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

A Preprint

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Abstract

Combining the functional and structural connectomes of the human brain on macro-scale could provide information on various brain diseases and conditions. Unfortunately, accomplishing such combination is not trivial as the connectomes are usually derived from different imaging and measuring modalities that are based on different biophysical effects. The functional connectome is typically obtained using fMRI, EEG,or MEG whereas the structural connectome relies on diffusion-weighted MRI tractography. This work proposes a way to perform this coupling using an analogy between brain connectomes and electric circuit. The idea is that functional correlations are treated as potentials and structural connections are treated as resistances in a circuit. In a sense, the proposal is a macro-scale version of the Hodkin-Huxley model. This work demonstrates how the proposed function-structure coupling can be applied as filtering for tractography by studying the Default Mode Network of a

subject from the Human Connectome Project. To provide a ground-truth example, a phantom simulation is used to detail how the method can solve functional connections in direct and indirect structural connection situations. Finally, the method is applied to a cohort of 207 subjects from HCP to combine their functional and structural connectivity matrices to demonstrate how this approach could be used in group-level analyses. Based on the results, the proposed coupling method provides a new way to filter tractograms and a new 'contrast' for brain connectomics.

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

1 Introduction

A recent review Greaves et al. (2025) highlighted a key challenge that persist in brain connectivity studies: how the functional connectome could be coupled with the structural connectome? This is difficult because on the macroscale, functional interactions between different brain regions might not be supported by any direct structural connections - so how to choose which structural pathways are used for any given functional signal? Structural connections are often estimated using tractography (Basser et al., 1994; Behrens and Sporns, 2012; Johansen-Berg and Rushworth, 2009; Le Bihan et al., 2001; Zhang et al., 2022) which is a method known to produce false-positive connections (Maier-Hein et al., 2016) further complicating the issue. This study proposes an idea that can combine connectomes in any structural network having potential applications in brain connectivity studies as well as in dMRI tractography.

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. (Damoiseaux and Greicius, 2009; Greicius et al., 2009; Hermundstad et al., 2013; Huang and Ding, 2016; Sporns, 2013; Suárez et al., 2020). Approaches such as multivariate regression have been applied attempting

to find explanatory factors between the two connectomes in e.g. (Liu et al., 2022) A potential pitfall in that is one can always add more variables to perfect the model fit without obtaining more understanding of underlying effects. Yet, it is very much reasonable to assume that these two connectomes are inherently linked as the brain could not support functions without the structure. Therefore some sort of model should be able to couple them. This study proposes a natural coupling approach that can be described as functional information flowing along gradient following the structural path of least effort which is a common theme in many natural processes.

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). (Sporns, 2013). Typically 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). Despite this, 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 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. Even with these complications, the structural connectome has provided new insights into the organization of the human brain in various conditions.

The proposal in this study is to construct the function-structure coupling using an analogy with a well-known natural phenomenon: electrical currents in a circuit. Similar analogy has been drawn before in a much smaller scale in classical Hodkin-Huxley model (Hodgkin and Huxley, 1952). This study focuses on a global brain networks and tractography and drives the coupling analogy from the Modified Nodal Analysis (MNA) (Ho et al., 1975; Wedepohl and Jackson, 2002) of electrical circuits.While this can sound arrogantly simple approximation of the human brain connectome, the reader is encouraged to continue. The idea is not to say that 'brain is a circuit' but to define a framework where tools that have been successfully been used to study electronical networks could be applied to brain networks. As far as the author is aware, this is the first time that MNA has been applied to study the human brain. So, regardless of the simplicity of the idea, this has not been done before and this study can be seen as a bridge between these two fields of research.

In the proposed analogy, the structural connectome is modelled as resistance and the functional connectome is modelled as electrical potential in an electrical circuit. Using this formulation, the variable of interest - current - explains how the functional information propagates through the structural network. While the actual method of functional signal traversing the brain is an electro-chemical process, at the macro-scale this analogy could provide a close-enough approximation of the process. This study demonstrates how this analogy can be used to select which tractography streamlines are necessary for functional information flow as well as how this idea can be used to form a completely new contrast for connectome analyses opening new ways to study the human brain. The developed algorithm to compute this 'information current' is provided as a Python code. [1]

2 Methods

This section is separated into four parts. The theoretical framework used in the proposed function-structure coupling 2.1, single subject example of tractogram fil-

[1] https://github.com/vilsaira/FSC

tering in Default Mode Network (Raichle et al., 2001) analysis 2.2, a ground-truth phantom simulation 2.3, group-level analysis of 207 subjects of the Human Connectome Project (Van Essen et al., 2012) 2.4.

2.1 Proposed function-structure coupling

This subsection demonstrates how the Modified Nodal (MNA) Analysis (Ho et al., 1975; Wedepohl and Jackson, 2002) can be applied to study the living brain. In MNA, unknown variables are nodal voltages $\mathbf{u}$ and currents flowing through the independent voltage sources $\mathbf{i_v}$. Known variables, independent voltage sources $\mathbf{V}$ and resistances are $\mathbf{R}$ are derived from the functional and structural connectivity.

