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Diffusion MRI: From Principles To Modelling And Clinical Applications

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INTRODUCTION

Diffusion weighted imaging (DWI) is the set of methodologies developed to investigate structural properties of brain tissues by analyzing water molecules diffusion process. Indeed, presence of biological barriers influences water displacement both in terms of velocity and directionality. DWI has the unique ability to provide, non-invasively and in-vivo, clues at microscopic level starting from data acquired at macroscopic scales. A number of models have been proposed in literature to highlight different aspects of diffusion. The main focus is put on white matter (WM), since it is even possible to visualize main WM pathways thanks to particular techniques that go under the name of tractography. Nevertheless, DWI has been successfully adopted to probe grey matter (GM), as well as other non-brain tissues, like skeletal muscles, peripheral nervous system, myocardium or kidneys.

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An exhaustive treatment of diffusion literature would require much more space than what can be dedicated here. It is our intent to highlight principal aspects of diffusion phenomenon in a framework that could result understandable and intriguing to readers with a medical background that aim to start understanding and applying diffusion MRI in their research.

Chapter is organized as follows: in order to understand principles behind diffusion MRI (dMRI), we describe basics of resonance imaging and diffusion mechanisms. Then, principal diffusion models proposed in literature are introduced. Particular attention is subsequently given to clinical applications, from non-invasive investigation of brain pathways anatomy to diffusion based analyses adopted to investigate neurological disorders and brain gliomas; limitations of dMRI are moreover discussed. Eventually, integrated approaches used in current research and clinical setting are described.

BASICS OF DIFFUSION MRI

MR Images

At molecular level, our body is mainly constituted by hydrogen nuclei which rotate around their own axes determining a magnetic moment μ. In normal conditions, hydrogen spins randomly rotate nullifying total magnetization. Within the scanner, a constant magnetic field $\overrightarrow{B_0}$ causes spins to start a *precession movement* around $\overrightarrow{B_0}$ direction at the so-called *Larmor frequency*. If we apply a strong radio-frequency pulse (*RF pulse)*, perpendicularly to $\overrightarrow{B_0}$ at the same frequency, spins are forced to rotate in the new direction (*resonance*). After pulse action, spins rotate back to previous position, thus inducing an electrical field that can be measured by antennas placed close to the body (*coils*). A complex action of different *magnetic field gradients* allows to give to a certain region of space (*voxel*) an unique oscillation frequency. Thus, if we apply a RF pulse at the same frequency, we can measure signal intensity coming only from that portion of the tissue; in this way we obtain an *image* of the structure we are interested to.

Diffusion Mechanisms

Diffusion consists in thermal driven random particles motion in a medium [1]; microscopically, it is caused by millions of collisions. At the beginning of 20^{th} century, Einstein gave a probabilistic interpretation of such brownian motion:

$$<x^2> = 6\,D\tau$$

he directly related molecular displacement, within a timeframe τ, to medium characteristics, the latters being encoded into a *diffusion coefficient D*. When water is free to diffuse, we talk about *isotropic* diffusion.

Diffusion Weighted Sequences

Nowadays, sensitization to diffusion is obtained on the basis of PGSE sequence [2]: if two inverted RF pulses are applied to non-moving spins, they change accordingly their precession

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phase, eventually having the same phase. Particles can be spatially encoded along a certain direction with a *diffusion gradient*: if particles move in between the application of inverted pulses, spins are no longer in phase. Such dephasing causes a signal loss that can be compared with an equivalent configuration in which diffusion gradient is not applied. Signals measured with and without diffusion gradient are related by a mono-exponential decay law driven by two quantities: *b-value*, which encloses (among others) sequence specifics, and the *apparent diffusion coefficient D* (or ADC) [3]. "Apparent" term is used since ADC depends both on the medium properties and on the particular timeframe spins are allowed to diffuse before signal acquisition [1]. From the physical point of view, ADC represents average diffusivity of water molecules in a given direction, and it is measured in m^2/s:

$$S_g = S_0 \exp(-b\,D)$$

Modelling and Quantifying Diffusion

What do we measure with diffusion MRI?

