Diffantom: whole-brain diffusion MRI phantoms derived from real datasets of the Human Connectome Project

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INTRODUCTION

Fiber tracking on diffusion MRI (dMRI) data has become an important tool for the in-vivo investigation of the structural configuration of fiber bundles at the macroscale. Tractography is fundamental to gain information about white matter (WM) morphology in many clinical applications like neurosurgical planning (Golby et al., 2011), post-surgery evaluations (Toda et al., 2014), and the study of neurological diseases as in (Chua et al., 2008) addressing multiple sclerosis and Alzheimer’s disease. The analysis of structural brain networks using graph theory is also applied on tractography, for instance in the definition of the unique subject-wise patterns of connectivity (Sporns et al., 2005), in the assessment of neurological diseases (Griffa et al., 2013), and in the study of the link between structural and functional connectivity (Messé et al., 2015). However, the development of the field is limited by the lack of a gold standard to test and compare the wide range of methodologies available for processing and analyzing dMRI.

Large efforts have been devoted to the development of physical phantoms (Lin et al., 2001; Campbell et al., 2005; Perrin et al., 2005; Fieremans et al., 2008; Tournier et al., 2008). Côté et al. (2013) conducted a thorough review of tractography methodologies using the so-called FiberCup phantom (Poupon et al., 2008; Fillard et al., 2011). These phantoms are appropriate to evaluate the angular resolution in fiber crossings and accuracy of direction-independent scalar parameters in very simplistic geometries. Digital simulations are increasingly popular because the complexity of whole-brain tractography can not be accounted for with current materials and proposed methodologies to build physical phantoms. Early digital phantoms started with simulation of simple geometries (Basser et al., 2000; Gössl et al., 2002; Tournier et al., 2002; Leemans et al., 2005) to evaluate the angular resolution as well. These tools generally implemented the multi-tensor model (Alexander et al., 2001; Tuch et al., 2002) to simulate fiber crossing, fanning, kissing,
etc. Close et al. (2009) presented the Numerical Fibre Generator, a software to simulate spherical shapes filled with digital fiber tracts. Caruyer et al. (2014) proposed Phantomas to simulate any kind of analytic geometry inside a sphere. Phantomas models diffusion by a restricted and a hindered compartment, similar to (Assaf and Basser, 2005). Wilkins et al. (2014) proposed a whole-brain simulated phantom derived from voxel-wise orientation of fibers averaged from real dMRI scans and the multi-tensor model with a compartment of isotropic diffusion. Neher et al. (2014) proposed FiberFox, a visualization software to develop complex geometries and their analytical description. Once the geometries are obtained, the software generates the corresponding dMRI signal with a methodology very close to that implemented in Phantomas. An interesting outcome of FiberFox is the phantom dataset1 created for the Tractography Challenge held in ISMRM 2015. This dataset was derived from the tractography extracted in one Human Connectome Project (HCP, Van Essen et al. (2012)) dataset. In the tractogram, 25 fiber bundles of interest were manually segmented by experts. Using FiberFox, the segmentation of each bundle was mapped to an analytical description, and finally simulated the signal.

In this data report we present Diffantom, an in-silico dataset to assess tractography and connectivity pipelines using dMRI real data as source microstructural information. Diffantom is inspired by the work of Wilkins et al. (2014), with two principal novelties. First, since we use a dataset from the HCP as input, data are already corrected for the most relevant distortions. The second improvement is a more advanced signal model to generate the phantom using the hindered and restricted diffusion model of Phantomas (Caruyer et al., 2014). As a result, we provide a whole-brain digital phantom of dMRI data with structural information derived from an HCP dataset. We also openly release the diffantomizer workflow, the software package necessary to generate custom diffantoms. Diffantom is originally designed for the investigation of susceptibility-derived distortions, a typical artifact that produces geometrical warping in certain regions of dMRI datasets. In (Esteban et al., 2014) we addressed this phenomenon and concluded that the connectivity matrix of Phantomas was not dense enough to evaluate the integration of correction methods in pipelines for the connectome extraction.