A voltage source matrix $\mathbf{V}$ is defined as the functional connectivity matrix. Meaning voltage sources can be defined in as many ways as the functional connectivity e.g., resting-state networks or a task-specific activity in fMRI, EEG, or MEG. In this adaptation, the voltage sources are independent. In the future, this could be changed to study causality between functional correlations.

A resistance matrix $\mathbf{R}$ is defined as the structural connectivity matrix. Meaning the resistance matrix can be defined based various tractography algorithms and their outputs e.g., the streamline length, average fractional anisotropy, or even degree of myelination in some cases. The 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 from the same structural locations.

In general, MNA can be expressed in a matrix form as follows (Wedepohl and Jackson, 2002):

$$\begin{bmatrix} \mathbf{G} & \mathbf{B} \\ \mathbf{C} & \mathbf{D} \end{bmatrix} \begin{bmatrix} \mathbf{u} \\ \mathbf{i_v} \end{bmatrix} = \begin{bmatrix} \mathbf{i} \\ \mathbf{v} \end{bmatrix} \tag{1}$$

,

with the conductance matrix $\mathbf{G}$, an incidence matrices $\mathbf{B}$ and $\mathbf{C}$, an association matrix between voltage sources and dependent voltage sources $\mathbf{D}$, vectors of nodal voltages $\mathbf{u}$, currents through voltages sources $\mathbf{i_v}$, independent current sources $\mathbf{i}$, and independent voltage sources $\mathbf{v}$ i.e. the vectorized functional correlations.

With assumptions that *i*) there are no dependent voltage sources $\mathbf{D} = \mathbf{0}$ and $\mathbf{C} = \mathbf{B}^\top$ and *ii*) there are no current sources $\mathbf{i} = \mathbf{0}$, equation 1 can be simplified to

$$\begin{bmatrix} \mathbf{G} & \mathbf{B} \\ \mathbf{B}^\top & \mathbf{0} \end{bmatrix} \begin{bmatrix} \mathbf{u} \\ \mathbf{i_v} \end{bmatrix} = \begin{bmatrix} \mathbf{0} \\ \mathbf{v} \end{bmatrix} \tag{2}$$

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Conductance is the reciprocal of the resistance, therefore $\mathbf{G}$ can be calculated from the resistance matrix $\mathbf{R}$ with the following logic. The diagonal elements 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 ensuring the conservation of charge i.e. that the sum of currents entering and leaving any node is zero.

The incidence matrix $\mathbf{B}$ contains 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 $B_{ij} = -B_{ji}$.

nodal voltages $\mathbf{u}$ solved from equation 2, can be used to calculate the currents I flowing through each edge of the network using Ohm's law $I = \frac{U}{R}$ where U contains nodal voltages, and R contains resistances. If resistances are defined as a structural connectome, this yields a new connectivity matrix that describes how the functional information flows through the structural network. Alternatively, resistances can be defined as tractography streamlines resulting in streamline-wise currents which could be used to filter unnecessary streamlines as well as to visualize the pathways in the brain that carry the functional information.

2.2 Default Mode Network example

A subject (100307) from the Human Connectome Project was used as a case example as it provided both the preprocessed resting-state fMRI with independent component analysis (ICA) results and diffusion-weighted MRI data.

A Default Mode Network atlas (Smith and Nichols, 2009) was used to identify which of the the ICA terms represented the DMN with the highest correlation. The resulting subject-wise DMN mask was then separated into six regions of interests that were used to form the functional and structural connectivity matrices. The regions were associated wtih anatomical locations of the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), left and right inferior parietal lobules (IPL), and left and right temporal lobes (TL). The strength of the functional connectivity was defined as Pearson's correlation coefficient between the average intensities of these regions from the fMRI time series.

MRtrix (Tournier et al., 2019) was used to perform multi-shell multi-tissue anatomically constrained whole-brain tractography (Dhollander et al., 2016; Smith et al., 2012). A total of a million streamlines were calculated with maximum and minimum lengths of 250 mm and 5 mm. Normalized white matter FOD cutoff was 0.05. The structural connectivity matrix by using the the number of streamlines between the DMN nodes as edge weights. With the electrical circuit analogy, this can be seen as multiple identical parallel wires between two nodes making it easy path for the current. In the future, this is definitely something to investigate further, i.e. this weight could be replaced by streamline myelination or some combination of multiple metrics of interest.

The functional and structural connectomes were coupled using the proposed method described in section 2.1 and the ensuing nodal voltages were used to calculate the current matrix. For the streamline-wise analysis, a Steiner tree algorithm (Kou et al., 1981) was applied to select the edges with the highest currents. The corresponding nodal voltages were then used to calculate the streamline-wise current weights.

2.3 Ground-truth simulation

The FiberCup phantom (Fillard et al., 2011; Poupon et al., 2010, 2008) was used as a ground-truth structure for this simulation as it provided simple structure that allowed both direct and indirect functional correlation simulations. The phantom was separated into five functional subnetworks depicted in figure 4 A. The first four subnetworks were direct networks meaning that each of the functional network node was connected with a direct structural pathway. The fifth subnetwork was an indirect with one intermediate node. The fourth network was the secluded U-shape of the phantom working as a simple sanity check of the results as it should not have any effect on the other networks.

