is found. The structural connections from R_ITG onwards show a link to R_MTG completing the circuit from the source to the target. This was a simple example of how the proposed FCS analysis could be used to follow the functional information flow in the structural brain network. The figure 2 repeats this demonstration using Chord plots which could be more useful in real-life situations. This kind of connection specific analysis could be helpful when a specific location in the brain is of interest.

The proposed FSC analysis is not limited to any specific connections. The same analysis approach can be applied to the whole-brain functional and structural connectivity matrices as shown in the figure 3. This kind of whole-brain analysis could be helpful in the investigation of diseases such as Alzheimer's or multiple sclerosis.

3 Discussion

This work has demonstrated that an analogy between the human brain and an electric circuit can be used to combine functional and structural connectivity matrices. This is achieved by using the functional connectivity as voltage sources in the circuit and the structural connectivity as resistances of the elements in the circuit. Node-wise voltages are solved by applying the Modified Nodal Analysis (Ho et al., 1975; Wedepohl and Jackson, 2002). Ohm's law is then applied to the voltage differences between the nodes and resistances to obtain the currents flowing in the circuit. This work coined this flow as functio-structural current or FSC. In a sense, the proposed model can be seen as a macro-scale version of the Hodkin-Huxley model (Hodgkin and Huxley, 1952).

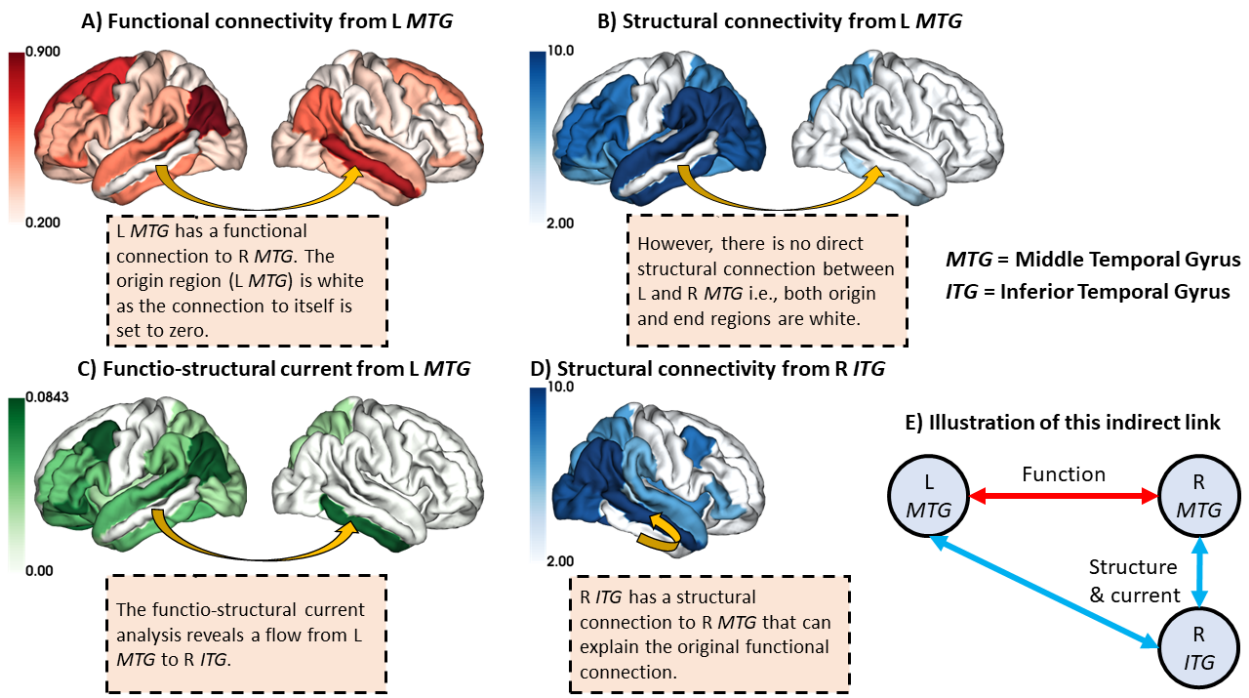

Figure 1: A demonstration of the functio-structural current analysis. Using an analogy to an electric circuit with (**A**) functional connectivity being voltage sources, (**B**) structural connectivity being resistance, (**C**) the functio-structural current, an equivalent for electrical current, can be derived. An example: There is no current between L and R MTG because they have no structural connection (**B**). However, the FSC shows a high current through R ITG and by analyzing the structural connections from R ITG, a link to R MTG is found explaining (**D**) the original functional connection shown in (**A**). A simple schematic illustration of this indirect link is shown in (**E**).

