

# BrainDiffusion: A Python package for brain anatomic connectivity matrix.

17 July 2023

## Summary

**BrainDiffusion** is a Python package for creating a weighted graph representing brain white-matter fiber tract connectivity between gray matter regions. Such graphs are commonly used in neuroimaging workflows. The code input is (1) a magnetic resonance (MR) T1 image; (2) an MR diffusion-tensor image (DTI); and (3) a brain parcellation, which segments the MR T1 image into regions of interest (ROIs). The code output is a directed graph with vertices as gray matter ROIs, and edge weights indicating inter-region connectivity strength. In contrast to traditional methods involving parameter tuning relating to denoising, fiber groupings, and resolving fiber intersections, **BrainDiffusion** uses a different approach. It solves an anisotropic partial differential equation (PDE) on the MR image space to construct an anatomical connectivity matrix. To find the edge weights between a vertex (source ROI) to the all the other vertices (target ROIs), the algorithm assigns a pseudo-concentration in the start ROI, solves a mass diffusion equation, and integrates the resulting concentration in the target ROIs. These per-ROI integrals are the edge weights. The graph weights are computed by repeating this step for each vertex. Notably, this technique does not reconstruct explicit fiber tracks; it only relies on MR DTI and parcellation data. The method requires  $O(m)$  PDE solves, where  $m$  is the number of parcels.

## Statement of need

Brain white-matter connectivity and graph-based representations have diverse applications in neuroscience and clinical neuroimaging, including mental health (Eickhoff, Yeo, and Genon 2018), oncology, functional connectivity analysis (Biswal et al. 1995), disease diagnosis and classification (Craddock et al. 2009), surgical planning (Potgieser et al. 2014), and population studies. Brain parcellation and graph abstraction are used as a means of compression, denoising, and summarization. Furthermore a brain’s adjacency matrix unveils complex ROI relationships, offering insights into behavior and cognition (Lang et al. 2012).

There are several software packages with comparable functionalities (Iturria-Medina et al. 2008; Lazar 2010; Tournier et al. 2019) to ours. But these techniques have some limitations. Streamline tractography methods construct anatomical fiber tracts, but this process may lead to curvature overshoot bias, termination bias (where streamlines halt in white matter), and connectivity density bias (resulting in inaccurate streamline count estimates) (Zhang et al. 2022). In our approach, streamlines are not explicitly constructed. Additionally, the proposed method circumvents streamline-to-node assignment challenges, a limitation associated with streamline-based approaches. Currently, tractography is unable to robustly trace fibers between and within multiple gray matter regions, resulting in unreliable connectome quantification (Yeh et al. 2021). The limitation of **BrainDiffusion** is that it does not explicitly reconstruct the fibers.

## Formulation and algorithm

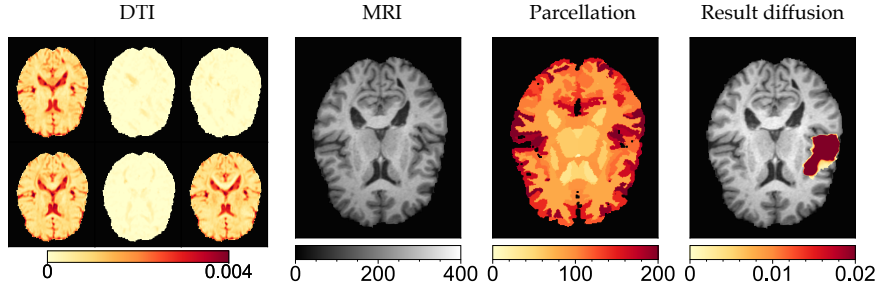


Figure 1: Data used in software. Our software employs key data components, depicted from left to right. We start with patient DTI data, informing diffusivity intensity across six directions per voxel. Then, we integrate Magnetic Resonance Imaging (MRI) data, segmenting the brain into white and gray matter. The brain parcellation forms a graph. Lastly, we illustrate a PDE solution with one ROI chosen as the edge-start, known as the “Result diffusion”.