The strength of the functional correlation (potential) in all the subnetworks was set as one. The structural connectome was obtained using CSD tractography in MRtrix (Tournier et al., 2019) to produce a million streamlines. Analysis was separated into two parts. First, to evaluate the global tractogram filtering and second, to evaluate the correctness of all the subnetworks.

2.4 General feasibility of the proposed method

To illustrate how the proposed method could be applied to study large cohorts, a group of unrelated healthy adults ($n = 207$, with 83 males, ages ranging from 22 to 36 years with mean $\pm$ std being 28.73 ± 3.73) from the HCP (Van Essen et al., 2012) that was used (Larivière et al., 2021, 2020). The average structural and functional connectivity matrices of this sample were obtained using the ENIGMA Toolbox (Larivière et al., 2021). For the complete details on how these matrices were calculated, please see the "Connectivity data for macroscale connectome models" section by Larivière et al. (2021). For the demonstration purposes, the default parcellation scheme (Desikan-Killiany) was selected resulting in 68 times 68 connectivity matrices. Functional and structural connectivity matrices were used to calculate the current matrix.

3 Results

A single subject (100307) and a dataset of an unrelated cohort of 207 healthy adult subjects from the Human Connectome Project (Larivière et al., 2021; Van Essen et al., 2012) were used in this study. The human examples provided real world demonstrations of the applicability of the proposed method. Complementary to human data, a simulation based on the FiberCup phantom (Fillard et al., 2011; Poupon et al., 2010, 2008) was used to provide a more intuitive demonstration of the method with known ground-truth specifications.

3.1 Default Mode Network example

An estimate for the location of the DMN nodes in the subject's brain was obtained by finding which ICA volume had the highest correlation with the DMN atlas (Smith and Nichols, 2009). This volume was spatially smoothed and thresholded to obtain subject-wise DMN nodes shown in figure 1. The six nodes found for this experiment roughly represent the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), left and right inferior parietal lobules (IPL), and left and right temporal lobes (TL). This experiment is not aimed to describe how the DMN should be defined but to demonstrate how the proposed coupling algorithm could be applied to study any such network combination.

The subject's DMN mask was used to find all dMRI tractography streamlines that were connected to the DMN and are shown in figure 3 A. This tractogram was then filtered based on the function-structure coupling with streamlines that had zero or near zero current removed as shown in figure 2 B. Furthermore, the streamline-wise currents were used as the colormap in the latter image to visualize the parts of the structural network that carry most of the functional information. the functional information. Figure 3 demonstrates how the streamline-wise currents can be visualized Together with the nodal potentials.