How this additional 'functional flow' could be used? One approach could be the filtering of possible structural connections (Sairanen et al., 2021) which are known to contain large numbers of false positive findings (Maier-Hein et al., 2016). If there are structural connections that do not carry any currents, those could be pruned as false connections. Another application could be to study if these currents are somehow affected by various diseases. E.g. as a biomarker for early Alzheimer's disease. Alzheimer's might cause a lower information flow overall in their brain or some specific regions or connections. A similar hypothesis could be set for any disease or condition that affects the brain. Typical network analysis tools that have previously been applied to study functional and structural connectivity matrices can readily be applied to these information flow matrices as well.

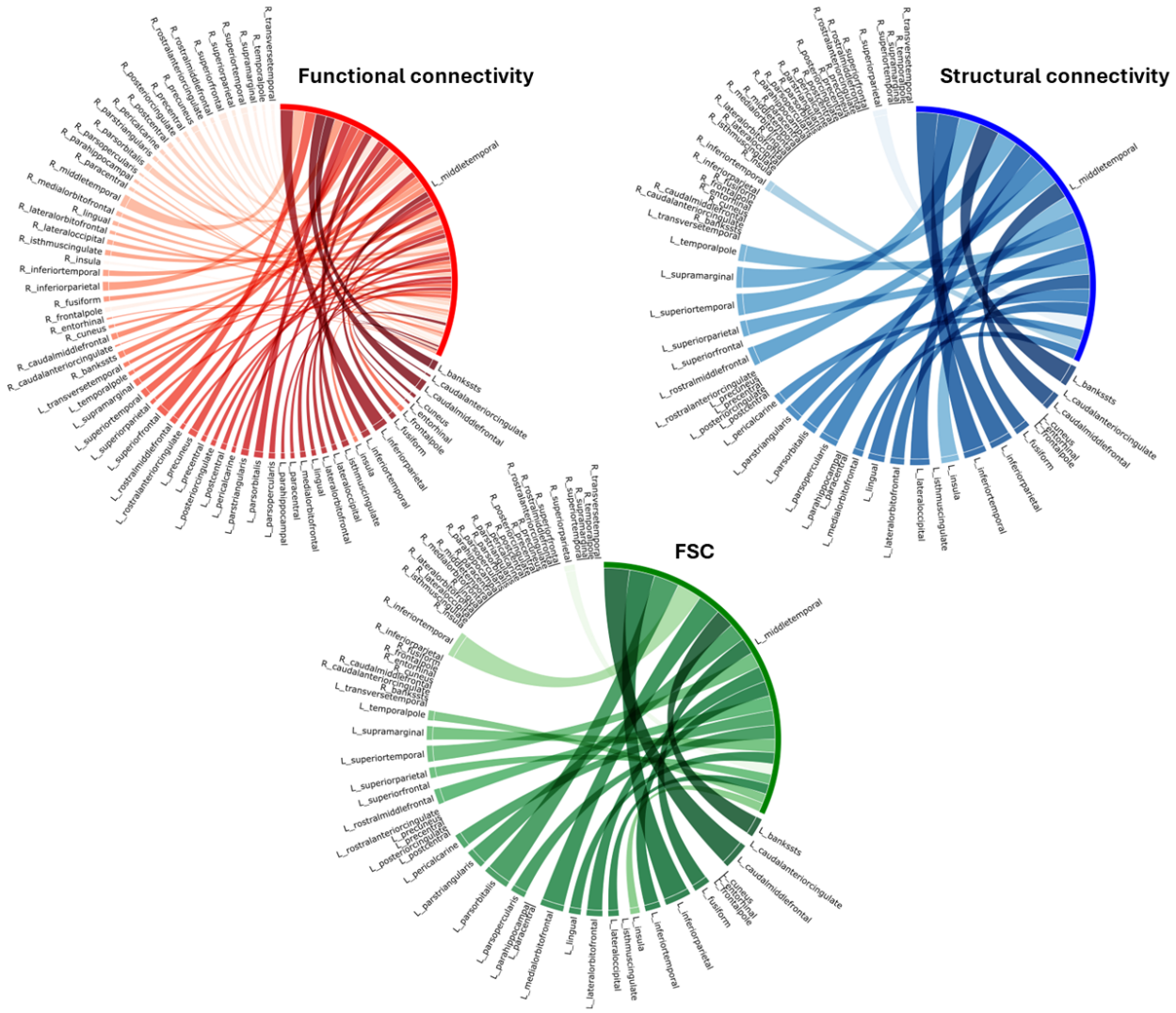

Figure 2: Connections from the left middle temporal gyrus (source). Red shows the functional connectivity, blue structural connectivity, and green functio-structural current (FCS). For example, the second strongest functional link with the source is the right middle temporal gyrus (target). However, there is no direct structural link between them, but there is a weak structural connection between the source and right inferior temporal gyrus which is known to have a structural link with the target. Despite the weak structural connection, the FSC from the source to the right inferior temporal gyrus is high to facilitate this functional connection between the source and target. This kind of analysis could be applied to study changes in FSC due to various brain conditions as well as before and after a surgical operation, for example.

The proposed analogy could be used to model the causality of brain functions to some extent as well. This is because the modified nodal analysis can be used to analyze circuits containing dependent voltage sources (Ho et al., 1975). In the brain, such

