ANISOTROPIC PHANTOM
FOR DIFFUSION WEIGHTED MRI APPLICATIONS

Instruction Manual

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1 Product Classification and Purpose

The anisotropic PHANTOM is a synthetic physical auxiliary device for diffusion weighted (DW) magnetic resonance imaging (MRI) studies.

Diffusion tensor-based fiber tracking is limited in resolving complex white matter of cytoarchitecture, such as diverging or crossing nerve fibers. [1] Fiber properties, measurement parameters, and resulting data quality as well as reconstruction algorithms determine the visualization of fiber bundles, not only its precision or accuracy but also its reproducibility.

Hardware phantoms have the advantage of a controllable standard going beyond computer simulations. They can be also subject to simulation studies.

In comparison to reference [1] this Anisotropic Phantom contains both 3 straight, nearly orthogonal phantoms and 1 crossing phantom. Its structural design, the polyester fiber material arranged in a particular way in tubes, the isotropic, and anisotropic properties of included water allow the evaluation of data acquisition conditions you might look for quality control measures or calibration of DW-MRI sequences, DW-MRI sequence development, multi-center DW-MRI studies comparability tests as well as for studying new data analysis and visualization algorithms to tackle fiber tractography problems.

This auxiliary device has no measurement function itself. Within the tolerances of manufacturing process, or the uniformity of the test probes, it is possible to control the factors affecting anisotropic water diffusion.

The Phantom can be used in combination with the BrainVoyager QX software for analysis and visualizations of DW images. This software is not part of this device and contract but can be purchased at Brain Innovation. The Phantom can also be used with other imaging software packages.

The Phantom cannot be declared as “Medical Product” for diagnostic and therapy of humans and shall not be used indirectly for this purpose. Due to its model character it is for research and academic applications only. It is not suitable for simultaneous measurements with humans or animals in the MR scanner.
Limited Purpose and Knowledge Transfer.

According to Hubbard and Parker [2] “… the design of (such a) phantom is inevitably an approximation to brain tissue, which means that significant uncertainty remains in the extrapolation of our understanding of the diffusion signal obtained from the physical phantoms to the in vivo experiment.” Synthetic fiber phantoms are powerful to provide evidence of the performance of a diffusion MRI measurement and/or of a given tracking algorithm in a controlled environment. “However, the dissimilarity between the microscopic geometry and permeability characteristics of the phantoms and that of brain tissue sets a limit on the degree of validation that they can provide.”

2 Phantom Design and Test Measurement

2.1 Phantom Construction and Material

The Phantom contains of 3 tubular anisotropic diffusion phantoms and 1 crossing phantom. The 3 straight tubular phantoms are arranged in nearly orthogonal directions (see Figures 2 and 3). The small angles of the crossing phantom are roughly 60 degrees each.

The tubular phantoms are 135-140 mm long, and the diameter is 6.5-7.5 mm.

![Figure 4 Scheme of Phantom tube construction with crossing yarn fiber bundles inside](image)

Each tube contains 10,000 (-2) parallel polyester yarns (KUAG Diolen, 22 dtex 18). Fibers are solid (not hollow), thus the phantom is a model for extra-cellular restricted diffusion. Each yarn is made up of 18 fibers, so each tubular phantom contains 180,000 (-36) fibers.

One leg of the crossing phantoms contains 25 * 400 yarns * 18 fibers = 180,000 (-36) fibers.

The yarns are constrained by a color-less polyolefin shrink tube (Farnell inOne, NL).

The 4 phantoms are set up in a spherical 16 cm plastic sphere. The rods supporting the tubular phantoms are made from acrylate.

The phantom is filled with a solution of 0.03 g/l MnCl₂·4H₂O mimicking human white matter T₂ at 3 Tesla, 0.5 g/l NaN₃ and 4 g/l NaCl, for conservation and coil loading in de-mineralized (distilled) water.

A more detailed description of the Phantom production process and its properties can be found in reference [1].

All used material is of course MR compatible.
2.2 Test DTI measurement.

In our test we measure the apparent diffusion of the Phantom, calculate the mean diffusivity relative to a spatial unit = voxel, and the fractional anisotropy.

