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Time-dependent diffusion magnetic resonance imaging: measurement, modeling, and applications

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Abstract: Increasingly, attention is being directed towards time-dependent diffusion magnetic resonance imaging (TDDMRI), a method that reveals time-related changes in the diffusional behavior of water molecules in biological tissues, thereby enabling us to probe related microstructure events. With ongoing improvements in hardware and advanced pulse sequences, significant progress has been made in applying TDDMRI to clinical research. The development of accurate mathematical models and computational methods has bolstered theoretical support for TDDMRI and elevated our understanding of molecular diffusion. In this review, we introduce the concept and basic physics of TDDMRI, and then focus on the measurement strategies and modeling approaches in short and long diffusion time domains. Finally, we discuss the challenges in this field, including the requirement for efficient scanning and data processing technologies, the development of more precise models depicting time-dependent molecular diffusion, and critical clinical applications.

Key words: time-dependent diffusion; diffusion magnetic resonance imaging; microstructure imaging; microstructural model

1 Introduction

Diffusion Magnetic Resonance Imaging (dMRI) is a promising "Super Resolution" technology widely used in preclinical and clinical research, which probes the microstructure of tissues by measuring the diffusion behavior of water in different microenvironments and enables non-invasive depiction of voxel averaged information of biological tissues at the cellular scale.

Time-dependency is a fundamental characteristic of the diffusion behavior of water molecules in biological tissues. The diffusion process is significantly influenced by cellular and subcellular structures. During short diffusion times, the diffusion distance is limited and the molecules hardly encounter tissue structures, behaving more as if in free diffusion. However, as the diffusion time increases, the diffusion distance also increases, leading to a higher likelihood of water molecules interacting with obstacles within the tissue. When the diffusion time is sufficiently long, the molecules become restricted within a compartment or move by exchange from the initial compartment to another. These effects are reflected in MRI signals, manifested as diffusion signal values positively correlated with diffusion time due to restriction in short timeframes, and approaching a negative correlation with diffusion time near the long-time limit due to exchange. It is important to note that with increasing diffusion time, the signal becomes more coarse-grained, resulting in the loss of microstructural details that reflect specific shapes, while the proportion of information representing global characteristics increases (Lemberskiy et al., 2017b; Reynaud, 2017; Novikov et al., 2019b; Xu, 2021; Wu et al., 2024).

To more accurately describe and quantify the time-dependent characteristics of molecular diffusion, researchers have proposed a series of mathematical models and computational methods (Kärger, 1985; Kärger et al., 1988; Novikov et al., 2011; Novikov and Kiselev, 2011; Novikov et al., 2014; Panagiotaki

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et al., 2014; Jiang et al., 2016; Reynaud et al., 2016; Jelescu et al., 2022; Olesen et al., 2022; Gardier et al., 2023). These models and methods not only provide strong theoretical support for time-dependent diffusion magnetic resonance imaging (TDDMRI) but also bring our understanding of molecular diffusion to a new level, forming the basis of the TDDMRITDDMRI technique. The models mentioned in this review are listed in Table 1.

Table 1. Summary of existing signal models mentioned in the paper

Model	Acquisition	Status of application	First proposed
POMACE	OGSE, PGSE	Animal model *in vivo* and *in vitro*	Reynaud et al., 2016
IMPULSED	OGSE, PGSE	Simulation, cell, animal *in vivo*, human *in vivo*	Jiang et al., 2017
VERDICT	PGSE	Cell, animal *in vivo*, human *in vivo*	Panagiotaki et al., 2014
rVERDICT	PGSE	Human *in vivo*	Palombo et al., 2023
SSIFT	OGSE, PGSE	Simulation, cell, animal *in vivo*, human *in vivo*	Devan et al., 2022
OGSE ActiveAx	OGSE	Simulation, animal tissue model	Kakkar et al., 2018
Power-law	OGSE, PGSE	Simulation, cell, animal *in vivo*, human *in vivo*	Novikov et al., 2014
RPBM	STEAM	Simulation, tissue, animal *in vivo*, human *in vivo*	Novikov et al., 2011
Karger model	PGSE	Simulation, cell, animal *in vivo*, human *in vivo*	Kärger, 1985
TDKI	STEAM	Simulation, phantom, animal *in vivo*, human *in vivo*	Jensen et al., 2005
JOINT	OGSE, PGSE	Simulation, cell, animal *in vivo*, human *in vivo*	Jiang et al., 2022
NEXI	PGSE	Simulation, animal *in vivo*,	Jelescu et al., 2022
CEXI	PGSE	Simulation	Gardier et al., 2023

TDDMRI has received increasing attention in recent years. It reveals changes in the diffusion behavior of molecules over time, allowing us to understand and reconstruct this complex biological process. The technique requires a series of time-series dMRI signals, which are decoupled to extract microstructural information by modeling the dMRI signal as a function of time, diffusion weighting, and microstructural parameters. Modern diffusion MRI is based mainly on a two-dimensional parameter space (*q-t* space) of gradient strength (diffusion weighting) and diffusion time (Burcaw et al., 2015). Previous studies have focused mainly on exploring the q-space as extensively as possible within clinical constraints, akin to observing the details of static samples with higher magnification and more orientations using a microscope. Recently, there has been a shift towards *t*-space-based research, which concentrates on discovering features by observing the dynamic changes of samples. This distinction represents a pivotal difference between these two categories of studies. However, it is essential to recognize that research within the *q-t* space is not disjointed: studies in the t-space also necessitate diffusion weighting to some extent. Thus, the TDDMRI used in this study includes diffusion MRI encoding that varies diffusion-time with or without changed diffusion-weightings, and strongly relies on the time-dependency.