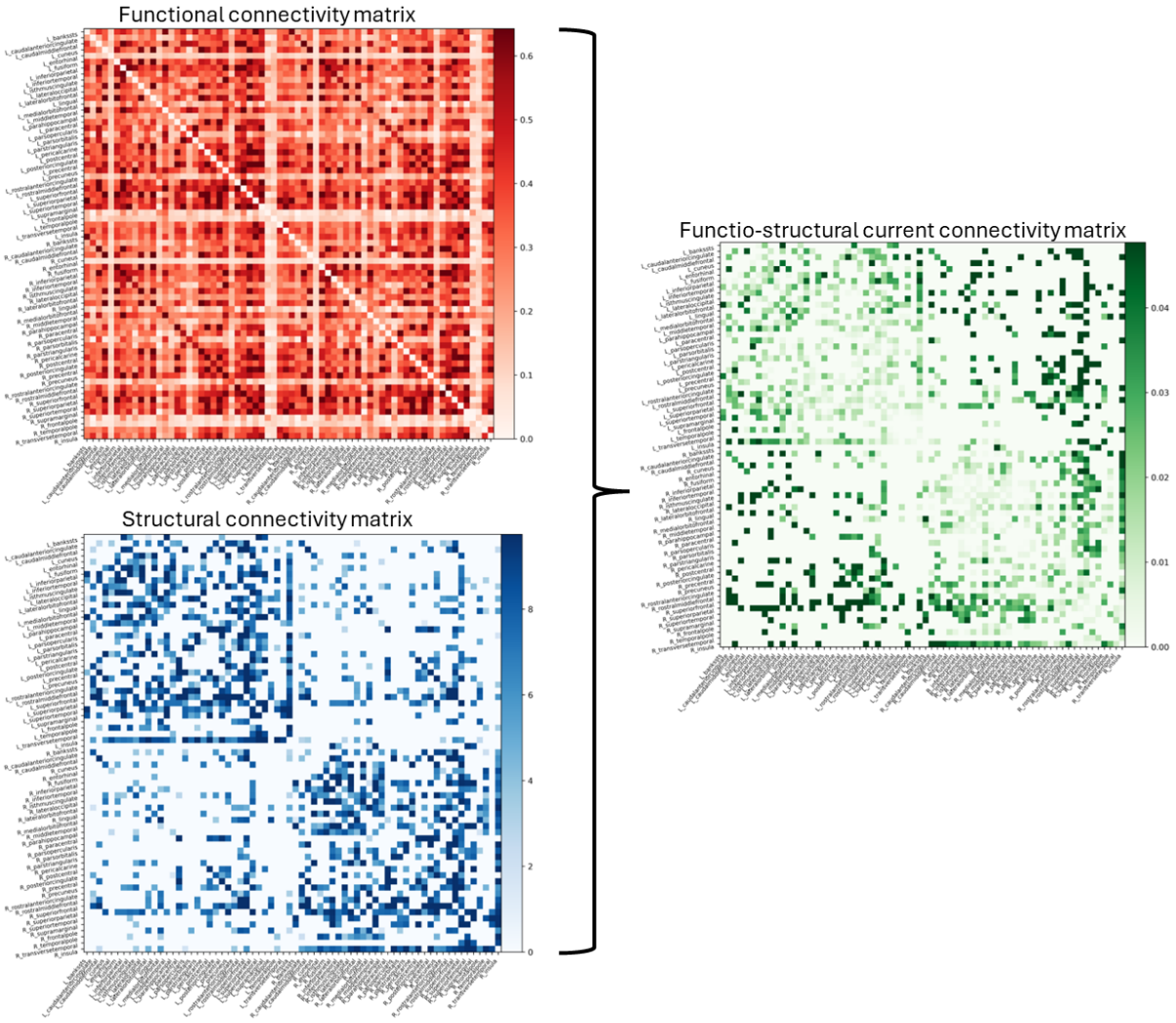

Figure 3: The proposed functio-structural current analysis is not limited to any one specific connection. Functional and structural connectivity matrices from the whole brain or sub-networks can be used as a basis to calculate the corresponding FSC matrix. This could be helpful for the investigation of diseases and conditions that affect the brain on a large scale such as Alzheimer's or multiple-sclerosis.

dependencies or causalities are likely more complex to model but in some cases, they could be identified. However, this discussion of causality delves towards effective connectivity (Friston, 2011) which is beyond the topic and data used in this study. In the future, with a suitable data set for causality modelling, this could be studied further.

The proposed FSC is limited by all the inaccuracies and assumptions that affect the functional and structural connectivity analyses. However, as it is based on the analysis of the connectivity matrices it is a relatively freely adaptable method. If new progress is made on functional or structural connectivity analyses, results from them can readily be used in the FSC to evaluate the changes.

In summary, this work combined functional and structural brain connectomes using an analogy to an electric circuit. This method provided a novel brain connectivity matrix that represents how the functional information flows in the structural brain network. As this work is a technical report, it considers only the proposed method and demonstrates how it can be applied to any pair of functional and structural connectivity matrices. Future studies with patients affected by various diseases or conditions are needed to evaluate, if the proposed functio-structural current has a place in neuroscience.

4 Methods

This section demonstrates how the modified nodal analysis is applied to study the living brain. First, a voltage source matrix $\mathbf{V}$ is defined as a copy of the functional connectivity matrix. This means that voltage source matrices can be defined in as many ways as the functional connectivity matrix e.g., as a resting state network or a task-specific activity in fMRI, EEG, or MEG. Second, a resistance matrix $\mathbf{R}$ is defined as a copy of the structural connectivity matrix. This means that the resistance matrix can also be defined with various tractography algorithms and be based on e.g., the streamline length, average fractional anisotropy, or degree of myelination. The main restriction is that both the functional and structural connectivity matrices should be generated using the same brain segmentations or atlas and therefore have the same number of parcellations.

As this study does not aim to improve or even comment on how structural or functional connectivity matrices are or should be derived, the preprocessed cortico-cortical functional and structural connectivity matrices of Human Connectome Project sub-

jects (Van Essen et al., 2012) were obtained as readily available results using the ENIGMA TOOLBOX (Larivière et al., 2021). The used brain parcellation was the default (Desikan-Killiany) resulting in 68 times 68 connectivity matrices. For the full details on how connectivity matrices were calculated, please see the ENIGMA TOOLBOX publication (Larivière et al., 2021).

