MODEL-FREE NOVELTY-BASED DIFFUSION MRI

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ABSTRACT

Many limitations of diffusion MRI are due to the instability of the model fitting procedure. Major shortcomings of the model-based approach are a partial information loss due to model simplicity, long scan time requirements due to fitting instability, and the lack of knowledge about how the parameters of a given model would respond to previously unseen microstructural changes, possibly failing to detect certain previously unseen pathologies. Here we show that diffusion MRI pathology detection is feasible without any models and without any prior knowledge of specific pathological changes whatsoever. Instead, raw q-space measurements are used directly without a model, only healthy population data is used for reference, and any deviations in a patient dataset from the healthy reference database are detected using novelty detection methods. This is done in each voxel independently, i.e. without spatial bias.

Index Terms— Model-free diffusion MRI, novelty detection

1. INTRODUCTION

Microstructural diffusion MRI consists of sampling the diffusion space (q-space) extensively, fitting a model to the measurements, and interpreting the estimated model parameters. Herein, by the term "model" we mean any handcrafted simplifications, i.e. physical models, mathematical signal representations, handcrafted calculations. Popular models include diffusion tensor imaging, diffusion kurtosis imaging, and neurite orientation dispersion and density imaging.

1.1. Current limitations of diffusion MRI

Many limitations of diffusion MRI are due to the instability of the model fitting procedure. Model fitting is ill-posed, particularly it cannot cope well with the data noise.

On one hand, this requires models to be simple enough for the fitting to work stably. It has been shown that the number of free parameters should be about 4 or 5 rather than 10 or 11 such that model complexity is appropriate for data from clinical MRI scans [1]. Besides, the models are handcrafted, which means that the reduction of degrees of freedom (e.g. from dozens of q-space measurements to about 4 or 5 model parameters) discards information in a suboptimal way [2].

On the other hand, model fitting requires high numbers of q-space samples to avoid instabilities. This causes long scan durations and high costs, and makes advanced protocols inapplicable if time is an issue, i.e. in case of urgency or for patients who are uncooperative, uncomfortable or unwell. The number of q-space samples required for fitting is disproportionate – approaches to estimate model parameters without fitting achieve twelve-fold shorter scan durations [3, 4, 2].

Besides, all model-based approaches require studying the relationship between model parameters and microstructural tissue changes *specifically* for each given disease and diffusion model. In other words, it is not known how the parameters of a given model would respond to previously unseen microstructural changes, and whether unstudied changes would go undetected.

1.2. Model-based approaches without fitting

1.2.1. Analytical solutions

Analytical solutions of model measure estimation [3, 4] require considerably shorter scan duration and processing duration compared to model fitting. They are limited to specific model measures and acquisition schemes.

1.2.2. Approximation

Simulations of simplified tissue models with extensive sets of diffusion weightings [5, 6] indicate that standard model fitting procedures can be replaced by approximation methods. Moreover, the feasibility of model measure estimation in a clinical setting without model fitting has been recently demonstrated, allowing *a drastic reduction of scan duration by a factor of twelve* [2].

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1.3. Model-free approach

The possibility to estimate tissue properties of interest (such as tissue type and pathology) directly from raw q-space data without using any models has been recently presented [2]. This data processing is *optimal* in the sense that it performs a state-of-the-art data transformation (deep learning [7]) which minimizes the output error for a training set. Its drawback is the requirement for labeled training data. This drawback is addressed in the present work.

1.4. Proposed approach

As a complement to the previously proposed model-free method [2] which is trained on labeled data, we herein propose a model-free method that does not require abnormal data for training. In the herein proposed model-free novelty-based approach, only healthy population data (or any otherwise "uninteresting" data) is used for reference. Any deviations in a patient dataset from the healthy reference database are detected using novelty detection [8] methods. This is done in each voxel independently, i.e. without spatial bias.

1.5. Additional remarks

The distinction between the aforementioned families of methods is in some cases smooth and open to interpretation. For instance, simple models such as the apparent diffusion coefficient can be considered closed-form solutions; least squares fitting can be implemented either by numerical procedures or in closed form (by precomputing the inverse of the system matrix), whereas maximum-likelihood-based fitting is usually iterative.

2. METHODS

To circumvent numerous drawbacks of the previous approaches as discussed in Section 1, we propose a method that requires neither models nor labeled training data.