The Apparent or measured Diffusion Constant (ADC) shows the amount of diffusion. It is the average of all the microscopic displacements, which are present in a displayed voxel. Mean Diffusivity (MD) is the mean diffusivity in a selected voxel. Fractional Anisotropy (FA) demonstrates that in a selected voxel (measurement unit), there is a preferred diffusion direction. Take care, low fractional anisotropy does not mean that there is no organization in that voxel.

Test measurement and data analysis

Scanning protocol

DW-MRI Data
- Siemens Allegra 3T, birdcage coil
- 12 directions + b0
- b=1000 s/mm^2
- 75 slices
- 128 x 128 matrix, FOV 256 x 256 mm, resulting in 2 x 2 x 2 mm voxels
- TR/TE 10300/85 ms

Anatomy
- ADNI MPRAGE
- 192 slices
- FOV 256 x 256 mm
- 1 x 1 x 1 mm voxels

Data processing

The DTI DICOM data and MPRAGE DICOM data of the Phantom have been imported into BrainVoyager QX. The DTI data have been analyzed in the DTI module.

This is the standard protocol for DW-MRI data processing in BrainVoyagerQX. For more information, see the DTI Getting Started Guide available via http://support.brainvoyager.com

1. DMR creation from DW-MRI data
2. tensor calculation, FA and ADC maps on the DMR
3. VMR creation from MPRAGE data
4. co-registration of DMR to VMR
5. VDW creation
6. mask creation on VMR to eliminate background noise
7. tensor, FA, ADC calculation using mask
8. fiber tracking

Below you can see details of MD and FA maps in slice-space calculated and displayed in
BrainVoyager QX.

**Fig 5** Phantom mean diffusivity (MD) map  **Fig 6** Phantom fractional anisotropy (FA) map

Below you can see details of MD and FA maps in volume-space in BrainVoyager QX. The data outside of the phantom are masked out.

**Figure 7** Phantom mean diffusivity (MD) map
Figure 8: Phantom fractional anisotropy (FA) map.

Figure 9: Phantom color direction map of tensors in 3D volume space in BrainVoyager QX.

Figure 10: Phantom 3D tensor display in the BrainVoyager QX Surface Module.
Figure 11: Phantom tensors and fiber tracks in BrainVoyager QX Surface Module.

Looking to the interrupted green fiber bundles of the right picture above, oriented in x-direction of the BrainVoyager QX Surface Module (equals y-direction of the Siemens Allegra scanner) you will notice that the tracking does not work so well in comparison to the y-direction fiber bundles (equals z-direction in Siemens system).

Here the crossing fibers were measured along the z-plane of the scanner and the fiber displays are better.

We observed ADC and FA values are not equal in the x, y and z oriented phantom tubes. According to our experience and with reference to the coordinate system of the Siemens MR scanner you receive the best ADC and FA values in z-direction and the worst ADC and FA values in y-direction, and in x-direction a quality of somehow in between.

You can explore those data.

Figure 12: Crossing phantom tensors in z-plane of BVQX SM.

These differences might be related to gradient miscalibration [4]. This effect was also observed in human white matter oriented parallel or perpendicular to the main magnetic field [5]. Here more research has to be done.

Remark: X, Y, Z direction naming might be different in other MR scanner systems. Check the vendor documentation.
3 Conditions of Use

3.1 General inspection. Setup suggestions

Brain Innovation cannot claim a general, scanner system independent, detailed, and precise instructions for a measurement or study involving the Phantom, since every MRI facility or MR scanner has its own properties and requirements. However, the physical properties of the phantom design shall not change except the measured diffusion anisotropy.

* Keep the environmental conditions (e.g. temperature) equal. The results obtained in [1] are valid for room temperature, therefore we recommend scanning at room temperature (18-23 deg. Celsius).

* Inspect the Phantom regularly before using it. Search for damage or leaks.

* Position the phantom in a holder suitable for spherical phantoms or on a bean bag.

* The tubular phantoms may be oriented in any direction, but a first measurement should start with the nearly orthogonal tubular phantoms oriented in the x (up-down), y (left – right direction) and z (direction of the bore) axes of the scanner. [Consider also our observations described on p 8].

* Evaluate also the crossing phantom in all 3 directions

3.2 Example MR protocol and procedure

First apply a localizer scan. Ensure that the phantom is in the center of the image and coil.