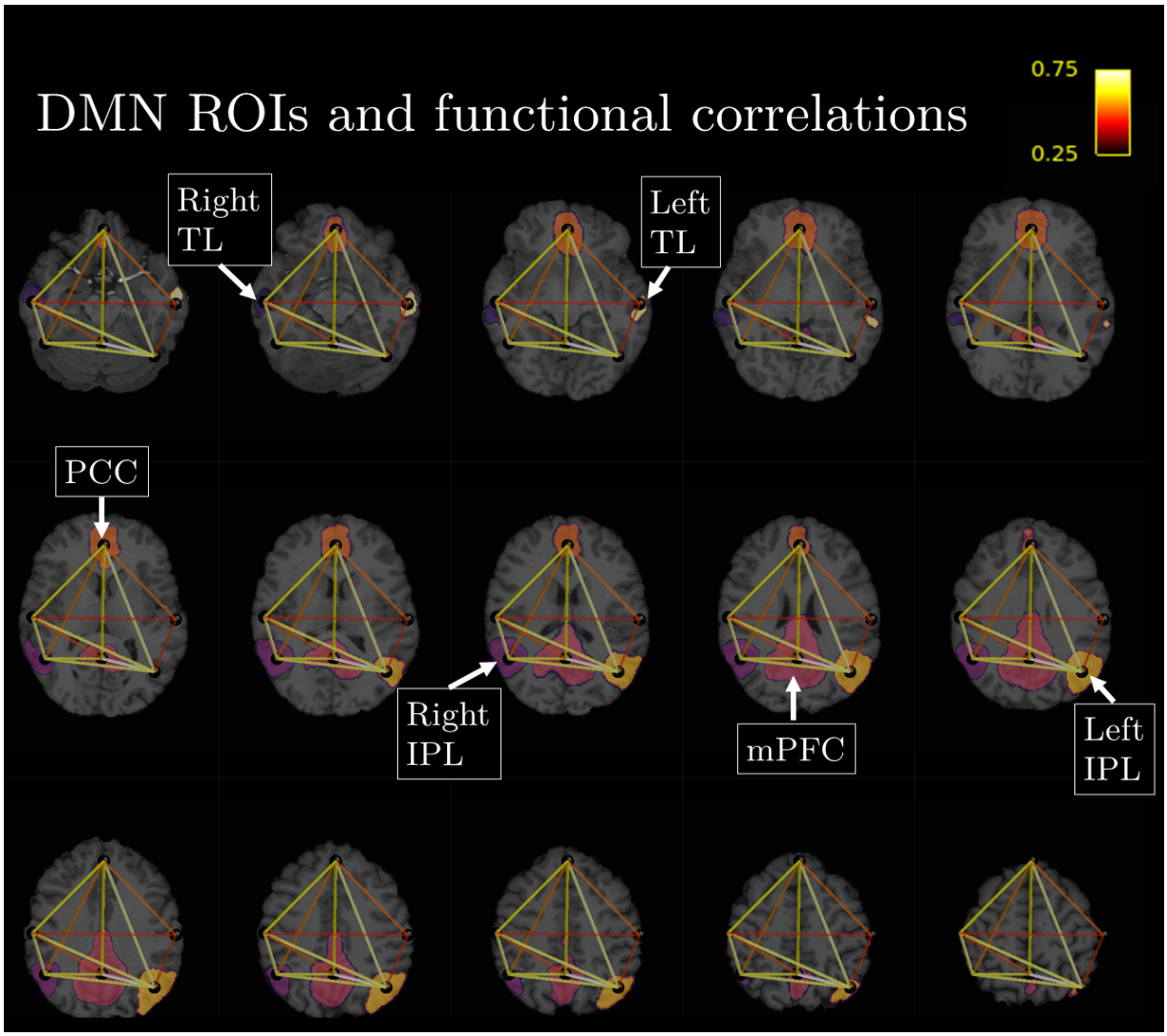

Figure 1: Visualization of the subject's Default Mode Network. The six regions of interest reflecting the network roughly are shown with different colours. The medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), left and right inferior parietal lobules (IPL), and left and right temporal lobes (TL). Respective functional network is depicted with a graph whose edge colour indicates functional correlations.

3.2 Ground-truth simulation

While the FiberCup phantom (Fillard et al., 2011; Poupon et al., 2010, 2008) can be seen as a simple toy example, it provides a known ground-truth structure that is simple enough to understand the results intuitively. The diffusion-weighted data of the phantom was appended with five functional subnetworks as shown in 4 A. The

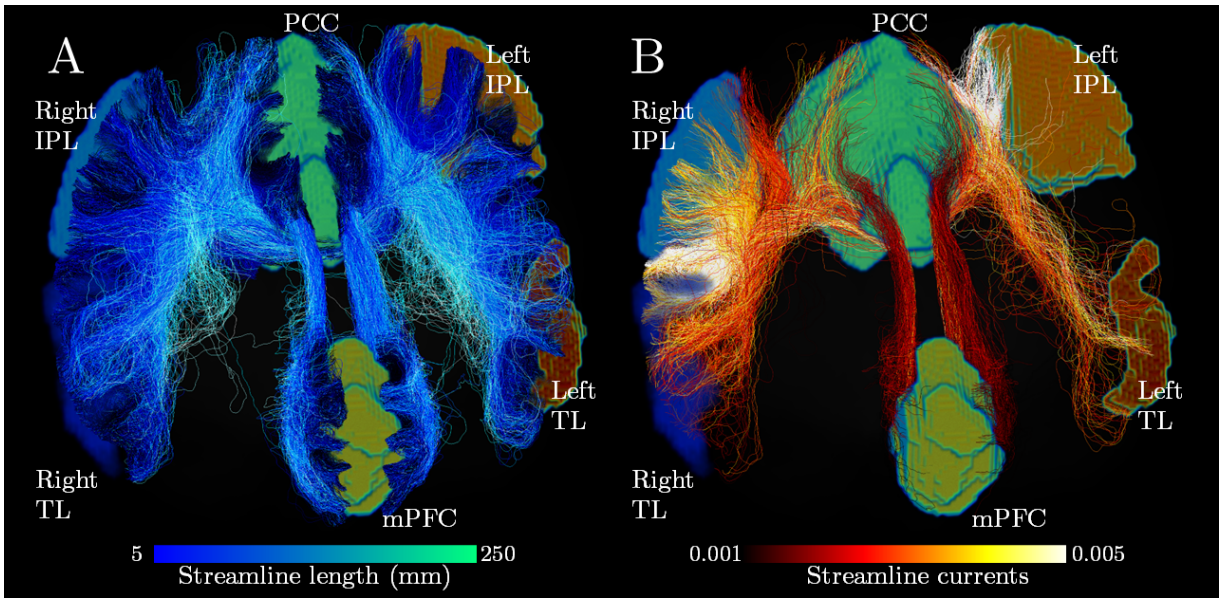

Figure 2: The proposed function-structure coupling can be used to filter tractograms. In this example, the default mode network defined by six brain regions PCC, mPFC, left and right IPL, and left and right TL is interconnected by the tractogram on the left (A). The blue-cyan colormap represents the length of the streamline in mm. By applying FSC (B), a notable amount of streamlines is pruned away as streamlines that do not carry meaningful current.

whole tractogram of the phantom is shown in figure 4 B with clearly all streamlines staying inside the phantom's 'white matter'.

Function-structure coupling was used to filter the whole tractogram in figure 4 C. As seen in the image, the unnecessary structural part of the phantom (in context of the simulated functional networks) is visibly missing from the results. This indicates that the algorithm can correctly detect which streamlines are necessary and optimal for the functional information flow.

A further analysis of the five functional subnetworks is shown in figure 5. All five subnetworks are identified correctly without any false-positive structural connections. Even the case of indirect connection via the opposite side of the phantom, the proposed algorithm correctly identifies the correct pathway.