2.1. Model-free novelty-based diffusion MRI

In model-free novelty-based diffusion MRI, the q-space measurements are used directly without a model, and abnormalities are detected by means of novelty detection. For this purpose, a database of "uninteresting" q-space data is constructed, and deviations from this data-driven notion of "normality" are detected by novelty detection methods [8]. A natural choice for "normal" data are healthy data (as used herein). For other options, see Section 4.

In our framework, one data sample is one voxel, and its n features are the q-space measurements and other image contrasts collected into a feature vector.

We use Matlab (The MathWorks, Natick, MA, USA) and a novelty detection toolbox [9, 8]. The "normal" data is affinely scaled to the interval $[0; 1]$ along each dimension individually, and the test data is scaled using the same transformation (i.e. not exactly to the same interval, but into the same data representation). We use a simple novelty detection method that calculates the Euclidean distance of each tested data point in n-dimensional feature space to its nearest neighbor from the "normal" dataset. The less usual the tested data point is, the higher is its distance to any of the normal data points, and thus the higher is its novelty score, measured in arbitrary units. The novelty score $r(x)$ for a tested data point x is thus

$$r(x) = \min_{y \in Y} d(x, y), \tag{1}$$

where Y is the "normal" set and

$$d(x, y) = \|x - y\|_2 = \sqrt{\sum_{i=1}^{n} (x_i - y_i)^2} \tag{2}$$

is the Euclidean distance between x and a "normal" sample y.

This is one of the most straightforward novelty detection methods. However, using q-space signals x, y directly without diffusion models and using novelty detection (i.e. doing without any prior knowledge of pathology) are novel approaches which allow to circumvent numerous drawbacks of previous approaches, as detailed in Section 1.

The bottleneck of the algorithm is the computation of the pairwise distance matrix between the tested samples and the "normal" database. To balance between computation duration and memory use, we used vectorization and recursive splitting of the data into smaller chunks.

Experiments with other novelty detection methods were performed for comparison. The k-nearest-neighbors (k-NN) approach [10] calculates the novelty score as

$$r(x) = \frac{1}{k} \sum_{y \in N_k(x)} d(x, y), \tag{3}$$

where $N_k(x)$ is the set of the k nearest neighbors of the tested point x among the "normal" set Y:

$$N_k(x) \subset Y, \ |N_k(x)| = k, \tag{4}$$

$$\forall y \in N_k(x) \ \forall \tilde{y} \in (Y \setminus N_k(x)) : d(x, y) \leq d(x, \tilde{y}). \tag{5}$$

For $k = 1$, Eq. (3) corresponds to the nearest-neighbor approach, Eq. (1).

We also tried novelty detection based on kernel density estimation [11] (KDE), i.e. $r(x) = \sum_{y \in Y} K(x, y)$, with various kernels $K(\cdot, \cdot)$ and radii, and the one-class SVM [12] with various parameter sets.

2.2. Data

The *in vivo* protocols were approved by our institutional review board and prior informed consent was obtained. Five multiple sclerosis patients were scanned on a 3T GE

MR750 MR scanner (GE Healthcare, Waukesha, WI, USA) equipped with a 32-channel head coil using echo-planar imaging and a diffusion spectrum [13] uniform random sampling pattern with 167 q-space samples, $b_{\max} = 3000\,\mathrm{s/mm^2}$, $T_E = 80.3\,\mathrm{ms}$, $T_R = 5.4\,\mathrm{s}$, FOV $= 24\,\mathrm{cm} \times 24\,\mathrm{cm} \times 12\,\mathrm{cm}$, isotropic voxel size $2.5\,\mathrm{mm}$, ASSET factor 2. FLAIR-, T_1- and T_2-weighted images were acquired for validation of diffusion-based lesion segmentation. The data underwent FSL topup distortion correction [14].

2.3. Validation

State-of-the-art automatic segmentation [15] (based on non-diffusion images with spatial priors) into healthy white matter (WM), grey matter (GM), cerebrospinal fluid (CSF) and multiple sclerosis lesions (Fig. 1a) was used in comparison to our proof-of-concept model-free novelty-based segmentation (based on diffusion images without spatial priors).

The healthy reference database is constructed from the healthy voxels (as determined by automatic non-diffusion segmentation) of four patients, and tested on the fifth patient. The healthy database thus contains about $300\,000$ healthy samples (voxels) and the test dataset contains about $90\,000$ healthy and diseased samples. Using healthy volunteers as the healthy database yielded very similar results (not shown).