The proposed nodal analysis aims to first calculate the nodal voltages $\mathbf{u}$ which are then used to solve the functio-structural current matrix $\mathbf{FSC}$. The voltage source matrix obtained from the functional connectivity should not be confused with the nodal voltages. Setting up the system of linear equations for solving these nodal voltages using MNA requires the following six steps.

First, the definition of a conductance matrix $\mathbf{G}$ with the conductance being the reciprocal of the resistance. The diagonal elements $\mathbf{G}_{ii}$ are the sum of all conductances connected to node i. All other elements ij with $i \neq j$ are the opposite of the sum of all conductances connected between nodes i and j.

Second, the definition of a $\mathbf{B}$ matrix that holds the information of positive and negative terminals in the circuit and has dimensions of the number of nodes N in the connectivity matrices times the number of voltage sources M. The number of voltage sources is the number of non-zero elements in the voltage matrix. While it is an arbitrary choice of which direction is positive or negative in the $\mathbf{B}$ matrix, in all cases $B_{ij} = -B_{ji}$.

Third, since the proposed model does not take into account any dependent voltage sources, the next matrices $\mathbf{C}$ and $\mathbf{D}$ needed for MNA are simply defined as $\mathbf{C} = \mathbf{B}^T$ and $\mathbf{D}$ is an M times M zero matrix. If dependent voltage sources would be of interest in future applications, these can readily be modified for them according to MNA rules (Ho et al., 1975; Wedepohl and Jackson, 2002).

Fourth, these matrices are concatenated into one $\mathbf{A} = \left[\begin{smallmatrix} \mathbf{G} & \mathbf{B} \\ \mathbf{C} & \mathbf{D} \end{smallmatrix}\right]$.

Fifth, a vector $\mathbf{z}$ with elements of N independent current sources and M independent voltage sources is defined. Note that the proposed model does not include independent

current sources therefore the first N elements are zeros in $\mathbf{z}$. The rest M elements are the independent voltage sources from the functional connectivity matrix.

Sixth, a ground node is selected. This is an arbitrary decision therefore selecting the first node as ground is as good as any other selection. Practically, this sixth step is done by removing the ground node from both $\mathbf{A}$ (the first row) and $\mathbf{z}$ (the first element). The nodal voltages $\mathbf{u}$ are then solved from the system of linear equations $\mathbf{Ax} = \mathbf{z}$ where the first $N - 1$ (-1 because the ground node was removed) elements of $\mathbf{x}$ are the nodal voltages of interest $\mathbf{u}$ and the rest M elements are the currents associated with the voltage sources (which are not considered in the proposed model but could be useful in future applications). The ground node with zero voltage is prepended as the first element into $\mathbf{u}$.

At this point, the MNA is completed and analysis continues to calculate the voltage difference or potential matrix $\mathbf{U}$ between the N nodes. The elements in this difference matrix are obtained from the nodal voltage vector as follows $U_{ij} = |u_i - u_j|$. Lastly, the functio-structural current matrix is calculated by applying Ohm's law $\mathbf{FSC} = \frac{\mathbf{U}}{\mathbf{R}}$.

References

Basser, P., Mattiello, J., and LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, 66(1):259–267.

Behrens, T. E. J. and Sporns, O. (2012). Human Connectomics. *Current Opinion in Neurobiology*, 22(1):144–153.

Chung, M. K., Hanson, J. L., Adluru, N., Alexander, A. L., Davidson, R. J., and Pollak, S. D. (2017). Integrative Structural Brain Network Analysis in Diffusion Tensor Imaging. *Brain Connectivity*, 7(6):331–346.

Damoiseaux, J. S. and Greicius, M. D. (2009). Greater than the sum of its parts: a review of studies combining structural connectivity and resting-state functional connectivity. *Brain Structure and Function*, 213(6):525–533.