Let  $\mathcal{B} \subset \mathbb{R}^3$  be the brain domain. Let  $\mathbf{x} \in \mathcal{B}$  denote a point. We denote  $\mathbf{c}(\mathbf{x}, t) \in [0, 1]$  as a pseudo-concentration at time  $t$ . We denote the source gray matter ROI by  $\mathcal{S} \subset \mathbb{R}^3$  and a target gray matter ROI as  $\mathcal{T} \subset \mathbb{R}^3$ . We use the concentration diffusion from  $\mathcal{S}$  to  $\mathcal{T}$  as a measure of the connectivity between  $\mathcal{S}$  and  $\mathcal{T}$ . The diffusion process is modeled by the following PDE:

$$\partial_t \mathbf{c} = \nabla \cdot (\mathbf{K}(\mathbf{x}) \nabla \mathbf{c}), \quad t \in (0, T], \quad (1a)$$

$$\mathbf{c}(\mathbf{x}, 0) = \begin{cases} 1 & \text{if } \mathbf{x} \in \mathcal{S} \\ 0 & \text{if } \mathbf{x} \in \mathcal{T}, \end{cases} \quad (1b)$$

$$\frac{\partial \mathbf{c}}{\partial n} = 0 \text{ on } \partial \mathcal{B}, \quad (1c)$$

where  $\mathbf{K}(\mathbf{x})$  is defined as

$$\mathbf{K}(\mathbf{x}) = \mathbf{D}(\mathbf{x})(\mathbf{m}_{\text{wm}} + \tilde{\alpha}\mathbf{m}_{\text{gm}}). \quad (2)$$

$\mathbf{D}(\mathbf{x})$  is a pointwise diffusion tensor which is extracted by the DTI,  $\mathbf{m}_{\text{wm}}$  and  $\mathbf{m}_{\text{gm}}$  are the segmentation mask of white matter and grey matter, and  $\tilde{\alpha} \in \mathbb{R}_+$  is the ratio between the diffusivity in the white matter over the gray matter. From the literature, we set  $\tilde{\alpha} = 10^{-2}$  (Giese et al. 1996). We solve the above PDE in the time period  $t \in [0, T]$ , where  $T$  is the time horizon. We set this time horizon to ensure the furthest edge-end region can always receive sufficient concentration. For the PDE solver, we use the Crank-Nicolson method for discretization in time in our solvers (Crank and Nicolson 1996). The spatial domain is discretized using a pseudo-spectral Fourier method (Gholami, Mang, and Biros 2016). The resulting linear system for the Crank-Nicolson method is solved using a matrix-free preconditioned Conjugate Gradient method. We present the input used in **BrainDiffusion** and the PDE output in Figure 1. The DTI, represented as  $\mathbf{D}(\mathbf{x})$ , provides information about diffusivity within the domain  $\mathcal{B}$ . The T1 MR image defines the white matter and gray matter regions. The brain parcellation operation establishes a graph structure, while the diffusion image serves as the solution to the aforementioned PDE, with one ROI being designated as the source region.

The construction of the graph adjacency matrix involves the following steps:

1. For each source ROI, we calculate the solution to the previously proposed PDE. This procedure is iteratively performed for all brain regions.
2. The concentration integral within each target ROI is computed for the resulting PDE solution with the following form

$$W_{ij} = \int_0^T \int_{\mathcal{T}_j} \mathbf{c}(\mathbf{x}, t) \mathbf{1}_{\{\mathbf{c} > \mathbf{c}_\infty\}} d\mathbf{x} dt. \quad (3)$$

Here,  $\mathcal{T}_j$  represents the volume region of the  $j$ th ROI.  $W_{ij}$  corresponds to the source  $\mathcal{S}$  for ROI  $i$ , and  $\mathbf{c}_\infty = \frac{1}{|\mathcal{B}|} \int_{\mathcal{S}} \mathbf{c}(\mathbf{x}, 0) d\mathbf{x}$  is the steady state ( $T = \infty$ ) solution for each voxel value.  $W_{ij}$  contributes to the off-diagonal weight in the adjacency matrix. We set the diagonal weight  $W_{ii} = \sum_{j \neq i} W_{ij}$ .

Our implementation requires GPU support and lacks a CPU version, with parallelization facilitated using Joblib. On a GPU card, we simultaneously solve four PDEs, enhancing computational efficiency and accelerating the graph construction process.

## Usage

**BrainDiffusion** requires GPUs and Python’s ‘cupy’. The package includes a main function file (‘BrainDiffusion/diffusion\_brain\_net.py’) and a utility file (‘BrainDiffusion/operators.py’). An example usage (‘example.py’) is also

provided. To effectively use the package, users should have processed DTI data and patient parcellation. A default dataset and parcellation are available in ‘example.py’. Users should keep the folder structure consistent with the example. For detailed installation, instructions, and testing, please refer to the package’s GitHub repository.