The next step is a diffusion-weighted scan. Use an isotropic voxel size and choose enough slices to cover the whole phantom. We advice to use a b-value of around 1000 s/mm², but other values may be used as well. Use at least 6 different diffusion directions + a b0 image to reconstruct the diffusion tensor and related measures such as mean diffusivity or fractional anisotropy.

Researchers who would like track fibers in BrainVoyager QX need a 3d T1 weighted structural MR scan (1*1*1 mm³) as reference for the DWI data reconstruction (suggested measurement direction - saggital slices).

4 Support

For further questions or customer support please write to support@brainvoyager.com.

Additional information may also be found at http://www.brainvoyager.com/diffusionphantoms
5  Safety Regulations/ WARNINGS

5.1 Temperature

Keep the phantom away from frost. Do not expose the phantom to extreme heat. It is recommended to store the phantom between 10 and 40 degrees Celsius.

5.2 Physical harm

To prevent damage to the phantom, do not puncture or drop and avoid contact with sharp objects. In the event the Phantom has a leaky gasket or broken sphere the item should not be used in the MR environment to avoid consequential damages of other equipment.

5.3 Chemical harm

The phantom contains a MRI solution, which is harmful to the environment and is dangerous when swallowed. Refer to chemical material safety sheets for disposal of the MRI solution. The solution is not for consumption.

This phantom is manufactured in The Netherlands. 
According to Dutch safety regulations, no warning signs need to be attached to the phantom, since concentrations of dangerous chemicals are low.

For the sake of completeness we include the safety sheets for the chemicals in the phantom:

MnCl$_2$ · 4 H$_2$O
R 22: Harmful if swallowed.
R 48: Danger of serious damage to health by prolonged exposure.
R 52: Harmful to aquatic organisms.

NaCl
S 24: Avoid contact with skin.
S 25: Avoid contact with eyes.

NaN$_3$
R 28: Very toxic if swallowed.
R 32: Contact with acids liberates very toxic gas.
R 50: Very toxic to aquatic organisms.
R 53: May cause long-term adverse effects in the aquatic environment.
S 45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).
S 60: This material and its container must be disposed of as hazardous waste.
S 61: Avoid release to the environment. Refer to special instructions / Safety data sheets.
6 End User Agreement. Warranty Conditions.

This end user and warranty agreement is a contract between the Manufacturer Brain Innovation (BI), the Seller and the Buyer or End User of the Phantom, as individual or legal entity. It shall protect all professional parties.

**Intellectual property** - The Phantom design (except general design of fiber tubes) and especially the manufacturing process are original ideas of its developer - WLPM Pullens (Brain Innovation bv, Maastricht, The Netherlands) [1].

**Copyright** - WLPM Pullens and Brain Innovation bv, Universiteitssingel 40, 6229 ER Maastricht, The Netherlands.

**Distribution right** Brain Innovation possesses international distribution rights for the Phantom exclusively. This right is extended to BI’s reseller network based on sales agreements.

**Applicable law** The Phantom is developed and manufactured at Brain Innovation in Maastricht, The Netherlands. Brain Innovation’s jurisdiction is Maastricht, NL. Brain Innovation is also first Seller of the device. In the case there are more Sellers included in the distribution process refer to their sales agreements. Certain rules might be different in other countries.

**Warranty of merchantability** Brain Innovation warrants that the phantom supplied under this contract shall at the date of delivery:
- be free from defects in material;
- be free from defects in workmanship;
- be free from defects inherent in design, including but not limited to the selection of material, and be fit for the purpose described in section 1.

If any defect provably present in any of the items on the date of delivery comes to light during the defects liability period, then the Buyer shall forthwith notify Brain Innovation or the Seller. Brain Innovation without undue delay, shall at his own risk and cost make good the defect.

Brain Innovation’s liability for defects is subject to the Buyer having adherent to all procedures and instructions applicable to the “Conditions of Use” of the Phantom, and expressly excludes damage to the goods caused by fair wear and tear or by misuse occurring after delivery.
Known issues of no defect quality

There might be some small air bubbles in the phantom. This is unavoidable in the production process, but they will in time aggregate to one air bubble.

If the air bubble has become too large, you might want to add a little demineralized (distilled) water by sticking a needle in the filler cap. A small drop of hard-plastic glue will seal the puncture hole.

