



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

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INTRODUCTION

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

11 Large efforts have been devoted to the development of physical phantoms (Lin et al., 2001; Campbell
12 et al., 2005; Perrin et al., 2005; Fieremans et al., 2008; Tournier et al., 2008). Côté et al. (2013) conducted a
13 thorough review of tractography methodologies using the so-called *FiberCup* phantom (Poupon et al., 2008;
14 Fillard et al., 2011). These phantoms are appropriate to evaluate the angular resolution in fiber crossings
15 and accuracy of direction-independent scalar parameters in very simplistic geometries. Digital simulations
16 are increasingly popular because the complexity of whole-brain tractography can not be accounted for
17 with current materials and proposed methodologies to build physical phantoms. Early digital phantoms
18 started with simulation of simple geometries (Basser et al., 2000; Gössl et al., 2002; Tournier et al., 2002;
19 Leemans et al., 2005) to evaluate the angular resolution as well. These tools generally implemented the
20 multi-tensor model (Alexander et al., 2001; Tuch et al., 2002) to simulate fiber crossing, fanning, kissing,

21 etc. Close et al. (2009) presented the *Numerical Fibre Generator*, a software to simulate spherical shapes
22 filled with digital fiber tracts. Caruyer et al. (2014) proposed *Phantomas* to simulate any kind of analytic
23 geometry inside a sphere. *Phantomas* models diffusion by a restricted and a hindered compartment, similar
24 to (Assaf and Basser, 2005). Wilkins et al. (2014) proposed a whole-brain simulated phantom derived
25 from voxel-wise orientation of fibers averaged from real dMRI scans and the multi-tensor model with
26 a compartment of isotropic diffusion. Neher et al. (2014) proposed *FiberFox*, a visualization software
27 to develop complex geometries and their analytical description. Once the geometries are obtained, the
28 software generates the corresponding dMRI signal with a methodology very close to that implemented
29 in *Phantomas*. An interesting outcome of *FiberFox* is the phantom dataset¹ created for the Tractography
30 Challenge held in ISMRM 2015. This dataset was derived from the tractography extracted in one Human
31 Connectome Project (HCP, Van Essen et al. (2012)) dataset. In the tractogram, 25 fiber bundles of interest
32 were manually segmented by experts. Using *FiberFox*, the segmentation of each bundle was mapped to an
33 analytical description, and finally simulated the signal.

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

DATA DESCRIPTION

46 **Microstructural model:** The simulation process relies on a microstructural model derived from real data.
47 On one hand, the *diffantomizer* workflow requires up to five fraction maps $\{T_j \mid j \in \{1, \dots, 5\}\}$ of free-
48 and hindered- diffusion (see Figure 1, panel A). These compartments will be derived from the macroscopic
49 structure of tissues within the brain, specified in the following order²: cortical gray matter (cGM), deep
50 gray matter (dGM), WM, cerebrospinal fluid (CSF), and abnormal tissue³. On the other hand, the restricted-
51 diffusion compartments are specified by up to three volume fractions $\{F_i \mid i \in \{1, 2, 3\}\}$ of three single
52 fiber populations per voxel along with their corresponding direction maps $\{\mathbf{V}_i \mid i \in \{1, 2, 3\}\}$.

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

¹ Available at http://www.tractometer.org/ismrm_2015_challenge/

² Corresponding to the *5TT format* established with the latest version 3.0 of *MRTrix* (Tournier et al., 2012)

³ Since here we simulate healthy subjects, the last fraction map T_5 is empty and can be omitted

60 a tensor model with *MRTrix*. As we shall see in the Appendix, the FA is used to infer F_1 (the fraction map
61 of the most prevalent fiber), avoiding the extremely noisy estimation of F'_1 performed by BEDPOSTX in
62 the previous step. 3) The original fiber fractions $\{F'_i\}$ and the FA map are denoised with a nonlocal means
63 filter included in *dipy* (Garyfallidis et al., 2014). This step produces an important smoothing of the maps,
64 while preserving the edges. Smoothing is also beneficial in simplifying the voxel-wise diffusion model. 4)
65 The macrostructural fractions $\{T'_j\}$ are extracted from the T1-weighted image of the dataset, using standard
66 *FSL* segmentation tools (Jenkinson et al., 2012). 5) The images obtained previously (FA map, $\{V_i\}$, $\{F'_i\}$,
67 and $\{T'_j\}$) are combined as described in the Appendix to generate the final microstructural model ($\{V_i\}$,
68 $\{F_i\}$, and $\{T_j\}$), presented in Figure 1-A.