## References

- Biswal, Bharat, F Zerrin Yetkin, Victor M Haughton, and James S Hyde. 1995. “Functional Connectivity in the Motor Cortex of Resting Human Brain Using Echo-Planar MRI.” *Magnetic Resonance in Medicine* 34 (4): 537–41. <https://doi.org/https://doi.org/10.1002/mrm.1910340409>.
- Craddock, R Cameron, Paul E Holtzheimer III, Xiaoping P Hu, and Helen S Mayberg. 2009. “Disease State Prediction from Resting State Functional Connectivity.” *Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine* 62 (6): 1619–28. <https://doi.org/https://doi.org/10.1002/mrm.22159>.
- Crank, John, and Phyllis Nicolson. 1996. “A Practical Method for Numerical Evaluation of Solutions of Partial Differential Equations of the Heat-Conduction Type.” *Advances in Computational Mathematics* 6 (1): 207–26. <https://doi.org/https://doi.org/10.1007/BF02127704>.
- Eickhoff, Simon B, BT Thomas Yeo, and Sarah Genon. 2018. “Imaging-Based Parcellations of the Human Brain.” *Nature Reviews Neuroscience* 19 (11): 672–86. <https://doi.org/https://doi.org/10.1038/s41583-018-0071-7>.
- Gholami, Amir, Andreas Mang, and George Biros. 2016. “An Inverse Problem Formulation for Parameter Estimation of a Reaction–Diffusion Model of Low Grade Gliomas.” *Journal of Mathematical Biology* 72: 409–33. <https://doi.org/https://doi.org/10.1007/s00285-015-0888-x>.
- Giese, Alf, Lan Kluwe, Britta Laube, Hildegard Meissner, Michael E Berens, and Manfred Westphal. 1996. “Migration of Human Glioma Cells on Myelin.” *Neurosurgery* 38 (4): 755–64. <https://doi.org/10.1227/00006123-199604000-00026>.
- Iturria-Medina, Yasser, Roberto C Sotero, Erick J Canales-Rodriguez, Yasser Aleman-Gomez, and Lester Melie-Garcia. 2008. “Studying the Human Brain Anatomical Network via Diffusion-Weighted MRI and Graph Theory.” *Neuroimage* 40 (3): 1064–76. <https://doi.org/https://doi.org/10.1016/j.neuroimage.2007.10.060>.
- Lang, Elmar Wolfgang, Ana Maria Tome, Ingo R Keck, JM Gorriz-Saez, and Carlos Garcia Puntonet. 2012. “Brain Connectivity Analysis: A Short Survey.” *Computational Intelligence and Neuroscience* 2012: 8–8. <https://doi.org/https://doi.org/10.1155/2012/412512>.
- Lazar, Mariana. 2010. “Mapping Brain Anatomical Connectivity Using White Matter Tractography.” *NMR in Biomedicine* 23 (7): 821–35. <https://doi.org/https://doi.org/10.1002/nbm.1579>.
- Potgieser, Adriaan RE, Michiel Wagemakers, Arjen LJ van Hulzen, Bauke M de

- Jong, Eelco W Hoving, and Rob JM Groen. 2014. “The Role of Diffusion Tensor Imaging in Brain Tumor Surgery: A Review of the Literature.” *Clinical Neurology and Neurosurgery* 124: 51–58. <https://doi.org/https://doi.org/10.1016/j.clineuro.2014.06.009>.
- Tournier, J-Donald, Robert Smith, David Raffelt, Rami Tabbara, Thijs Dhollander, Maximilian Pietsch, Daan Christiaens, Ben Jeurissen, Chun-Hung Yeh, and Alan Connelly. 2019. “MRtrix3: A Fast, Flexible and Open Software Framework for Medical Image Processing and Visualisation.” *Neuroimage* 202: 116137. <https://doi.org/https://doi.org/10.1016/j.neuroimage.2019.116137>.
- Yeh, Chun-Hung, Derek K Jones, Xiaoyun Liang, Maxime Descoteaux, and Alan Connelly. 2021. “Mapping Structural Connectivity Using Diffusion MRI: Challenges and Opportunities.” *Journal of Magnetic Resonance Imaging* 53 (6): 1666–82. <https://doi.org/https://doi.org/10.1002/jmri.27188>.
- Zhang, Fan, Alessandro Daducci, Yong He, Simona Schiavi, Caio Seguin, Robert E Smith, Chun-Hung Yeh, Tengda Zhao, and Lauren J O’Donnell. 2022. “Quantitative Mapping of the Brain’s Structural Connectivity Using Diffusion MRI Tractography: A Review.” *Neuroimage* 249: 118870. <https://doi.org/https://doi.org/10.1016/j.neuroimage.2021.118870>.