Several efforts have been made to develop improved hardware and optimize advanced sequences to address the challenges of clinical transformation (Xu 2021; Wu et al., 2024), and TDDMRI has become a vital tool in clinical experiments. Specifically, TDDMRI is used extensively in the preclinical investigation of animal models pertaining to tumors (Panagiotaki et al., 2014; Jiang et al., 2016; Reynaud et al., 2016; Jiang et al., 2017; Jiang et al., 2019; Xiaoyu et al., 2020; Jiang et al., 2024), brain diseases (Novikov et al., 2014; Lee et al., 2020b), and other diseases (Novikov et al., 2011; Winters et al., 2018), thereby contributing substantially to foundational research in these fields. Clinically, TDDMRI has improved our understanding of disease pathophysiology, such as changes in cell size and permeability during tumor progression, and has refined diagnostic approaches. It has also shown promise in early tumor detection and neurological disease assessment by enhancing diagnostic accuracy (Panagiotaki et al., 2015; Fieremans et al., 2017; Xu et al., 2020; Lemberskiy et al., 2021; Zhang et al., 2021; Solomon et al., 2023). In summary, though still

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in the early stages of clinical translation, TDDMRI has shown significant utility across various disease models and diagnostic applications.

Despite these crucial developments in TDDMRI research, we still face many challenges. In the iteration of hardware and acquisition schemes, we need to develop more efficient scanning and data processing technologies to improve the quality and efficiency of imaging. As for research on theory and methodology, we need to propose more scientific and accurate models to describe and quantify the time-dependent behavior of molecular diffusion. In clinical applications, we should strive to develop more clinical application scenarios to translate this technology from basic research to clinical applications. Besides, the broader clinical application of TDDMRI necessitates multi-center studies, which have yet to be conducted.

In this review, we focus mainly on the two extreme time domains: short diffusion time and infinitely long diffusion time. The short-time domain captures insights into constrained microstructural information, while the long-time domain reflects the transmembrane water exchange in the diffusion process. Note that some models may simultaneously use assumptions from both time domains. In this paper, we classify models based on the types of parameters they mainly focus on. We first introduce the physical picture of water molecules diffusing in these two domains and define the division of long- and short-time domains. We then discuss the primary sequence protocols used in the two time domains and detail some widely used analytical and microstructure modelling imaging methods, as well as the application of these methods and models to various tissues and diseases. Some views on possible future directions of time-dependent diffusion technology are also presented.

2 Concept and Fundamental Issues

The diffusion time td plays an important role in restricted diffusion systems, and dMRI signals vary with td (Stejskal and Tanner, 1965). Typical diffusion measurements are more sensitive to length scale L(t) related to the root-mean-square displacement of diffusion $\langle x^2(t)\rangle$, i.e., $L(t_d) = \sqrt{\langle x^2(t_d)\rangle} = \sqrt{2dDt_d}$ where d represents the diffusion dimension, D symbolizes the diffusion coefficient, and t_d stands for the diffusion time. As t_d increases, water molecules coarsen the underlying microscopic structure on an increasing length scale $L(t_d)$. When $L(t_d) \to \infty$, the medium becomes completely homogeneous, yielding the asymptotic diffusion coefficient $D_\infty = const$. Thus, the effective diffusion will exhibit different forms as diffusion time increases. Due to the complexity and heterogeneity of biological tissues, it is impossible to describe the whole evolution process of $D(t_d)$ or $L(t_d)$ using mathematical formulas. However, we can obtain analytic solutions for extreme cases, resulting in approximate expressions of diffusion signals and diffusion coefficients under specific conditions. Generally, the tissue characteristic diffusion time $t_c \sim \frac{R^2}{D}$ serves as the boundary, where R is the restriction size of the tissue. If $t_d \ll t_c$, it is considered a measurement in the short-time regime, whereas if $t_d \gg t_c$, it is considered a measurement in the long-time domain or approaches the tortuosity limit situation. In practical applications, the typical constraints on t_d tend to be less than or equal to t_c for a short-time regime and an order higher than t_c for a long-time regime. Note that short- or long-time regime categorization is a relative concept, as the t_c's are quite different in various microstructures. Most thin nerve fibers in humans were found to be shorter than 2 μm (Saliani et al., 2017). Given radial diffusivity of around 1.5 μm^2/ms (Lee et al., 2020a), a typical short-time regime is of the order of a few milliseconds according to the equation $t_c \sim \frac{R^2}{D}$, whereas the size of tumor cells generally varies between 10-20 μm (Hao et al., 2018), corresponding to a short-time regime in the tens of milliseconds range. Therefore, our subsequent division of the long- and short-time regimes was based solely on the relative size of t_d compared to t_c, rather than comparing it to a fixed time value.