69 **Diffusion signal generation:** Once a microstructural model of the subject has been synthesized, the fiber
70 orientation maps $\{V_i\}$ are weighted by the fiber-fraction maps $\{F_i\}$ and projected onto a continuous
71 representation of the fiber orientation distributions (FODs). A close-up showing how the FODs map looks
72 is presented in Figure 1B. The single fiber response is a Gaussian diffusion tensor with axial symmetry
73 and eigenvalues $\lambda_1 = 2.2 \cdot 10^{-3} \text{ mm}^2\text{s}^{-1}$ and $\lambda_{2,3} = 0.2 \cdot 10^{-3} \text{ mm}^2\text{s}^{-1}$. The resulting FODs map is then
74 combined with the free- and hindered-diffusion compartments corresponding to $\{T_j\}$. The free-diffusion
75 compartment corresponds to the CSF fraction map T_4 and is modeled with isotropic diffusivity D_{CSF} of
76 $3.0 \cdot 10^{-3} \text{ mm}^2\text{s}^{-1}$. The hindered-diffusion compartments correspond to $\{T_1, T_2, T_3\}$ and are also modeled
77 with isotropic diffusivity $D_{WM} = 2.0 \cdot 10^{-4}$, $D_{cGM} = 7.0 \cdot 10^{-4}$ and $D_{dGM} = 9.0 \cdot 10^{-4}$, respectively
78 [mm^2s^{-1}]. All these values for diffusivity (and the corresponding to the single-fiber response) can be
79 modified by the user with custom settings. The restricted- and hindered- compartments are then fed into
80 *Phantom*s (Caruyer et al., 2014) and the final dMRI signal is obtained. By default, diffusion data are
81 generated using a scheme of 100 directions distributed in one shell with uniform coverage (Caruyer et al.,
82 2013). Custom one- or multi-shell schemes can be generated supplying the tables of corresponding vectors
83 and b -values. Rician noise is also included in *Phantom*s, and the signal-to-noise ratio (SNR) can be set by
84 the user. The default value for SNR is preset to 30.0.

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

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

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

- 101 • Investigating the impact of different diffusion sampling schemes on the local microstructure model of
102 choice and on the subsequent global tractography outcome. Since the gradient scheme can be set by

- 103 the user, *Diffantom* can be seen as a mean to translate the so-called *b-matrix* of the source dataset to
104 any target scheme.
- 105 • Assessment of sensitivity and robustness to imaging artifacts (noise, partial volume effect and
106 CSF contamination, susceptibility-derived warping, Eddy-currents-derived distortions, etc.) at unit,
107 integration and systems testing levels.
 - 108 • Using *Diffantom* as in panel B of Figure 2, it is possible to apply binary classification measures
109 to evaluate the resulting connectivity matrix. Considering the connectivity matrix of the *reference*
110 *Diffantom* and the resulting matrix of the *test Diffantom*, the receiver operating characteristic (ROC) of
111 the pipeline can be characterized.
 - 112 • Simulation of pathological brains by altering the microstructural model accordingly (e.g. as tumors
113 were simulated in Kaus et al. (2000)).
- 114 In order to exemplify one of these intended uses, we also release a *Diffantom* including the susceptibility-
115 derived distortion in simulation.

DISCUSSION AND CONCLUSION

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

123 A possible competitor to *Diffantom* is the phantom generated for the Tractography Challenge in ISMRM
124 2015. Similarly to *Diffantom*, the organizers used an HCP subject as source of structural information.
125 While this phantom is designed for the bundle-wise evaluation of tractography (with the scores defined in
126 the *Tractometer* (Côté et al., 2013), such as geometrical coverage, valid connections, invalid connections,
127 missed connections, etc.), *Diffantom* is intended for the connectome-wise evaluation of results, yielding
128 a tractography with a large number of bundles. Therefore, *Diffantom* and *FiberFox* are complementary
129 as the hypotheses that can be investigated are different. Moreover, *Diffantom* does not require costly
130 manual segmentation of bundles, highly demanding in terms of physiology expertise and operation time.
131 The software workflow released with this data report (the *diffantomizer*) ensures the reproducibility of
132 *Diffantom* and enables the generation of custom *diffantoms*. The *diffantomizer* is designed for, but not
133 limited to, use HCP datasets as source of structural information.