DATA DESCRIPTION

Microstructural model: The simulation process relies on a microstructural model derived from real data. On one hand, the diffantomizer workflow requires up to five fraction maps \( \{ T_j \mid j \in \{1, \ldots, 5\} \} \) of free- and hindered diffusion (see Figure 1, panel A). These compartments will be derived from the macroscopic structure of tissues within the brain, specified in the following order: cortical gray matter (cGM), deep gray matter (dGM), WM, cerebrospinal fluid (CSF), and abnormal tissue. On the other hand, the restricted-diffusion compartments are specified by up to three volume fractions \( \{ F_i \mid i \in \{1, 2, 3\} \} \) of three single fiber populations per voxel along with their corresponding direction maps \( \{ V_i \mid i \in \{1, 2, 3\} \} \).

The process to obtain the microstructural model from one dataset of the HCP can be described as follows (see also Figure 1, panel B): 1) The fiber orientation maps \( \{ V_i \} \) and their corresponding estimations of volume fraction \( \{ F_i \} \) are obtained using the ball-and-stick model for multi-shell data of BEDPOSTX (Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques modelling crossing –X– fibres, Jbabdi et al. (2012)) on the dMRI data. The HCP recommends BEDPOSTX to reconstruct their data (Glasser et al., 2013). A further advantage is that BEDPOSTX exploits the multi-shell acquisitions of the HCP while operating at whole-brain level. 2) A fractional anisotropy (FA) map is obtained after fitting

\[ \frac{1}{2} \text{ Available at} \ http://www.tractometer.org/ismrm_2015_challenge/ \]

\[ 2 \text{ Corresponding to the STT format established with the latest version 3.0 of MRTrix (Tournier et al., 2012)} \]

\[ 3 \text{ Since here we simulate healthy subjects, the last fraction map } T_5 \text{ is empty and can be omitted} \]
Diffantoms (Caruyer et al., 2014) and the final dMRI signal is obtained. By default, diffusion data are generated using a scheme of 100 directions distributed in one shell with uniform coverage (Caruyer et al., 2013). Custom one- or multi-shell schemes can be generated supplying the tables of corresponding vectors and $b$-values. Rician noise is also included in Phantomas, and the signal-to-noise ratio (SNR) can be set by the user. The default value for SNR is preset to 30.0.

**Implementation and reproducibility:** We also provide the diffantomizer workflow, the software package used to generate diffantoms, so that users can regenerate similar datasets with different parameters. This workflow, presented in Figure 1, is implemented using nipype (Gorgolewski et al., 2011) to ensure reproducibility and usability.

**Interpretation and recommended uses:** To illustrate the features of Diffantom, the example dataset underwent a simplified connectivity pipeline including constrained spherical deconvolution (CSD) and probabilistic tractography from MRTrix (Tournier et al., 2012). CSD was reconstructed using 8th-order spherical harmonics, and tractography with $1.6 \cdot 10^6$ seed points evenly distributed across a dilated mask of the WM tissue. Figure 2, panels A1 and A3, show the result of the tractography obtained with such pipeline for the original Diffantom and a distorted version. Finally, we applied tract querier (Wassermann et al., 2013) to segment some fiber bundles such as the corticospinal tract (CST) and the forceps minor (see Figure 2, panels A2, A4). Particularly, due to its location nearby the orbitofrontal lobe, the forceps minor is generally affected by susceptibility distortions.

We recommend Diffantom as ground-truth in verification and validation frameworks (Figure 2, panel B) for testing pipelines. Diffantom is applicable in the unit testing of algorithms, the integration testing of modules in workflows, and the overall system testing. Some potential applications follow:

- Investigating the impact of different diffusion sampling schemes on the local microstructure model of choice and on the subsequent global tractography outcome. Since the gradient scheme can be set by
the user, Diffantom can be seen as a mean to translate the so-called \emph{b-matrix} of the source dataset to any target scheme.