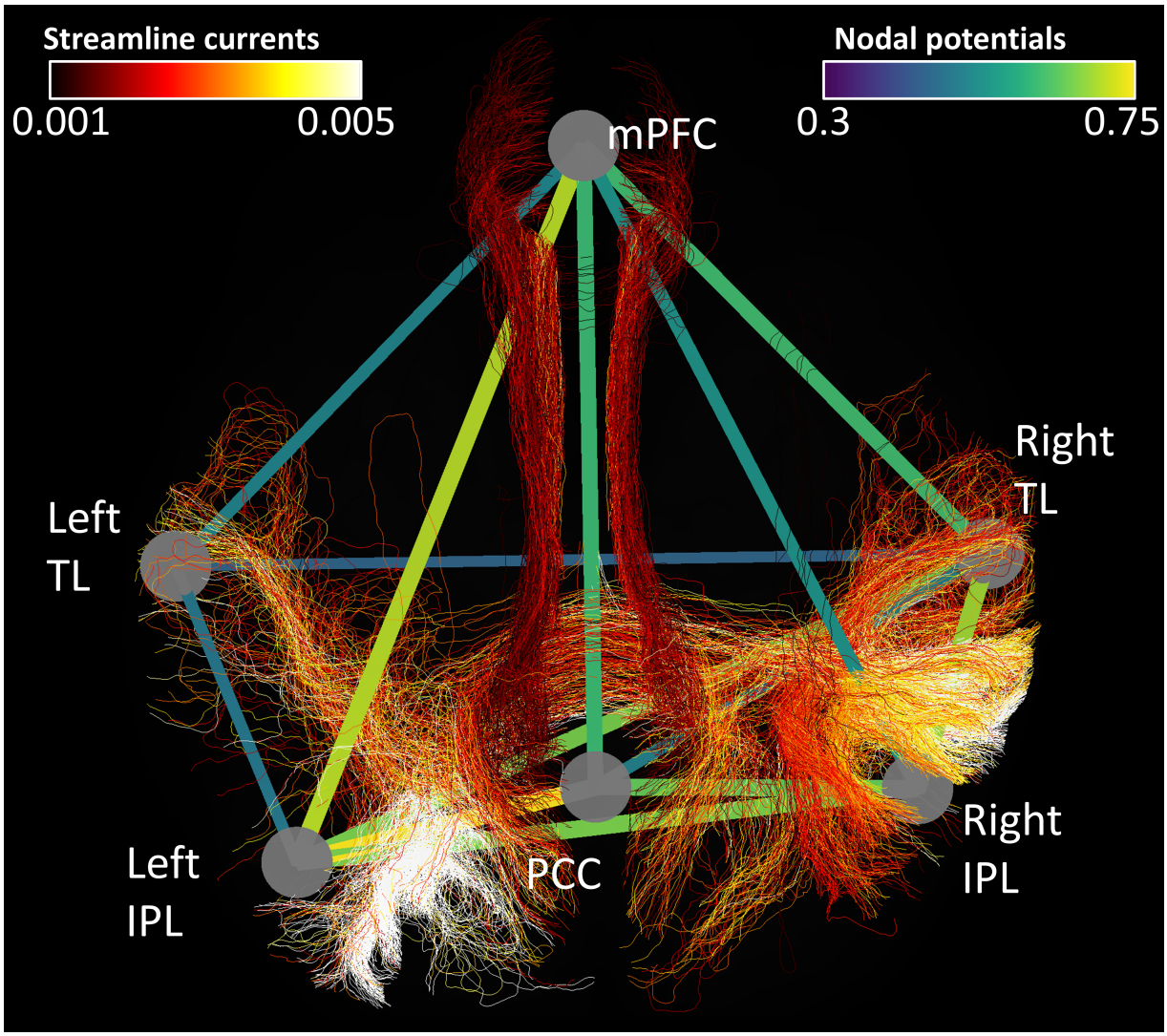

Figure 3: Obtained nodal voltages can be visualized together with the streamline-wise currents. In this example, subject's DMN is visualized by showing the nodal voltages as a graph with edges representing the voltage drop between each node. On top of this, a tractogram with streamlines colored by the streamline-wise currents. This type of visualization could be applied to any network and it is not limited to resting-state analyses.

3.3 General feasibility of the proposed method

Functional and structural connectivity matrices from 207 unrelated healthy adults from the Human Connectome Project (Van Essen et al., 2012) were used to calculate average functional and structural matrices using the ENIGMA Toolbox (Larivière