Understanding what we actually measure by means of DWI within a voxel is not straightforward. Factors influencing outcomes are manifolds: among others, diffusion time τ, b-values adopted, underlying biological features (for instance, fraction of intra-cellular and extra-cellular compartments). In [4] it was demonstrated that mono-exponential decay law should be replaced by a two-exponential fit:

$$S_g = S_0[\, f_{fast} \exp(-bD_{fast}) + f_{slow} \exp(-bD_{slow})]$$

This is due to the existence of two compartments showing different diffusion behavior, namely intra-cellular and extra-cellular ones. Water diffusion in extra-cellular compartment is correlated to a faster (and bigger) coefficient D_{fast}; a slower (and smaller) coefficient D_{Slow} is instead correlated to intra-cellular compartment, in which viscosity and cytosol slower diffusion process. These aspects can be observed with high b-values (b≥2000 s/mm2), and at small diffusion times [4]. At longer diffusion times ($\tau > 100ms$), and relatively small b- values (b≤2000 s/mm2), signal attenuation shows a mono-exponential behaviour: in such contexts, ADC measured is rather a weighted average of both compartments, with a predominance of extra-cellular component [5]. To increase sensitivity to slow diffusion, which is more intra- axonal driven, higher b-values should be required ($b \approx 3000\ s/mm^2$) [6].

Diffusion Tensor

A crucial role for ADC outcome is played by direction **g** of diffusion gradient; indeed, signal loss is strongly dependent on how much **g** is parallel to the principal diffusion direction [7]. Such directionality-dependence is called *anisotropy*. These considerations have led to introduction of diffusion *tensor* into exponential decay law, we discussed before [7,8].

$$\mathbf{S_g = S_0 \exp(-bg\, Dg^t)}$$

D is a symmetric matrix from which we three positive quantities can be extracted: the *eigenvalues.*

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They correspond to diffusivities along three orthogonal directions in space. To better understand meaning of tensor model we can consider its geometric representation, an ellipsoid (Figure 1a): if we imagine a particle quite in a certain position at time 0, it turns out that ellipsoid surface represents boundaries of a region where particle could have moved in a given time frame , with equal probability, because of diffusion process [7]. Hence, ellipsoid shape can help us understanding how tensor model probes brain tissues: if minimal or no obstacles are encountered, like in cerebrospinal fluid (CSF), ellipsoid is spherically shaped (Figure 1b). Instead, in presence of anisotropic diffusion, ellipsoid is more squashed along principal diffusion direction (Figure 1c). From tensor eigenvalues, a number of useful parameters have been introduced to highlight different aspects of diffusion, like axon integrity and myelination [9-12]. These indices are shown in Table 1; their meaning and biological interpretation are matter of discussion of next sections. For the moment it is worth to notice that, in a given voxel, the more a principal unique diffusion direction hinders diffusion, the higher the anisotropy in that voxel.