\begin{itemize}
  \item Assessment of sensitivity and robustness to imaging artifacts (noise, partial volume effect and CSF contamination, susceptibility-derived warping, Eddy-currents-derived distortions, etc.) at unit, integration and systems testing levels.
  \item Using Diffantom as in panel B of Figure 2, it is possible to apply binary classification measures to evaluate the resulting connectivity matrix. Considering the connectivity matrix of the reference Diffantom and the resulting matrix of the test Diffantom, the receiver operating characteristic (ROC) of the pipeline can be characterized.
  \item Simulation of pathological brains by altering the microstructural model accordingly (e.g. as tumors were simulated in Kaus et al. (2000)).
\end{itemize}

In order to exemplify one of these intended uses, we also release a Diffantom including the susceptibility-derived distortion in simulation.

**DISCUSSION AND CONCLUSION**

\emph{Discussion}: Whole-brain, realistic dMRI phantoms are necessary in the developing field of structural connectomics. Diffantom is a derivative of (Wilkins et al., 2014) in terms of methodology for simulation with two major advances. First, the correctness of the \emph{minimally preprocessed} data (Glasser et al., 2013) released within the HCP, Wilkins et al. (2014) explicitly state that their original data were not corrected for certain artifacts, and thus, generated data are affected correspondingly. Second, Diffantom implements the hindered and restricted compartments model (Assaf and Basser, 2005), which is a more complete model than the multi-tensor diffusion model.

A possible competitor to Diffantom is the phantom generated for the Tractography Challenge in ISMRM 2015. Similarly to Diffantom, the organizers used an HCP subject as source of structural information. While this phantom is designed for the bundle-wise evaluation of tractography (with the scores defined in the Tractometer (Côté et al., 2013), such as geometrical coverage, valid connections, invalid connections, missed connections, etc.), Diffantom is intended for the connectome-wise evaluation of results, yielding a tractography with a large number of bundles. Therefore, Diffantom and FiberFox are complementary as the hypotheses that can be investigated are different. Moreover, Diffantom does not require costly manual segmentation of bundles, highly demanding in terms of physiology expertise and operation time.

The software workflow released with this data report (the \emph{diffantomizer}) ensures the reproducibility of Diffantom and enables the generation of custom \emph{diffantoms}. The \emph{diffantomizer} is designed for, but not limited to, use HCP datasets as source of structural information.

\emph{Conclusion}: Diffantom is a whole-brain digital phantom generated from a dataset from the Human Connectome Project. Diffantom is presented here to be openly and freely distributed along with The \emph{diffantomizer} workflow to generate new \emph{diffantoms}. We encourage the neuroimage community to contribute with their own \emph{diffantoms} and share them openly.

**DATA SHARING**

The first Diffantom and its distorted version are available under the Creative Commons Zero licence (CC0) using the Dryad Digital Repository (reference here when published). The package is organized following the BIDS (Brain Imaging Data Structure, Gorgolewski et al. (2015)) standard. The associated software to
“diffantomize” real dMRI datasets is available at https://github.com/oesteban/diffantom under an MIT license. Phantomas is available in https://github.com/ecaruyer/Phantomas under the revised-BSD license.

DISCLOSURE

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed to this study. OE designed the data generation procedure, implemented the processing pipelines and generated the example dataset. EC implemented Phantomas (Caruyer et al., 2014), helped integrate the project with the simulation routines. OE, EC, AD thoroughly discussed and framed the aptness of the data in the community. AD, MBC, MJLC, and AS interpreted the resulting datasets. MBC, MJLC, and AS advised on all aspects of the study.