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

DATA SHARING

138 The first *Diffantom* and its distorted version are available under the Creative Commons Zero licence (CC0)
139 using the Dryad Digital Repository ([reference here when published](#)). The package is organized following
140 the BIDS (Brain Imaging Data Structure, Gorgolewski et al. (2015)) standard. The associated software to

141 “diffantomize” real dMRI datasets is available at <https://github.com/oesteban/diffantom>
142 under an MIT license. *Phantomas* is available in <https://github.com/ecaruyer/Phantomas>
143 under the revised-BSD license.

DISCLOSURE

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

AUTHOR CONTRIBUTIONS

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

ACKNOWLEDGMENTS

151 We thank Gert Wollny for his revision of this work. *Funding*: This study was supported by the
152 Spanish Ministry of Science and Innovation (projects TEC-2013-48251-C2-2-R and INNPACTO XIORT),
153 Comunidad de Madrid (TOPUS) and European Regional Development Funds, the Center for Biomedical
154 Imaging (CIBM) of the Geneva and Lausanne Universities and the EPFL, as well as the Leenaards and
155 Louis Jeantet Foundations.

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APPENDIX

156 Let $\{T'_j\}$ be the set of original fractions maps obtained with `act_anat_prepare_fsl`, a tool in *MRTrix*
157 that combines FAST (FMRIB's Automated Segmentation Tool, Zhang et al. (2001)) and FIRST (FMRIB's
158 Integrated Registration and Segmentation Tool, Patenaude et al. (2011)) to generate the macrostructural
159 5TT map. FA denotes the fractional anisotropy (FA) map obtained from the original diffusion MRI (dMRI)
160 data: the local fiber orientation maps $\{\mathbf{V}_i\}$ with their estimated volume fractions $\{F'_i\}$ calculated with
161 BEDPOSTX (Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques modelling
162 crossing –X– fibres, Jbabdi et al. (2012)). The final $\{T_j\}$ maps of isotropic fractions are computed as
163 follows:

$$T_1 = (1.0 - f_{cgm}) \cdot T'_1$$

$$T_2 = (1.0 - f_{dgm}) \cdot T'_2$$

$$T_3 = (1.0 - f_{wm}) \cdot T'_3$$

$$T_4 = T'_4$$

$$T_5 = 0.0$$

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

$$F_1 = f_{wm} \cdot T_2 \cdot \text{FA} + w_{f1}(f_{cgm} \cdot T_1 + f_{dgm} \cdot T_2)$$

$$F_2 = f_{wm} \cdot T_2 - (F_1 + F_3) + w_{f2}(f_{cgm} \cdot T_1 + f_{dgm} \cdot T_2)$$

$$F_3 = f_{wm} \cdot F'_3 + w_{f3}(f_{cgm} \cdot T_1 + f_{dgm} \cdot T_2)$$

170 where $w_{\{f1,f2,f3\}}$ are the contributions of the gray matter (GM) compartments to each fiber population.
171 By default: $w_{f1} = 48\%$, $w_{f2} = 37\%$, $w_{f3} = 15\%$. Finally, the resulting maps are normalized to fulfill
172 $\sum_j T_j + \sum_i F_i = 1.0$.