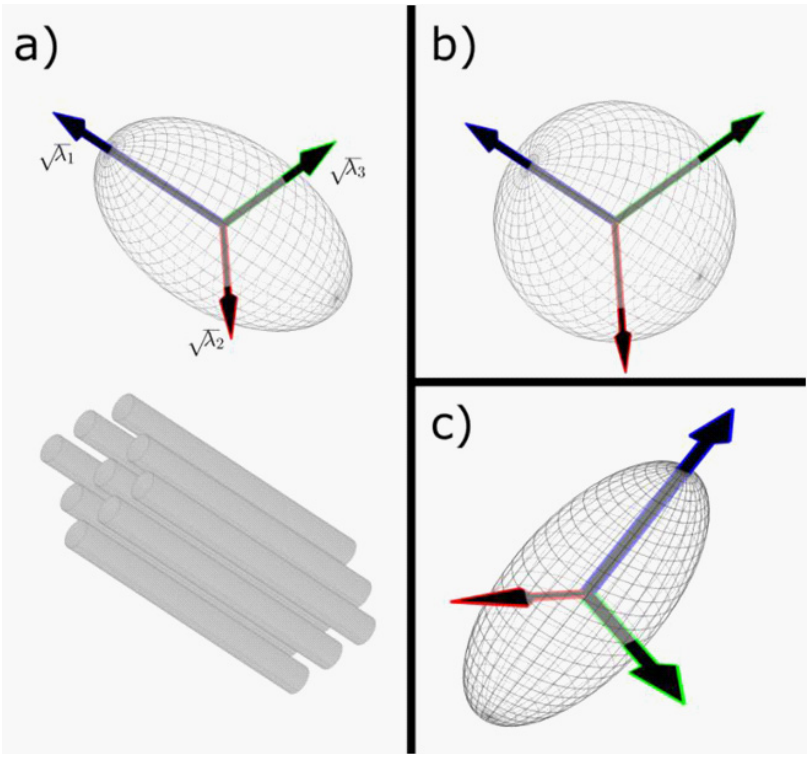


Figure 1: Diffusion Tensor and its geometric meaning. a) A tensor (upmost part of the panel) obtained from a simulation in which axons are coherently pointing in a given direction; for visualization purposes, axons are drawn in bottom part of the panel. A principal preferred diffusion direction is thus detected; diffusivity along that direction is quantified by highest eigenvalue λ1. b) In an isotropic scenario, ellipsoid is spherically shaped; a principal diffusion direction is not detected by tensor. c) Similarly to panel a, a tensor obtained from a voxel showing anisotropic diffusion is shown.

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Table 1: List of tensor based parameters most commonly used in literature.

Tensor feature	Formula
Trace	$TRA \stackrel{def}{=} \sum_{j=1,3} \lambda_j$
Mean Diffusivity	$MD \stackrel{def}{=} \frac{1}{3} \sum_{j=1,3} \lambda_j$
Fractional Anisotropy	$FA \stackrel{def}{=} \sqrt{\frac{3}{2}} \frac{\sqrt{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$
Axial Diffusivity	$AD \stackrel{def}{=} \lambda_1$
Radial Diffusivity	$RAD \stackrel{def}{=} \frac{\lambda_2 + \lambda_3}{2}$
Linear Coefficient	$CL \stackrel{def}{=} \frac{\lambda_1 - \lambda_2}{3\,MD}$
Planar Coefficient	$CP \stackrel{def}{=} \frac{2}{3} \frac{(\lambda_2 - \lambda_3)}{MD}$
Spherical Coefficient	$CS \stackrel{def}{=} \frac{\lambda_3}{MD}$

Beyond Tensor: Tissue Heterogeneity and Complex Modeling

At normal imaging scales (2mm), a typical WM voxel contains several biological structures, like axons, astrocytes, and glia. In this perspective, water molecules diffusion is *hindered* in extra-axonal space and *restricted* in the intra-axonal space [13]. If in a voxel a coherent structure is detected, namely a single group of axons (*fiber bundle),* tensor model is well suited to investigate diffusion. On the contrary, if complex fibers geometry occurs, like crossing, branching or kissing bundles, tensor model loses its meaningfulness as it represents a non-well defined average behavior coming from heterogeneous structures [14]. It has been demonstrated [15] that more than 90% of WM voxels actually contain fibers with complex configurations. For these reasons more sophisticated models have been proposed in literature: some of them still explore water spins displacement, like diffusion kurtosis [16], multitensor [17] or ball-and-stick models [18], QBI [19], DSI [20]. Others directly attempt to individuate discrete sets of fiber bundles, like in case of spherical deconvolution [21-23]. Recently, a multi-compartment model, called NODDI [24] has been introduced, with the goal to provide a new framework for analysis of WM and GM. It is important to notice that most of these models require sequences and acquisition times that can rarely be achieved in clinical practice; for this reason diffusion tensor is still today a widely accepted choice.

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To conclude we want to remark that, for a principled diffusion based quantification of brain tissues, one should have clear in mind that an unique solution does not exist; model choice has to be dictated by hardware constraints as well as biological question one aims to answer to.

Tractography

Tractography is the set of techniques able to detect and trace WM fiber bundles by means of dMRI [25]. Regardless to the diffusion model adopted, the main goal is to individuate and follow a discrete set of fibers starting from a certain spatial location (*seed*). Outcomes are a series of *streamlines* that can highlight major WM routes. With tensor model, we are most likely able to detect, within a voxel, only one main principal direction [25] (Figure 2). By using more sophisticated approaches, like Q-ball [19], CSD [21,22,26] or DSI [20], we can distinguish fibers arranged in more complex geometries (Figure 2). Usually stopping criteria are adopted, both based on spatial priors and diffusion based, to avoid tracts reaching unwanted regions, like deep GM or CSF. Tractography can be categorized into *deterministic* or *probabilistic*: in the former case, only one streamlining process is initialized from a seed voxel [25,27,28]; in the latter, several processes are run and different routes can be followed on the basis of how uncertainty is modeled in diffusion data [29-31]. Tractography has been extensively used in last years to explore brain structural connectivity in healthy brains and pathologies by means of connectivity analyses [32].