There might be small particles floating around in the water. Up to now it is not known that they influence the diffusion in the tubes. Because of their relative big size those molecules are not expected to change the diffusion in the tubes between the synthetic fibers.

When analyzing the data from a scan obtained when the phantom is positioned along the x, y and z direction in the scanner, ADC and FA values may not be equal in the x, y and z oriented phantom tubes. This is an expected result not related to Phantom construction and is probably related to gradient miscalibration [4] and this effect was also observed in human white matter oriented parallel or perpendicular to the main magnetic field [5].

The defects liability period shall end twenty-four month after date of invoice or after date of delivery, whichever is later, but in any case not later than twenty five month. The defects liability period shall be extended by a period equal to the period during which the goods cannot be used by reason of any defect, but not so as to extend the defects liability period for more than thirty-six month from the date of first delivery of goods repaired or replaced under this provision.

Notification of defects The Buyer shall notify Brain Innovation or the Seller forthwith of the coming to light of any defect.

The Phantom has been checked by the Manufacturer and Seller before sending. However, it is the Buyer’s duty having a first visual inspection of the Phantom after transport.

Furthermore a MR-DTI measurement and comparison with the included product data is suggested to check for more detailed defects caused by transport and handling.

The Buyer needs to send a short descriptive inspection report after receiving the Phantom to the Brain Innovation/ Seller (sales@BrainVoyager.com, Fax +31 43 3884271) within 2 weeks.

In the event of a defect coming to light and being notified to the Seller, the Seller shall, at his discretion and without undue delay repair or replace the defective item at is own risk and cost.

In the event of a defect coming to light (e.g. leaky gasket or broken sphere) the item should not be used in the MR environment to avoid consequential damages of other equipment.
Implied warranty of fitness/ warranty for a particular purpose As evaluated and described in reference 1 the anisotropic Phantom is suitable for the in section 1 circumscribed purpose.

The authors indicate expressively to the limitations of knowledge transfer collected with the anisotropic Phantom to true organic tissue (nerve fiber bundles). That will be subject of further studies.

7 References


Appendix A: Diffusion MRI Concepts

The following section shall explain some theoretical concepts of DTI research for non-experts reading this document. For detailed descriptions we refer to the in chapter 7 scientific literature.

A.1 Diffusion, Isotropic and Anisotropic Diffusion, Diffusion MRI

Diffusion is a mass transport process arising in nature, which results in molecular or particle mixing without bulk motion.

The sensitivity of the diffusion coefficient on the local microstructure enables its use as probe of physical properties of biological tissue. On a molecular level diffusive mixing is solely a result of collisions between atoms or molecules in the liquid or gas state.

The physical law that explains this phenomenon is called Fick’s first Law (Fick 1855 a, b), which relates s the diffusive flux to any concentration difference through the relationship

\[ J = -D \nabla C \]

\( J \) is the net particle flux (vector), \( C \) is the particle concentration, and the constant proportionality. In the case of diffusion, the rate of the flux is proportional to the concentration gradient as well as the diffusion coefficient. The diffusion coefficient is an intrinsic property of the medium, and its value is determined by the size of the molecules and the temperature and micro-structural features of the environment.

Isotropic diffusion is a phenomenon explained within Robert Brown’s framework of perpetual, random moving particles or here molecules (1828, Brownian motion).

\( \langle x^2 \rangle = 2 DT_d \)

Brownian motion is by the Mean square distance equals 2 times diffusion constant times temperature. E.g. for water at 37°C, \( D = 3 \times 10^{-3} \text{ mm}^2/\text{s} \), which is an average displacement of 17µm in 50ms, \( D \) is material dependent!

Albert Einstein (1905, 1926) unaware of the other two researchers’ work developed a probabilistic framework to describe motion of an ensemble of particles undergoing diffusion, which led to a coherent description of diffusion, reconciling the other two’s pictures. He introduced the displacement distribution for this purpose, which quantifies the fraction of particles that will traverse a certain distance within a particular timeframe, or equivalently, the likelihood that a single given particle will undergo that displacement.