Frau-Pascual, A., Augustinack, J., Varadarajan, D., Yendiki, A., Salat, D. H., Fischl, B., and Aganj, I. (2021). Conductance-Based Structural Brain Connectivity in Aging

and Dementia. *Brain Connectivity*, 11(7):566–583. Publisher: Mary Ann Liebert, Inc., publishers.

Frau-Pascual, A., Fogarty, M., Fischl, B., Yendiki, A., and Aganj, I. (2019). Quantification of Structural Brain Connectivity via a Conductance Model. *NeuroImage*, 189:485–496.

Friston, K. J. (2011). Functional and effective connectivity: a review. *Brain*, 1(1):13–36. MAG ID: 2061564920.

Greicius, M. D., Supekar, K., Menon, V., and Dougherty, R. F. (2009). Resting-State Functional Connectivity Reflects Structural Connectivity in the Default Mode Network. *Cerebral Cortex*, 19(1):72–78. MAG ID: 2106396500.

Hermundstad, A. M., Bassett, D. S., Brown, K. K., Brown, K. S., Aminoff, E., Clewett, D., Freeman, S., Frithsen, A., Johnson, A., Tipper, C. M., Miller, M. B., Grafton, S. T., and Carlson, J. M. (2013). Structural foundations of resting-state and task-based functional connectivity in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, 110(15):6169–6174. MAG ID: 2002807356.

Ho, C.-W., Ruehli, A., and Brennan, P. (1975). The modified nodal approach to network analysis. *IEEE Transactions on Circuits and Systems*, 22(6):504–509. Conference Name: IEEE Transactions on Circuits and Systems.

Hodgkin, A. L. and Huxley, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of Physiology*, 117(4):500–544.

Huang, H. and Ding, M. (2016). Linking Functional Connectivity and Structural Connectivity Quantitatively: A Comparison of Methods. *Brain*, 6(2):99–108. MAG ID: 2229937548.

Johansen-Berg, H. and Rushworth, M. F. (2009). Using Diffusion Imaging to Study Human Connectional Anatomy. *Annual Review of Neuroscience*, 32(1):75–94. _eprint: https://doi.org/10.1146/annurev.neuro.051508.135735.

Larivière, S., Paquola, C., Park, B.-y., Royer, J., Wang, Y., Benkarim, O., Vos de Wael, R., Valk, S. L., Thomopoulos, S. I., Kirschner, M., Lewis, L. B., Evans, A. C., Sisodiya, S. M., McDonald, C. R., Thompson, P. M., and Bernhardt, B. C. (2021). The ENIGMA Toolbox: multiscale neural contextualization of multisite neuroimaging datasets. *Nature Methods*, 18(7):698–700. Number: 7 Publisher: Nature Publishing Group.

Le Bihan, D., Mangin, J.-F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., and Chabriat, H. (2001). Diffusion tensor imaging: Concepts and applications. *Journal of Magnetic Resonance Imaging*, 13(4):534–546. _eprint: https://onlinelibrary.wiley.com/doi/pdf/10.1002/jmri.1076.