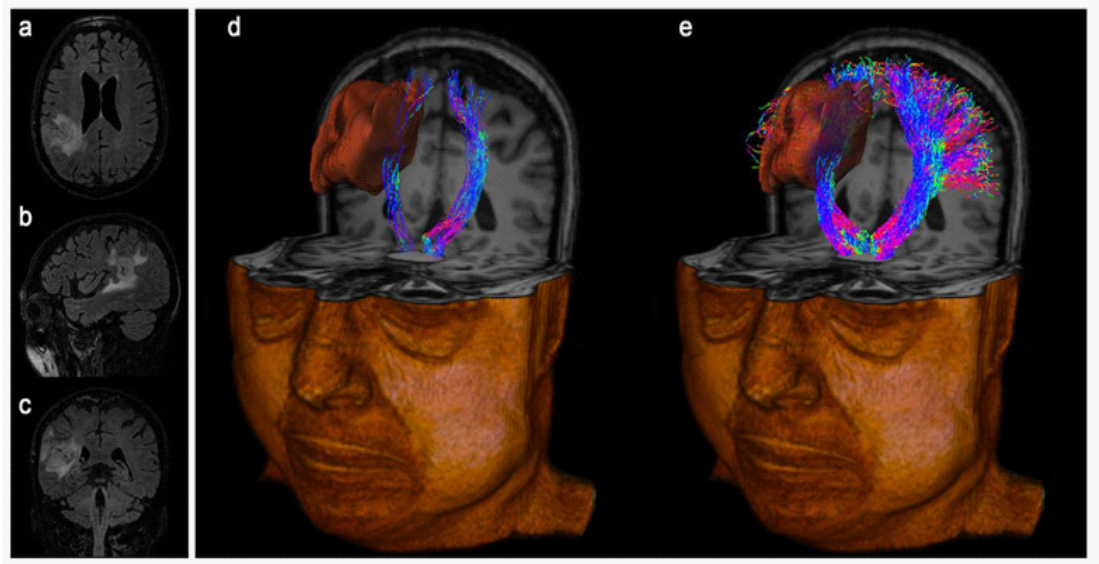


Figure 2: Tractographic reconstruction of right and left corticospinal tract (CST) in a case of high-grade glioma (brown ROI).

The neoplasm is shown in all radiological planes by means of FLAIR images (a-b-c). DTI-based reconstructions (d) showed a poor CST reconstruction in the healthy side, if compared to CSD-based one (e). Moreover, DTI resulted inadequate to detect CST in the affected side, in terms of both bundle's involvement and anatomical relationship with neoplasm.

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CLINICAL APPLICATIONS

Diffusion-based techniques are widely used in clinical settings, since they are able to provide very useful information both in physiological and pathological contexts. A typical diffusion study workflow with possible variables that should be considered by operators is shown in Figure 3. The description of principal application fields of dMRI are given below.