FIGURES

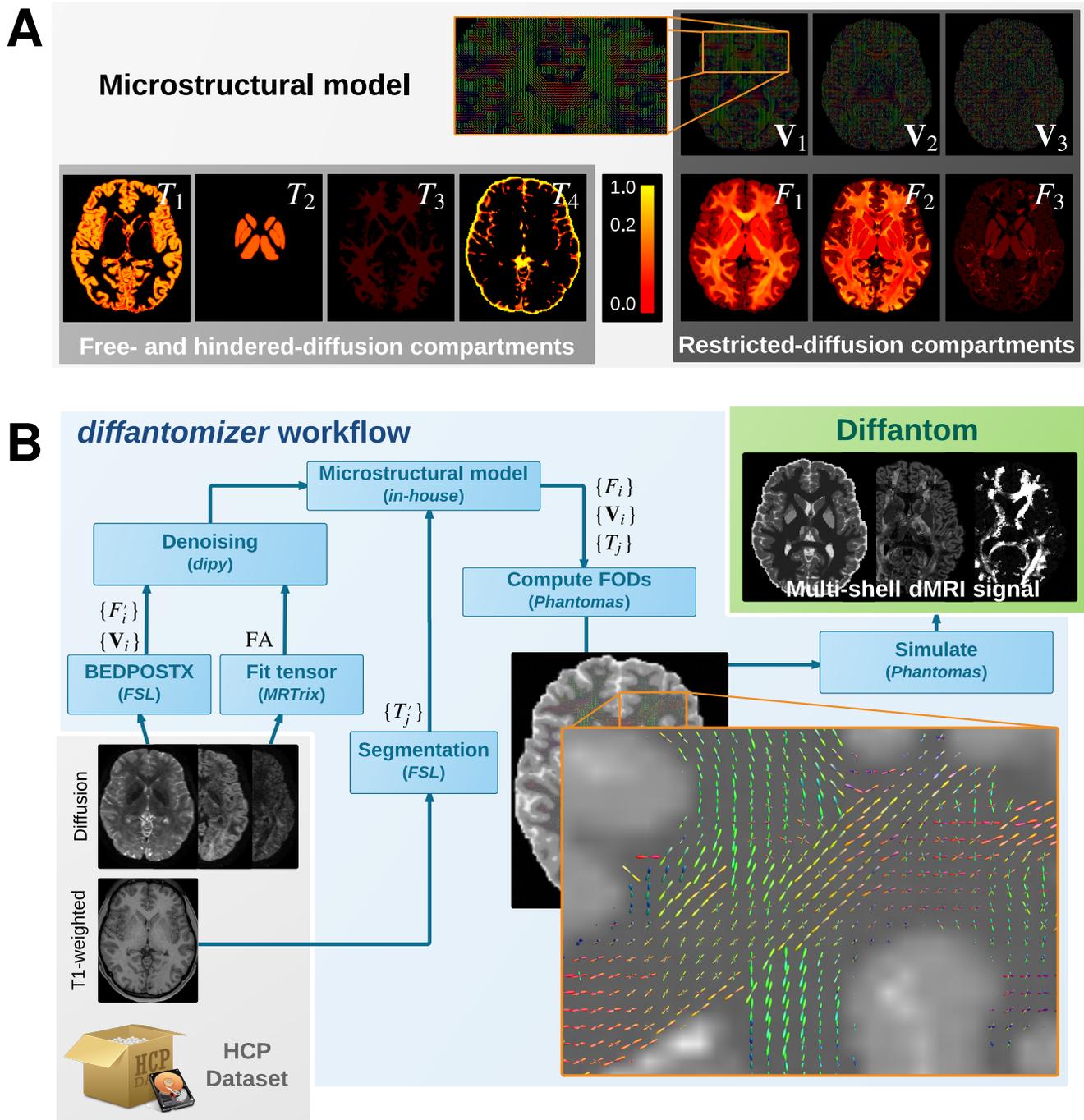
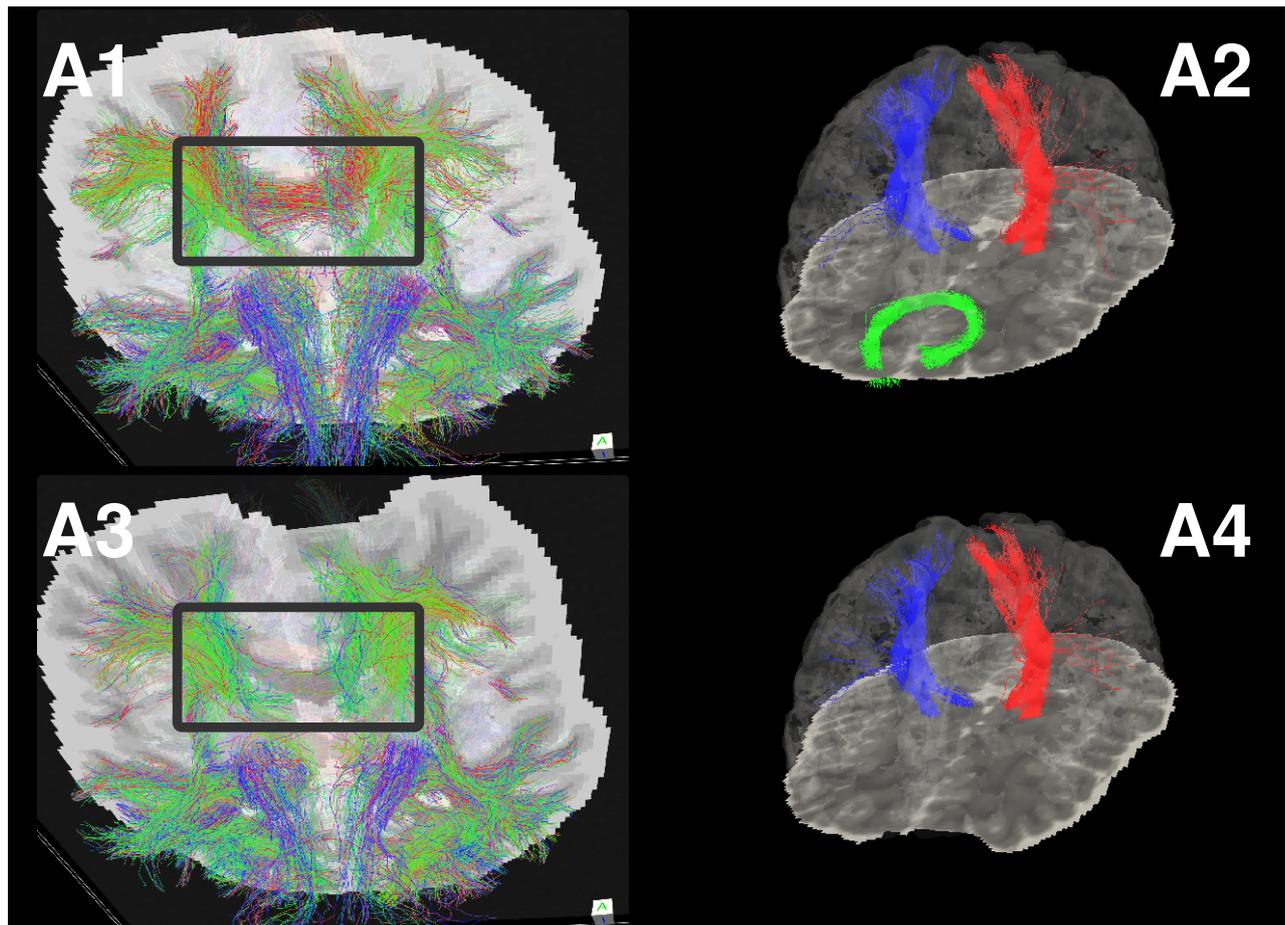