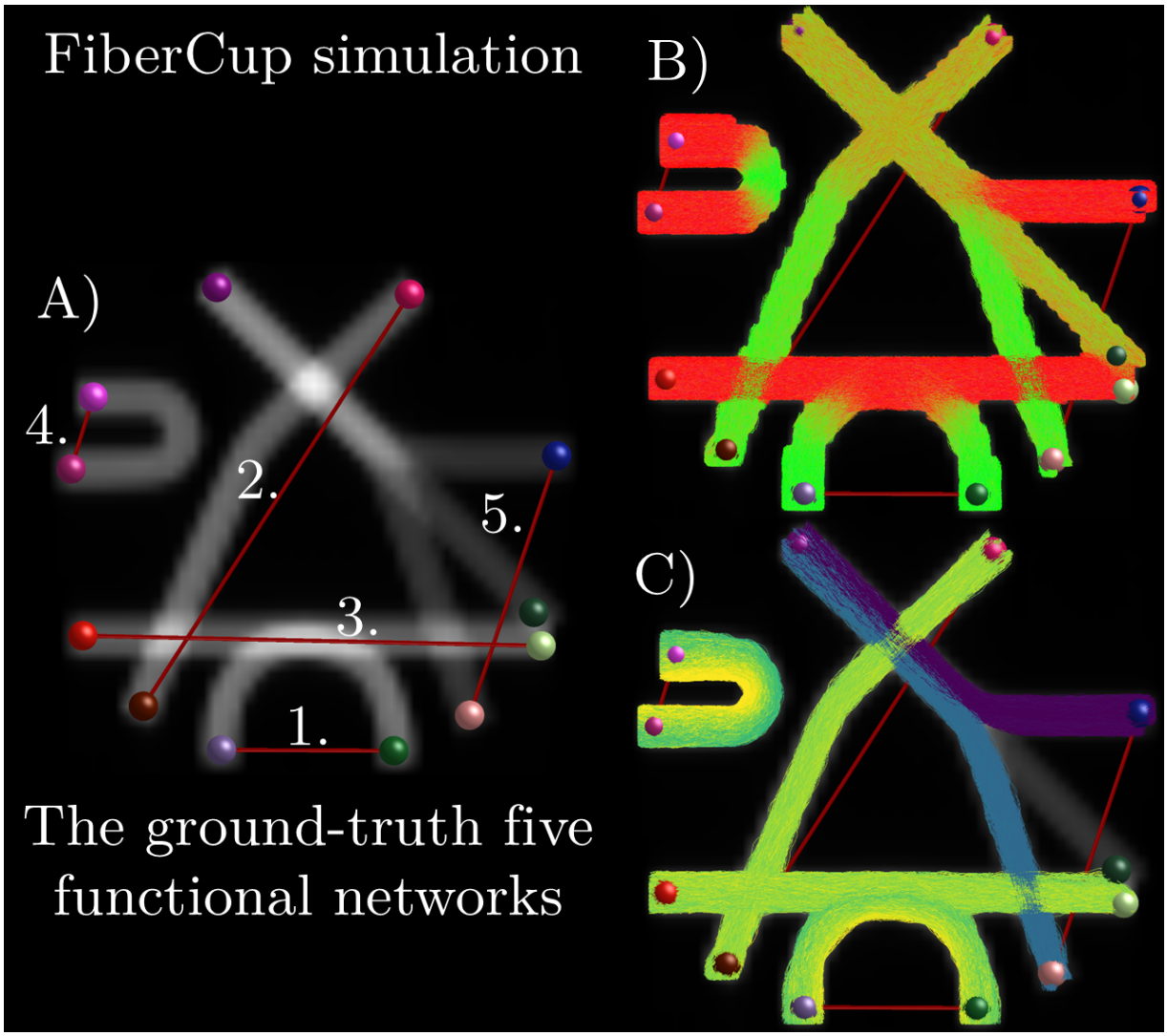

Figure 4: The ground-truth phantom simulation. A) The FiberCup phantom was separated into five simulated functional networks of which the fifth was an indirect connection i.e. there is no direct structural connection between the nodes. B) Whole tractogram of the phantom depicts the expected structure. C) The proposed method is used to filter the whole tractogram. The unnecessary structural part of the phantom is visibly missing from the results indicating that the algorithm can correctly detect which streamlines are necessary and optimal for the functional information flow.

et al., 2021). These average connectivity matrices were used to demonstrate the general feasibility of the proposed function-structure coupling.

In figure 6, the functional (red) and structural (blue) connectome are shown together with the resulting current (green) connectome. Notably, the novel connectome seem