In free diffusion the displacement is a Gaussian function. Larger diffusion coefficients lead to broader displacement probabilities suggesting increased diffusional mobility. Based on this displacement distribution concept Einstein was able to derive an explicit relationship between the mean-squared displacement of the ensemble, characterizing its Brownian motion, and the classical diffusion coefficient, \( D \), as in Fick’s First Law, given by

\( \langle x^2 \rangle = 2D\Delta \),

where \( \langle x^2 \rangle \) is the mean squared displacement of particles during a diffusion time \( \Delta \), and \( D \) is the same classical diffusion coefficient appearing in Fick’s first law.
Following Assaf and Cohen [3], Diffusion MRI has the potential to infer features of complex tissue structures as it actually measures the mean displacement of water molecules rather than their diffusion coefficient. Thus, assuming that the displacement of water molecules is affected by tissue microstructure, diffusion MRI should become sensitive to structural parameters of the tissue. … Biological cells may hinder the Brownian motion (free motion) of extra-cellular water molecules. Inside each cell, diffusion may be envisioned to be restricted by the cellular membranes. Non-free motion may be anisotropic.

**Figure 14: Diffusion types.**

**Figure 15: Diffusion directions in neural fibers.**

Water is more restricted in its diffusion perpendicular to the axons, than it is parallel to the axons. I.e. Diffusion becomes anisotropic: it is larger along some directions than others. \[D_{\parallel} > D_{\perp}\]

**Figure 16: Three magnitudes, three directions.**

**Figure 17: From diffusion to the tensor model.**

Isotropic diffusion is free diffusion of molecules with same likelihood to move in all directions resulting in a modeled round diffusion sphere.

Anisotropic diffusion is represented as a diffusion ellipsoid reflecting diffusion parallel or perpendicular to certain structures, in biological tissue/ neural fibers – extra-cellular as well intra-cellular, mainly in the axons.

There is observed evidence that restricted diffusion is apparent in neuronal tissues
with water molecule diffusion within the axons as the main contributor to it (80%) versus 20% extra-cellular. The intracelluar diffusion is the principle source. Thus, restricted diffusion as measured by MRI enables quantitative, morphologically related, parameters such as the axon density and axon diameter distribution to be extracted.

Figure 18: Cell probes of nerve/ axonal bundles.

Different analysis routines and their bio-physical meaning along with selected applications can be tested with the physical synthetic phantom in its defined structural parameters described in section 2.1.

Measured/apparent diffusion constant. The measured diffusion constant is the apparent diffusion constant, not real diffusion constant. It is the statistical average of all the microscopic displacement distributions which are present in a displayed voxel (spatial unit). It is dependent on the measurement sequence. To probe the direction in tissue we apply gradients in several directions.

The following slides offer a quick discourse through the mathematics:

Figure 19: We need at least to measure 6 directions to fill the tensor.

Figure 20: From tensor to scalar measures.
A.2 Studying Fiber Configurations and Tractography

Seunarine and Alexander are giving a theoretical overview of this topic in “Multiple Fibers: Beyond the Diffusion Tensor”, see [3].

One central goal when we analyze DTI data is to discriminate between discrete and continuous fibers in special fiber configurations for fiber tracking, like parallel fibers, fanning, bending, acute crossing and general crossing configurations.

Unfortunately, DTI acquisitions produce only a discrete, coarsely sampled representation \([v(I, j, k)]\) of the continuous fiber tract direction field \([v(x, y, z)]\). That makes certain configurations extremely difficult to classify (e.g. crossing versus touching). Our goal is to reconstruct trajectories of bundles of fibers from the direction field extracted from diffusion tensor data in the phantom configuration. This can be done within BrainVoyager QX or with other software algorithms.

The discrimination of such problematic properties even in a synthetic phantom are dependent on the DTI acquisition sequence, magnetic field properties (e.g. homogeneity) and other acquisition parameters, voxel resolution, position of the phantom relative to the magnetic field, post-hoc data correction algorithms, reconstruction algorithms beside other variables adding in in-vivo measurements of human brain structure (e.g. head motion etc.).

\(\text{Figure 21 A: Voxel-based DTI data in volume-space with tensors; B: Discrete, coarsely sampled representation } [v(I, j, k)] \text{ of the continuous fiber tract direction field } [v(x, y, z)] \text{ and reconstruction of trajectory fiber bundles.}\)