3. RESULTS

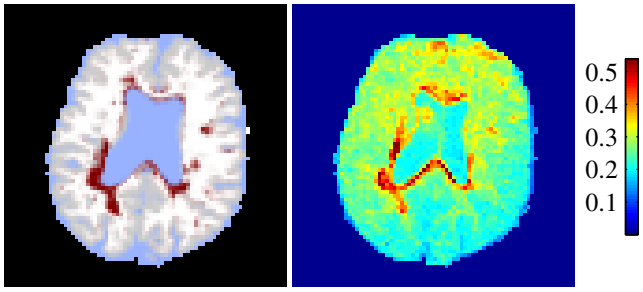
Model-free novelty detection of q-space data applied to a multiple sclerosis patient dataset is shown in Fig. 1b. Gold standard multiple sclerosis lesion segmentation based on FLAIR-, T_1- and T_2-weighted images and spatial priors is shown for comparison in Fig. 1a.

The concordance between the gold standard lesion segmentation and the novelty score obtained by our method is quantified in terms of the receiver operating characteristic in Fig. 2. The area under the curve (AUC) is 0.82. Computation time was about two minutes on a laptop computer.

The AUC was minimally higher for k-NN, with a maximal value of 0.83 attained at $k = 40$. The AUC was slightly higher for one-class SVM (experiments only with a small subset of data due to long computation time; not shown) at the cost of longer computation and the need for parameter tuning. KDE-based novelty detection did not detect lesions well; instead, it yielded very different values for healthy WM, GM and CSF instead of a uniformly low novelty score.

4. DISCUSSION AND CONCLUSIONS

We demonstrated the feasibility of a diffusion MRI processing method that is sensitive to microstructural changes without using models and without prior knowledge about the impact of the changes on the signal. This alleviates the drawbacks of model fitting and provides the potential for automatic detection of understudied abnormalities.



(a) Ground truth (b) Novelty score

Fig. 1. Feasibility of model-free novelty-based diffusion MRI. (a) Standard segmentation of tissue types WM/GM/CSF (shown in white/grey/blue) and multiple sclerosis lesions (shown in red). (b) Abnormality score obtained from diffusion MRI data without any models and without any prior knowledge of disease.

Results of k-NN are stable across different choices of k. For $k = 1$ (i.e. nearest neighbor) results are good and fast to compute (taking the minimum rather than sorting). KDE-based methods are less appropriate because the density of the points in feature space is highly heterogeneous. As extreme examples, CSF voxels are abundant and all very similar (high density in feature space), whereas each voxel in the corpus callosum is almost unique (low density in feature space).

Disparity of the results compared to FLAIR-based segmentation can be partly attributed to an unequal impact on the FLAIR signal vs. the q-space signal of various subtle disease-related effects.

The setting is a model-free framework [2], i.e. using the raw q-space data directly without any models. This avoids the problems of an unstable model fitting procedure which on one hand requires long scan durations [2], and on the other hand requires model simplicity [1] and thus causes information loss [2].

Moreover, *the model-free approach otherwise would require supervised training with the lesion class, so that the proposed novelty-based approach is its ideal complement*. It can be applied in situations where complete knowledge of all disease effects on diffusion properties cannot be obtained.

Additional imaging contrasts can be combined with raw

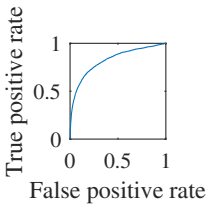


Fig. 2. Receiver operating characteristic for novelty-based results of Fig. 1. The area under the curve is 0.82.

q-space data to gain additional information, as previously shown [2]. Spatial variations of "normality" could also be considered. Future work will focus on treating q-space data as additional channels in multiparametric imaging, merging different resolutions and nonlocal information, and applying the supervised model-free [2] and novelty-based model-free methods to various conditions.

Besides healthy data, other studies might include common, well-detectable diseases into the "uninsteresting" database, such that rare or previously unknown disease effects on q-space signal are detected as deviations from the "known". Also a process of elimination can be implemented by testing against several databases containing different conditions.

The danger of biasing the healthy database by asymptomatic patients can be reduced by using anomaly detection (as opposed to novelty detection) to detect self-inconsistencies (outliers) within the database itself.

Many current diffusion MRI models have a limited complexity in order to allow a stable fit [1] (limited number of free parameters). In contrast, we show that fitting is not required. Thus, models can be more complex (more accurately describe the tissue microstructure) to guide the understanding of microstructure effects on q-space signal, the design of q-space sampling schemes sensitive to disease, and the simulation-based training [5, 6] of fitting-free methods.