Figure 1. A. Microstructural model of *Diffantom*. The phantom is simulated from an underlying microstructural model specified with the following volume-fraction maps: three hindered-diffusion compartments $\{T_1, T_2, T_3\}$, one free-diffusion compartment T_4 corresponding to the cerebrospinal fluid (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 *Phantoms* to finally simulate the signal.



B

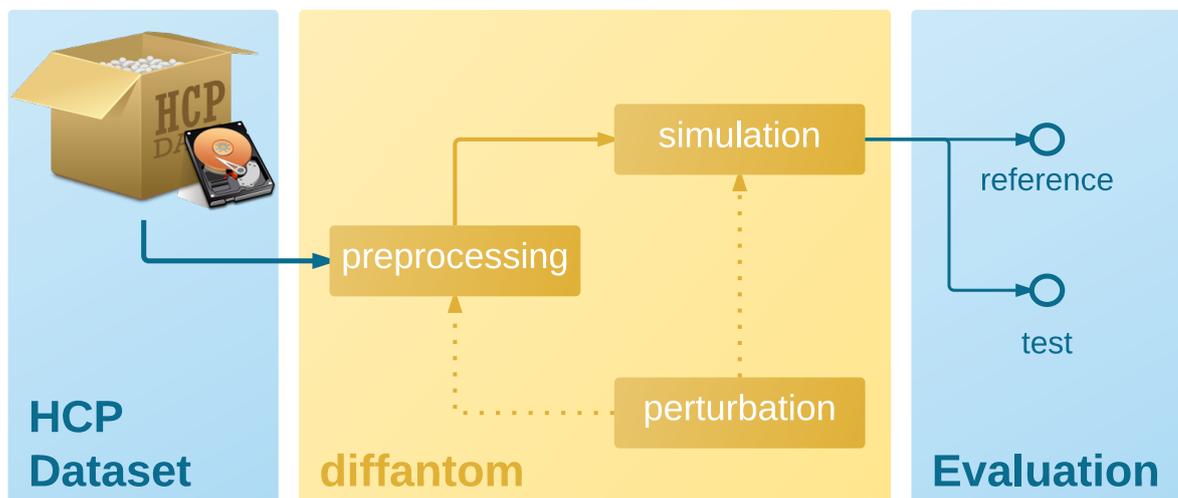


Figure 2. A. Example dataset. A1 and A3 show the tractogram of fibers crossing slice 56 of *Diffantom* as extracted with *MRTrix*, represented over the corresponding slice of the b_0 volume for the original (A1) and the distorted (A3) phantoms, with a gray frame highlighting the absence of important 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 b_0 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.