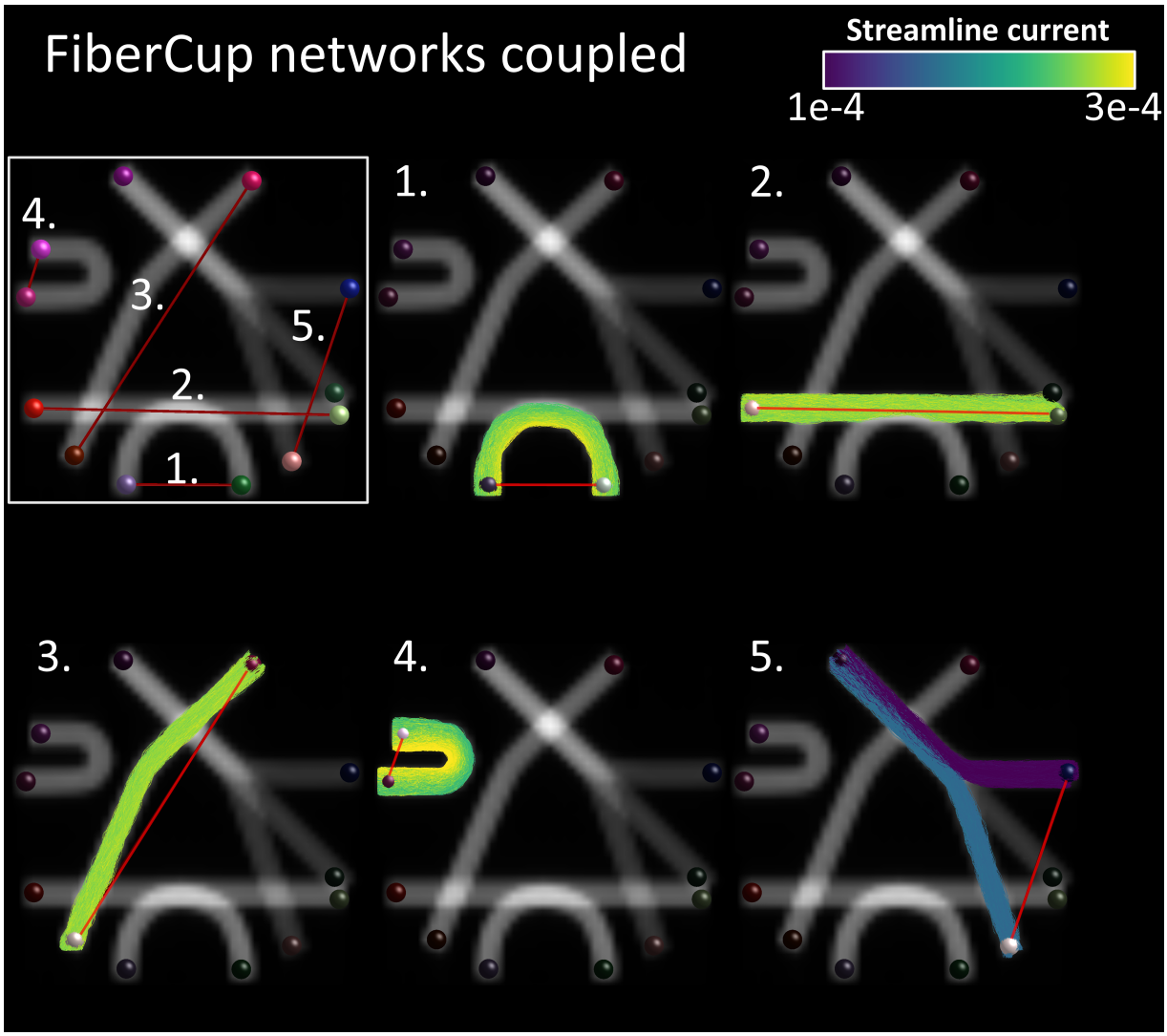

Figure 5: A further analysis of the five functional subnetworks in the ground-truth simulation. On the left top, the simulation setup is repeated. As seen in all subnetwork images, the proposed method correctly identifies the optimal pathway between any two nodes. Even the case with indirect connection via the opposite side of the phantom, the algorithm can find the connecting path. The color bar indicates the streamline-wise current which is notably smaller for the fifth subnetwork as the resistance in that network was higher due to longer travel path.

more sparse than either of other two. This could indicate, that many functional signals traverse via the same structural paths.