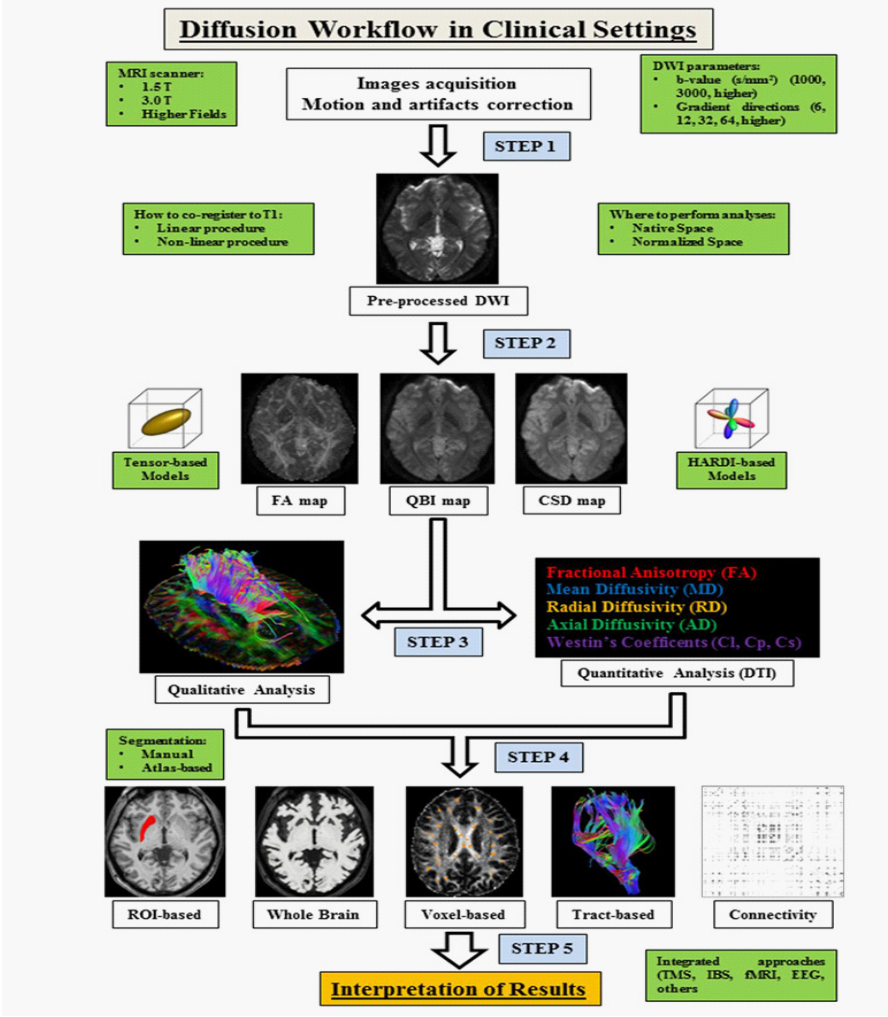


Figure 3: Workflow of a diffusion-based study in clinical settings.

Blue boxes show the main steps usually followed during the study; green boxes show the main variables that can be chosen before as well as during the analyses. First of all, DWI images are acquired (STEP 1) and corrected for distortion artifacts. The choice of MRI scanner and acquisition parameters may influence the study repeatability [33] as well as sensitivity and reliability reached by post-processing analyses [34]. Moreover, operator has to decide whether to work in native or normalized space as well as the method to co-register DWI images to T1w ones (this step is useful to obtain anatomical landmarks).

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Diffusion model chosen is applied to pre-processed DWI images (STEP 2), in order to obtain parameters-weighted maps. As written in the text, model may have an impact on post-processing analyses in terms of biases and sensitivity [14,35]. Researchers can now choose which kind of information (qualitative and/or quantitative) they want to extrapolate from their dataset (STEP 3) as well as how to obtain them (STEP 4). If ROIs are needed for the study, operator can use manual or atlas-based approaches. Finally, results obtained can be interpreted for making inference or they can be integrated with other techniques (STEP 5).

Anatomy and Physiology

Diffusion-based techniques represent one of the most powerful investigative approaches to study connections between brain structures non-invasively. The qualitative analysis of brain pathways provided by tractography has helped to understand the structural bases of brain functional phenomena observed by means of modalities such as functional MRI (fMRI) or brain stimulation. Moreover, tractography has provided over the years several suggestions regarding novel brain pathways which may shed new lights for understanding of brain functions.

Tractography has been widely adopted to detect well-known WM fibers bundles, such as corpus callosum, arcuate fasciculus and corticospinal tract [27,36-38]. The most intriguing aspect of tractography is the opportunity to isolate and study fiber bundles non-invasively in vivo; indeed, before its advent, they were studied only by means of invasive approaches, such as postmortem dissection. For this reason, *virtual dissection* terminology is sometimes used when performing tractographic analyses. Furthermore, several attempts have been made to explore possible existence of new fiber pathways, such as the direct cortico-pallidal or the cerebellar-hippocampal one [39-41]. Interesting findings have been provided regarding claustral connections in human brain [42,43]. Exploration of new pathways is prone to criticisms, due to intrinsic limitations of tractographic process; thus, diffusion based conclusions should be taken cautiously [44]. Nevertheless, it has been demonstrated that by means of tractography it is possible to obtain comparable results to those achieved in animal models by means of invasive techniques like virus tracing studies. Diffusion-based investigations have provided also interesting information in subjects with congenital malformations, such as cerebellar or callosal agenesis, offering a structural basis to explain clinical deficits as well as functional compensation observed [45-47].