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APPENDIX

Let \( \{ T'_j \} \) be the set of original fractions maps obtained with `act_anat_prepare_fsl`, a tool in \texttt{MRTrix} that combines FAST (FMRIB’s Automated Segmentation Tool, Zhang et al. (2001)) and FIRST (FMRIB’s Integrated Registration and Segmentation Tool, Patenaude et al. (2011)) to generate the macrostructural 5TT map. FA denotes the fractional anisotropy (FA) map obtained from the original diffusion MRI (dMRI) data: the local fiber orientation maps \( \{ V_i \} \) with their estimated volume fractions \( \{ F'_i \} \) calculated with \texttt{BEDPOSTX} (Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques modelling crossing –X– fibres, Jbabdi et al. (2012)). The final \( \{ T_j \} \) maps of isotropic fractions are computed as follows:

\[
egin{align*}
T_1 &= (1.0 - f_{cgm}) \cdot T'_1 \\
T_2 &= (1.0 - f_{dgm}) \cdot T'_2 \\
T_3 &= (1.0 - f_{wm}) \cdot T'_3 \\
T_4 &= T'_4 \\
T_5 &= 0.0
\end{align*}
\]

where \( f_{\{cgm,dgm,wm\}} \) are the fractions of restricted diffusion for each tissue. Sepehrband et al. (2015) found out that the fiber fraction ranges across the corpus callosum from the 70±8% in its body to an upper bound of 80±11% in the splenium. Therefore, we choose \( f_{wm} = 80\% \) as default fraction of restricted diffusion in the white matter (WM). To our knowledge, restricted diffusion fractions have been studied only for WM. Therefore, we set \( f_{cgm} = 25\% \) and \( f_{dgm} = 50\% \) as they yield plausible FA and anisotropic diffusion coefficient (ADC) maps, assessed visually. The final \( \{ F_i \} \) maps are computed as follows:

\[
egin{align*}
F_1 &= f_{wm} \cdot T_2 \cdot FA + w_{f1}(f_{cgm} \cdot T_1 + f_{dgm} \cdot T_2) \\
F_2 &= f_{wm} \cdot T_2 - (F_1 + F_3) + w_{f2}(f_{cgm} \cdot T_1 + f_{dgm} \cdot T_2) \\
F_3 &= f_{wm} \cdot F'_3 + w_{f3}(f_{cgm} \cdot T_1 + f_{dgm} \cdot T_2)
\end{align*}
\]

where \( w_{\{f1,f2,f3\}} \) are the contributions of the gray matter (GM) compartments to each fiber population. By default: \( w_{f1} = 48\% \), \( w_{f2} = 37\% \), \( w_{f3} = 15\% \). Finally, the resulting maps are normalized to fulfill \( \sum_j T_j + \sum_i F_i = 1.0 \).
FIGURES
Figure 1. A. Microstructural model of Diffantom. The phantom is simulated from an underlying microstructural model specified with the following volume-fraction maps: three hindered-diffusion compartments \( \{T_1, T_2, T_3\} \), one free-diffusion compartment \( T_4 \) corresponding to the cerebrospinal fluid (CSF), three restricted-diffusion compartments \( \{F_i\} \), and three vectorial maps associated with the local fiber directions \( \{V_i\} \). Please note the piece-wise linear function of the color scale to enable visibility of small volume fractions. B. The diffantomizer workflow, a workflow to generate diffantoms. The pipeline to generate phantoms from any Human Connectome Project (HCP, Van Essen et al. (2012)) dataset is presented in the lower panel. Once the microstructural model shown in the upper panel has been prepared as described in Data description, the local orientations are computed and fed into Phantomas to finally simulate the signal.
Figure 2. A. Example dataset. A1 and A3 show the tractogram of fibers crossing slice 56 of Diffantom as extracted with MRTrix, represented over the corresponding slice of the $b0$ volume for the original (A1) and the distorted (A3) phantoms, with a gray frame highlighting the absence of important tracks. Panels A2 and A4 show the segmentation of the right corticospinal tract (CST) represented with blue streamlines, the left CST (red streamlines), and the forceps minor (green streamlines) using tract_querier. A2 and A4 include the slice 56 of the $b0$ and the pial surface is represented with transparency. In the distorted Diffantom (A4) the forceps minor was not detected. B. Recommended use of Diffantom. The phantom is designed to be used as ground-truth information in evaluation frameworks, to implement unit test of algorithms, to check integration of processing units within pipelines or to validate complete workflows. For instance, in order to evaluate artifacts, a perturbation can be induced in the microstructural model or after simulation to provide reference and test datasets.