Maier-Hein, K. H., Neher, P. F., Jean-Christophe Houde, Houde, J.-C., Côté, M.-A., Garyfallidis, E., Jidan Zhong, Zhong, J., Jidan Zhong, Chamberland, M., Fang-Cheng Yeh, Yeh, F.-C., Lin, Y.-C., Qing Ji, Ji, Q., Reddick, W. E., Glass, J. O., David Chen, David Qixiang Chen, David Qixiang Chen, Chen, D., Chen, D., Yuanjing Feng, Feng, Y., Chengfeng, G., Wu, Y., Ma, J., Renjie, H., Li, Q., Carl-Fredrik Westin, Westin, C.-F., Samuel Deslauriers-Gauthier, Deslauriers-Gauthier, S., Gonzalez, J. O. O., Paquette, M., St-Jean, S., Gabriel Girard, Girard, G., François Rheault, Rheault, F., Sidhu, J., Chantal M. W. Tax, Tax, C. M. W., Fenghua Guo, Guo, F., Mesri, H. Y., Szabolcs Dávid, David, S., Froeling, M., Heemskerk, A. M., Alexander Leemans, Leemans, A., Boré, A., Pinsard, B., Christophe Bedetti, Bedetti, C., Desrosiers, M., Brambati, S. M., Brambati, S. M., Doyon, J., Sarica, A., Vasta, R., Cerasa, A., Aldo Quattrone, Quattrone, A., Yeatman, J. D., Khan, A. R., Hodges, W., Wes Hodges, Wes Hodges, Alexander, S. P., Simon Alexander, Simon Alexander, Alexander, S., David Romascano, Romascano, D., Barakovic, M., Auria, A., Esteban, O., Lemkaddem, A., Thiran, J.-P., Jean-Philippe Thiran, Jean-Philippe Thiran, Jean-Philippe Thiran, Cetingul, H. E., Cetingul, H. E., Odry, B. L., Mailhe, B., Nadar, M. S., Mariappan S. Nadar, Nadar, M. S., Pizzagalli, F., Prasad, G., Villalon-Reina, J. E., Galvis, J., Thompson, P. M., De Santiago Requejo, F., Laguna, P. L., Lacerda, L., Rachel Barrett, Barrett, R., Flavio Dell'Acqua, Dell'Acqua, F., Catani, M., Petit, L., Caruyer, E., Daducci, A., Dyrby, T. B., Holland-Letz, T., Hilgetag,

C. C., Stieltjes, B., Bram Stieltjes, and Descoteaux, M. (2016). Tractography-based connectomes are dominated by false-positive connections. *bioRxiv*, page 084137. MAG ID: 2550828940.

Rubinov, M. and Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, 52(3):1059–1069.

Sairanen, V. and Andersson, J. (2023). Outliers in diffusion-weighted MRI: Exploring detection models and mitigation strategies. *NeuroImage*, 283:120397.

Sairanen, V., Ocampo-Pineda, M., Granziera, C., Schiavi, S., and Daducci, A. (2021). Incorporating outlier information into diffusion MR tractogram filtering for robust structural brain connectivity and microstructural analyses. Technical report. Company: Cold Spring Harbor Laboratory Distributor: Cold Spring Harbor Laboratory Label: Cold Spring Harbor Laboratory Section: New Results Type: article.

Smith, S. M., Miller, K. L., Salimi-Khorshidi, G., Webster, M., Beckmann, C. F., Nichols, T. E., Ramsey, J. D., and Woolrich, M. W. (2011). Network modelling methods for FMRI. *NeuroImage*, 54(2):875–891.

Sporns, O. (2013). Structure and function of complex brain networks. *Dialogues in Clinical Neuroscience*, 15(3):247–262.

Sporns, O., Tononi, G., and Kötter, R. (2005). The Human Connectome: A Structural Description of the Human Brain. *PLOS Computational Biology*, 1(4). MAG ID: 2146693559.

Suárez, L. E., Markello, R. D., Betzel, R. F., and Misic, B. (2020). Linking Structure and Function in Macroscale Brain Networks. *Trends in Cognitive Sciences*, 24(4):302–315.

Van Essen, D. C., Ugurbil, K., Auerbach, E. J., Behrens, T. E., Bucholz, R. D., R. Bucholz, Chang, A., Chen, L., Maurizio Corbetta, Corbetta, M., Della Penna, S., Curtiss, S. W., Della Penna, S., Feinberg, D. A., Glasser, M. F., Heath, A. C., Harel, N., Heath, A. C., Larson-Prior, L. J., Marcus, D. S., Michalareas, G., Moeller, S., Oostenveld, R., Petersen, S., Petersen, S. E., Prior, F. W., Schlaggar, B. L., Smith, S. M., Snyder, A. Z., Xu, J., and Yacoub, E. (2012). The Human Connectome

Project: A data acquisition perspective. *NeuroImage*, 62(4):2222–2231. MAG ID: 2020519533.

Wedepohl, L. M. and Jackson, L. (2002). Modified nodal analysis: an essential addition to electrical circuit theory and analysis. *Engineering Science & Education Journal*, 11(3):84–92. Publisher: IET Digital Library.

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