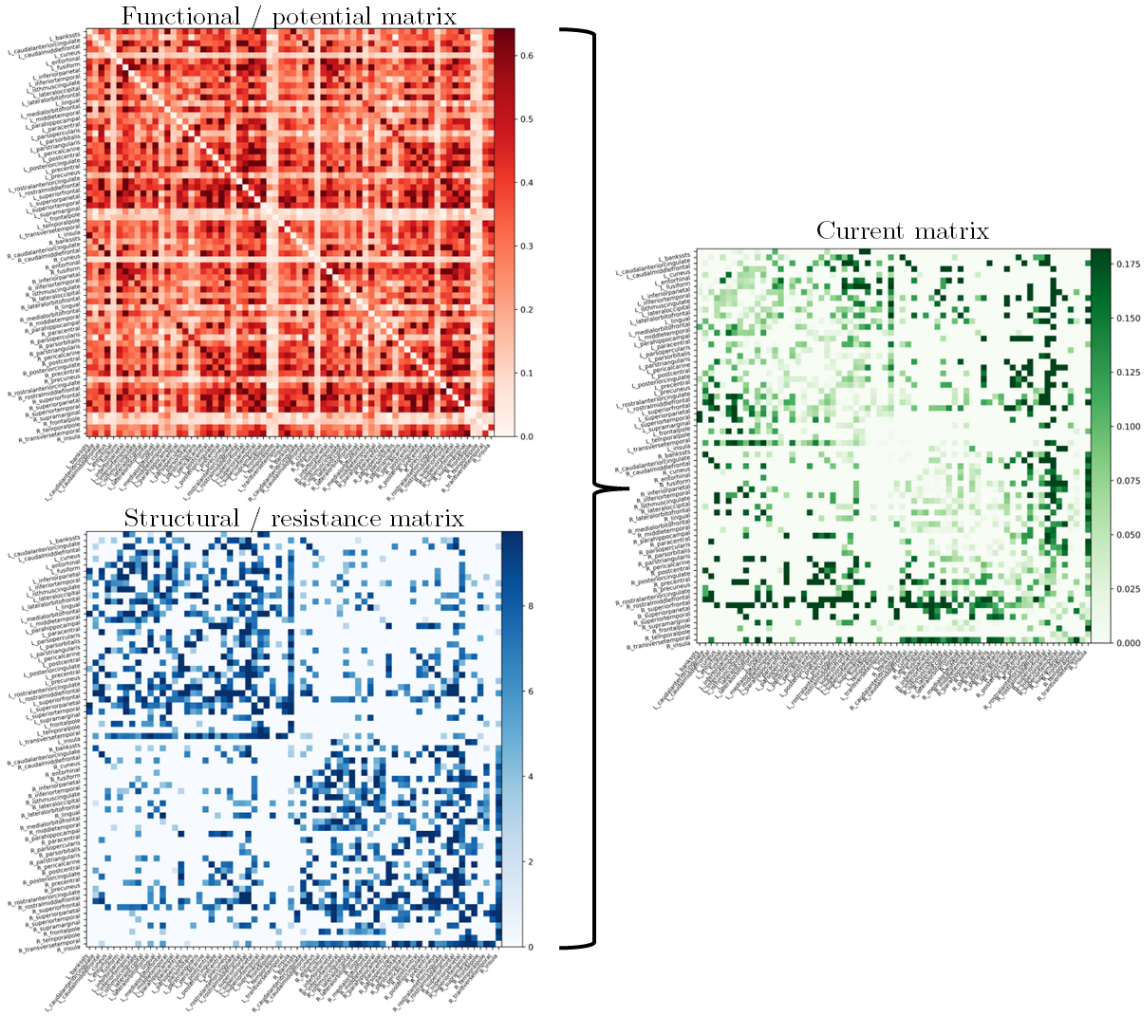

Figure 6: A new connectome 'contrast' can be produced by the proposed function-structure coupling method. Functional (red) and structural (blue) connectivity matrices can be used as a basis to calculate the corresponding current (green) connectome. This figure demonstrates that connectomes calculated from a large cohort can be studied with the proposed method.

4 Discussion

This study set out to investigate if an analysis method used to study electrical circuits (Modified Nodal Analysis, MNA) (Ho et al., 1975; Wedepohl and Jackson, 2002) could be used to study the macro-scale connectivity of the living human brain. While this can sound like an outrageously simplifying model for a such complex organ, the presented results indicate that this could be a 'good enough' approximation on the

global brain connectivity. Similar to the classical Hodkin-Huxley model (Hodgkin and Huxley, 1952) it is reasonable to assume that this model too needs to be adjusted for further accuracy.

At this point, the reader might think, so what? What is the benefit of this model?

The reader is very much right to ask this question as it baffles the author too. At this point, the author thinks that computational neuroscience community *might* benefit from this model. It answers to a question that has been asked in the community: how the functional and structural connectomes could be combined? (Greaves et al., 2025). While statistical correlations between the connectomes have been studied (Fotiadis et al., 2024) and multivariate regression methods have been used to find explanatory factors between the connectomes (Liu et al., 2022), these approaches do not explain the coupling between connectomes but only describes or summarizes them.

Additionally, as far as the author knows, this is the first time that MNA is applied to study the human brain networks. Therefore, it fills a gap in the scientific literature and if it turns out to be incorrect model, it can be seen as a negative finding in the end. At the very least, the proposed method seem to be capable of filtering tractograms.

In the future, the proposed method could be used to append tractogram filtering methods that rely solely on structural information (Sairanen et al., 2021; Smith et al., 2015). In this study, these tools were left out as a deliberate choice to keep the investigation focused on the proposed method and comparing all of the existing algorithms would be beyond the scope of this study. It is reasonable to assume that addition of functional information could improve on the existing methods but remains to be demonstrated.

If the proposed method is correct, visualizations such as figure 2 B or figure 3 could be used to study how various diseases or conditions alter the functional information flow in the human brain. For example, how might a lesion change the current flow? Could that explain why some patients are more affected by a lesion than others? Quite many research questions can arise from this.

The proposed function-structure coupling produces effectively an adjacency matrix, therefore many existing network analysis tools can be readily applied to study it further (Sporns, 2013). Similarly, existing tractography visualization tools can readily be applied to display the streamline-wise currents as shown in figure 3. The open source code provided as part of this study readily integrates with these tools that already exist in the computational neuroscience community.

To indulge the reader's imagination, the author speculates that in the future, the proposed method could be used to model effective connectivity i.e. to study causality in the brain (Friston, 2011). In this study, MNA terms dedicated to dependent current and voltage sources were omitted. However, the proposed algorithm can be easily modified to take them into account if seen useful. Imagine a video where streamline-wise currents indicate how the functional information propagates in the structural network firing new event after another.

Descending to reality, the proposed method is limited by all the inaccuracies and assumptions that affect the functional and structural connectivity analyses. As it is with all models, a new layer of analysis adds a layer of error propagation too. Therefore, this coupling method should be applied to data that has been acquired and processed with the best available methods for structural and functional connectivity analyses.

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 proof-of-concept study, it considers only data from healthy human brains and simulations with 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 function-structure coupling has a place in neuroscience.

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