Neurological Disorders

As it has been already mentioned before, DWI is highly sensitive in detecting white matter alterations. For instance, through quantitative evaluation of tensor based parameters we have previously introduced, radiologists and clinicians are able to obtain accurate evaluation of axonal integrity. In this context we want to focus in particular onto *fractional anisotropy* (FA) and mean diffusivity (MD), which are considered two indirect markers of axonal integrity: MD provides information about average local diffusivity. FA is a measure of the water anisotropy. If axonal structure is compromised by a pathological process, membrane disruption induces changes in relationship between intra-axonal diffusivity which decreases (FA decrement) and subsequent

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increasing of global diffusivity due to diminished hindrance (MD increment) [48] (Figure 4). Presence of edema, axonal swelling, ischemic injury or other conditions, such as alterations of other glial components, also participate to diffusion parameters alterations [48]. A recent validation study has demonstrated that diffusion parameters measurements can be considered effectively useful biomarker for evaluating white matter damages; combined use of FA and MD with other parameters, such as AD and RD, may thus allow to increase sensitivity in detecting and distinguish different types of brain alterations [49].

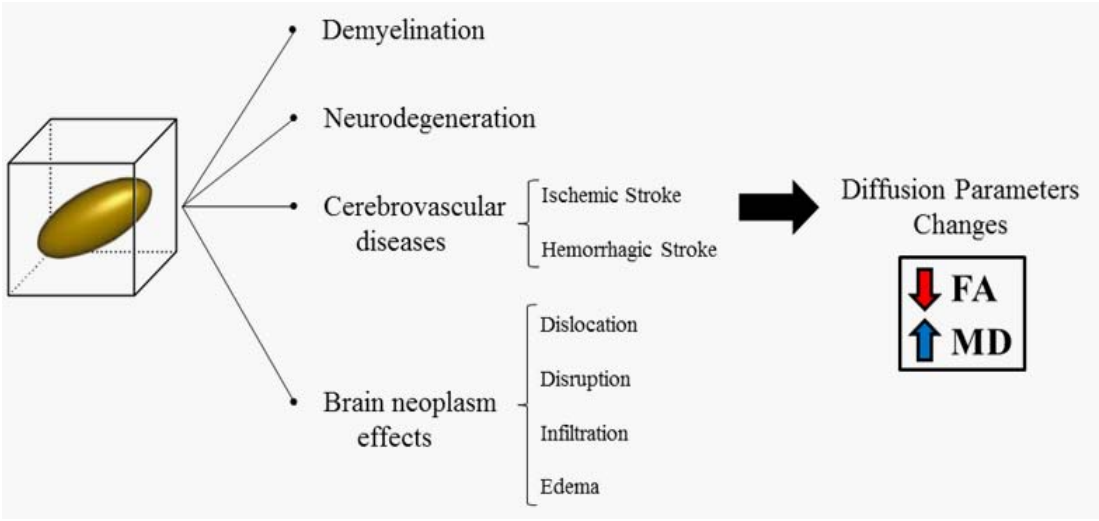


Figure 4: Main causes of diffusion parameters changes in pathological contexts.

Thanks to such powerful tool, almost all neurological disorders can be investigated. Since it is impossible to fully describe all results achieved in this field, only illustrative cases of the most common neurological diseases are provided. Parkinson's disease (PD) is a common neurological disorder characterized by dopaminergic neurons loss.

Diffusion-based evaluations have contributed both to understand structural changes as well as to differentiate different forms of PD. First of all, by analyzing tensor parameter changes in a voxel-based fashion, dMRI has been used to distinguish typical PD from atypical parkinsonian syndromes (like Multiple System Atrophy and Progressive Supranuclear Palsy). In literature, following structures have been investigated: frontal lobe, substantia nigra, corpus callosum, cerebellum, cerebellar peduncles, pons, internal capsule, thalamus, basal ganglia [50-60]. Moreover, these techniques are able to differentiate degenerative parkinsonian syndromes from vascular ones [61] as well as from patients affected by familiar essential tremor [62]. In parkinsonian patients tractographic reconstructions have been found useful for evaluating white matter changes, in this case by means of tract-based approaches, as well as to perform pre-surgical planning in cases of deep brain stimulation surgery [51,63-66].

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Diffusion-based evaluations are widespread used in cognitive disorders as well; for instance, they contributed to demonstrate that Alzheimer's disease (AD) is only related to GM alterations. GM and WM analyses have helped indeed to better characterize AD etiopathogenesis as well as its progression [67,68]. Tractographic and diffusion parameters evaluations of brain pathways have revealed wide alterations of WM connections, helping to localize which brain circuits are mainly affected, such as frontal, temporal and limbic ones [69-71]. It has been also possible to differentiate AD from other cognitive diseases, such as mild cognitive impairment and vascular dementia [72,73]. Attempts have been made in order to early detect of WM alterations at pre-clinical stages [74] as well as to predict of atrophic progression [75-77].