To summarize: If a condition affects the q-space signal in a measurable way, the proposed method will mark it as a deviation from normal data. This happens regardless of any model-based simplifications or any prior knowledge of the disease effect on the q-space signal.

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Model-Free Novelty-Based Diffusion MRI

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Introduction

Diffusion MRI Processing Methods

Model-Based

By "model" we mean any handcrafted simplifications:

- physical models
- mathematical signal representations
- handcrafted calculations

Examples: DTI, DKI, NODDI, …

– models are handcrafted, thus suboptimal ⇒ information loss

– preliminary model-specific disease-specific studies required

– not known how model parameters would respond to previously unseen microstructural changes

– not known whether unstudied changes would go undetected

Model-Free

Direct estimation of tissue properties from raw q-space signal

\+ no model simplicity, no model suboptimality ⇒ no information loss [1,2]

Fitting-Based (currently used almost everywhere)

Fitting of model parameters

– unstable, ill-posed, susceptible to noise

⇒ requires low model complexity [3]

⇒ information loss

⇒ requires many samples

⇒ long scans

⇒ high costs

⇒ inapplicable if time is an issue

Fitting-Free

Analytical Solutions

Fitting replaced by closed-form formulas [4,5]

\+ very short scans

\+ fast processing

– limited to specific measures and sampling schemes

Approximation

Fitting replaced by deep learning [1,2]

\+ optimal (minimizes training error)

\+ very short scans

\+ fast processing

\+ arbitrary measures and sampling schemes

Supervised / Label-Based

Deep learning to estimate tissue type directly [1,2]

\+ optimal (minimizes training error)

– requires disease-specific labeled training data

Novelty-Based (proposed here)

Detection of any deviations from a reference (healthy) database

\+ abnormal data not required for training

Methods: **Model-Free Novelty-Based Diffusion MRI**

- Construct database of healthy (or otherwise "uninteresting"/"normal") data
- Novelty detection methods (see box) detect deviation from the "normal" database → disease (here: multiple sclerosis)
- One data sample is one voxel; its n features are the raw q-space measurements collected into a feature vector x
- Data: Multiple sclerosis patients, 3T, 32-channel head coil, EPI, DSI random sampling, 167 q-space samples, b_{max}=3000s/mm², TE=80.3ms, TR=5.4s, FOV = 24×24×12cm, voxel iso 2.5mm, ASSET factor 2, FLAIR/T1w/T2w for validation of diffusion-based lesion segmentation, FSL topup

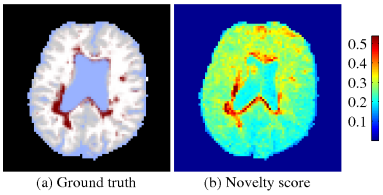
Results

(a) State-of-the-art automatic segmentation (based on non-diffusion images with spatial priors)

(b) Proposed novelty-based segmentation (based on diffusion images without spatial priors)

(c) Receiver operating characteristic; area under the curve (AUC): 0.82

All novelty detection methods yield similarly good lesion detection and AUC (except kernel density methods, see paper)



(a) Ground truth (b) Novelty score

Novelty Detection

- Scale the training data to interval [0;1]
- Apply same transformation to test data
- Let Y be the set of "normal" reference data and $r(x)$ the novelty score of tested data point x
- Different novelty detection methods [6,7]:
  - Euclidean distance to nearest "normal" neighbor:
    $$r(x) = \min_{y \in Y} \|x - y\|_2 .$$
    We use a fast implementation of pairwise distances, vectorization, and splitting of the data into smaller chunks.
  - k-nearest-neighbors (k-NN) approach [8]:
    $$r(x) = \frac{1}{k} \sum_{y \in N_k(x)} \|x - y\|_2 ,$$
    where $N_k(x)$ is the set of the k nearest neighbors of x among Y
    (k-NN corresponds to nearest neighbor for $k = 1$)
  - One-class SVM [10] with various parameter sets

Discussion & Conclusions

- If a disease affects the q-space signal in a measurable way, the proposed method will mark it as a deviation from normal data
- No models, avoidance of drawbacks of model-based methods
- No requirement for prior knowledge about the impact of microstructural changes on the signal
- Potential for automatic detection of understudied abnormalities
- Combination with additional imaging contrasts is straightforward
- "Uninteresting" database can be constructed in other ways: known diseases, process of elimination…
- Anomaly detection (as opposed to novelty detection) to check the database consistency
- Fitting-free and model-free approaches have high potential

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