dMRI has proven its ability to better understand and characterize stroke. First of all, a breakthrough has been achieved for accurate diagnosis and staging of ischemic stroke; indeed, evaluation of the triphasic progression of apparent ADC allows in differentiating between acute, sub-acute and chronic stages [78]. Moreover, the combined use of diffusion-based acquisition and perfusion-based one allows the evaluation of the so called *ischemic penumbra*, i.e. a hypo-perfused area surrounding the ischemic core which can be recovered by means of an immediate therapeutical intervention [79]. Similar useful information can be obtained in hemorrhagic stroke [80]. Moreover, tractographic and quantitative evaluations of eloquent WM pathways can help to predict functional recovery after acute event as well as patients' outcome [81-83]. Summary of the most common clinical applications based on tensor parameters changes are shown in Table 2.

Table 2: Clinical applications of diffusion-based qualitative and quantitative analyses in common brain diseases. Main diffusion parameters changes are reported as well.

Brain Disease	Clinical Application	Main Diffusion Parameters Changes
Brain Neoplasms and Metastases	Detection and Evaluation of Eloquent Pathways in Pre-Surgical Planning	FA decrement and MD increment due to loss of structural integrity, mass effect on white matter bundles and peritumoral edema.
Neurodegenerativ Disorders	White and Grey Matters Changes Detection through connectivity, voxel-based, tract- based and quantitative analyses	FA decrement and MD increment due to loss of axonal structural integrity, precipitation of pathological components, neuroinflammation.
Ischemic Cerebrovascular Disorders	White and Grey Matters Changes Detection through connectivity, voxel-based, tract- based and quantitative analyses	ADC decrement (acute phase); ADC normalization (subacute phase); ADC increment (chronic phase). FA decrement due to structural damage.
Hemorrhagic Cerebrovascular Disorders	White and Grey Matters Changes Detection through connectivity, voxel-based, tract- based and quantitative analyses	FA decrement and MD increment.

Pre-Surgical Planning

DWI has been adopted to perform pre-surgical investigation of brain pathways, i.e. pre-surgical planning. This is required both in neoplastic patients as well as in all other cases requiring neurosurgical intervention, such as epilepsy surgery or the abovementioned deep brain stimulation. The goal is to optimize surgery preserving brain functions. This is particularly important for eloquent pathways, such as corticospinal tract, arcuate fasciculus and optic

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radiations, whose damages have a bad impact on patients' quality of life. In combination with other techniques such as intra-operative stimulation and neuronavigation systems, tractographic pre-surgical planning of brain neoplasm has been demonstrated to improve patients' prognosis by optimizing maximal safe resection margins and also significantly reducing post-surgical deficits [84,85]. Thanks to dMRI, surgical improvement as well as brain functions preservation in patients with drug-resistant epilepsy [86,87] or brainstem cavernous malformations [88] has been shown.

The use of more advanced diffusion models (such as CSD) has been demonstrated to be able to further improve information obtained for pre-surgical planning by reducing limitations of DTI- based approaches [89,90]. In particular, moving beyond DTI, more advanced approaches have been found to be more sensitive in distinguishing different neoplastic effects on WM bundles, such as dislocation, infiltration, disruption and edematous involvement.

Validation and Limitations of Diffusion MRI Tractography

The proper validation of diffusion MRI tractography has represented an issue from the beginning of its discovery. Since an adequate gold standard is lacking, different studies have tried to validate the proper recognition of complex axonal configurations both in human and in animal models. Using a highly gyrated porcine brain, Dyrby and colleagues [91] have assessed the anatomical validity and reproducibility of in vitro multi-fiber probabilistic tractography against invasive tracers. They have demonstrated that probabilistic MRI tractography is able to reliably detect specific pathways. In a similar recent study performed on macaque's brain again [92], a good fidelity of dMRI tractography in estimating the presence or absence of WM connections has been suggested. Moreover, a strong agreement between DTI fitted principal diffusion direction and myelin orientations has been demonstrated at high spatial resolution and ultra-high field (9.4Tesla) in post mortem human brain tissue [93].

As we have already mentioned in the text, dMRI tractography suffers from a number of limitations; in some cases those may be knock out with different MR sequences expedients, choice of the tractographic reconstruction algorithms and proper MRI scanner settings. On the other hand, numerous inherent limitations – that cannot be overcome with current technologies – affect tractography. Most of them are related to the intrinsic inability to demonstrate the existence of synapses and gap junctions, as well as the signal directionality of transmission inside a tract [94]. Hence, one has to bear in mind that a reconstructed streamline should never be considered a real WM tract, but rather the mathematically driven most likely path that may suggest existence of an underlying given anatomical pathway. All these limitations are needed to be particularly taken into account in the evaluation of pathological conditions, such as stroke, demyelinating diseases or brain neoplasms.

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Integrated Approaches

In this section dMRI integration with other investigative approaches is briefly discussed. Their combined use has allowed to investigate different brain characteristics both in physiology and in brain diseases, providing an improvement in knowledge of brain processes and neurological pathologies. As a fundamental premise, although this section has been developed considering these techniques coupled in order to simplify the discussion, it should be underlined that often integrated methods include more than two different approaches.

Diffusion with fMRI

Functional MRI (fMRI) is a technique able to analyze blood oxygenation level dependent (BOLD) signal within each voxel in order to localize brain structures recruited during a given task. Combining this functional information with structural one provided by diffusion, it is possible to achieve different goals. First of all, one of the most challenging questions regarding tractography regards ROIs placement for tracking fibers bundles. Manual and automatic approaches are widely used, both suffering from different limitations (i.e. operator dependent bias for manual selection and imperfect ROIs matching for automatic ones). In this context, the use of fMRI-derived ROIs for reconstructing a specific circuit may offer a more subject-specific investigative approach [95], although it requires an increased scan time. Moreover, it is possible to combine functional connectivity with structural one in order to obtain a global view of specific brain processes investigating also the relationship between structure and function of a given circuit [96]. Furthermore, diffusion-fMRI combined approach has been found very useful for study of brain diseases, allowing correlations between fMRI signals changes and structural integrity alterations as well as detection of aberrant circuits [97-99].

Diffusion with brain stimulation

The integration of diffusion-based techniques with both non-invasive and invasive brain stimulation ones is largely adopted in research, clinical as well as surgical contexts. Diffusion combined with transcranial magnetic stimulation (TMS) can provide useful information regarding physiological aspects of a given circuit as well as connectivity changes induced by neuroplasticity processes; this multimodal non-invasive approach has been found also a useful tool to assess functional recovery after acute events as well as the effects of rehabilitation protocols [100-102].

On the other side, invasive deep brain stimulation used together with dMRI has allowed a better detection of eloquent bundles before neurosurgery as well as a better surgical management of neoplastic patients both in terms of surgical effectiveness and in reduction of postoperative deficits [66,103]. From this point of view, it is worth to notice that the integration of diffusion MRI data into neuronavigation systems has significantly improved surgical outcomes in terms of neoplasm's resection, functional deficits and patients' survival [84].

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Diffusion with EEG

Electroencephalography (EEG) used in combination with DWI offers several interesting hints both for researchers and clinicians. Indeed, information obtained by means of this multi-methodological approach have been incorporated in order to investigate networks and brain connectivity; for instance, it has been possible to draw inferences regarding the plausibility of EEG electrical activations with respect to a given pathway [104,105]. In pathological contexts, such as AD, mild traumatic brain injury and epilepsy, dMRI-EEG combined investigation have permitted to introduce new features for diagnosis, altered pathways localization, management and progression assessment [106-110].

Diffusion with neuropsychological tests

A number of neuropsychological tests are commonly used to evaluate cognitive functions. By attributing scores for each skill investigated, it is possible to have a view of cognitive deficits in brain diseases. In this context, diffusion-based tractographic and quantitative evaluations are employed to verify whether the clinical assessment is supported by brain structural alterations; diffusion tensor parameters evaluation have been demonstrated to provide correlations between loss of brain structural integrity and cognitive impairment [111-115]. Moreover, this combined analysis is also able to verify progression of cognitive impairment as well as to understand whether cognitive rehabilitations protocols provide clinical recovery due to neuroplasticity [116]. Finally, moving beyond pathological contexts, this kind of evaluation has been demonstrated to provide information regarding physiological progression of aging effects on brain connectivity and functions [117].

CONCLUSION

In this chapter a didactic and complete description of diffusion MRI approaches was reported. We showed diffusion theoretic principles in an understandable way for clinicians. Moreover, we described the main clinical applications of such approaches, alone or in combination with other investigative techniques; we reported also differences and possible analysis improvement provided by the choice of advanced diffusion modeling algorithms. Finally, we described how diffusion techniques have been histologically validated as well as the principal limitations of diffusion-based approaches.

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