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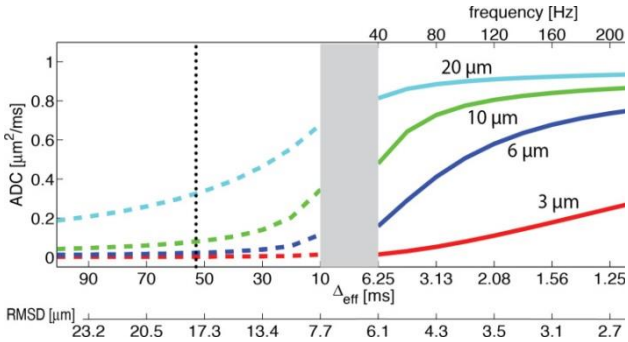

Fig. 1 The relationship between effective diffusion time (Δ_{eff}) and root mean square displacement (RMSD) in time-dependent diffusion, along with an example of time-dependent diffusion: Diffusion spectra of restricted water diffusion inside impermeable spheres with diameters of 3, 6, 10, and 20 µm. The gray band divides the spectrum into two regions, representing the readily accessible spectral ranges for PGSE (left) and OGSE (right) methods, respectively. Reprinted from Jiang et al. (2016).

3 Measurement strategies

3.1 Measurement in the short-time regime

The sensitivity to tissue microstructure depends on the applied gradient waveform for acquiring dMRI data. Measurements in the short-time regime generally apply the oscillating gradient spin echo (OGSE) sequence (Stejskal and Tanner, 1965; Mitra et al., 1992; Schachter et al., 2000), which replaces oscillating gradients with pulsed gradients (**Fig. 2A**), thereby achieving a shorter diffusion time under hardware limitations. The higher the oscillation frequency of OGSE, the shorter the achievable diffusion time. It is generally considered that the frequency f is related to the effective diffusion time t_{eff} according to $t_{eff} = \frac{1}{4f}$ (Parsons et al., 2003; Baron and Beaulieu, 2014; Xu et al., 2014). However, some research suggests this relationship might not be accurate (Lemberskiy et al., 2017a; Xu, 2021). Early OGSE imaging research used sine or cosine modulated gradient waveforms. To ensure a concentrated sampling frequency and achieve high b-values at a certain maximum gradient amplitude, cosine modulated trapezoidal waves (commonly referred to as cosine trapezoidal waves) (Van et al., 2014) were introduced and have been widely used in almost all recent human OGSE imaging studies (Gore et al., 2010; Xu, 2021). On standard clinical MRI systems (with maximum gradient G_{max} = 80 mT/m and maximum slew rate SR_{max} = 200 T/m/s), the realizable OGSE is generally f = 50 Hz and b = 500 s/mm^2. Recent preliminary measurements of OGSE using MAGNUS yielded f = 105 Hz and b = 1000 s/mm^2 with G_{max} = 200 mT/m and SR_{max} = 500 T/m/s (Foo et al., 2020; Tan et al., 2020).

3.2 Measurement in the long-time regime

For long-time regime measurements, the pulsed gradient spin echo (PGSE) sequence (Stejskal and Tanner, 1965) is widely applied for diffusion encoding due to its efficient diffusion weighting. This method uses two pulse diffusion gradients, each with a duration of δ and an interval time of Δ (**Fig. 2B**). The effective diffusion time is generally represented as $t_{eff} = \Delta - \delta/3$ (Stejskal and Tanner, 1965). In human MRI systems, due to hardware limitations, PGSE is capable of achieving only relatively longer diffusion times (e.g., t_{eff} = 20-100 ms) (Clark et al., 2001; Grussu et al., 2019; Lee et al., 2020b). Furthermore, the T2 relaxation in the spin-echo measurements at relatively long echo times greatly reduces the signal-to-noise ratio (SNR). Stimulated echo acquisition mode (STEAM) sequence (Merboldt et al., 1991) is also used for TDDMRI. The waveform is shown in **Fig. 2C**. After applying diffusion gradients, a third 90° pulse is applied to store the signal on the longitudinal plane. After a mixing time tm, another 90° pulse returns the longitudinal pulse to the transverse plane, thus eliminating signal T2 decay during the diffusion time. This effectively renders a more extended diffusion time and improves sensitivity to longer diffusion times (e.g., t_{eff} = 100-800 ms) (Zhang et al., 2021; Solomon et al., 2023). However, DW-STEAM leads to a reduction in signal by half, resulting in a lower SNR compared to traditional sequences (Kleinnijenhuis et al., 2018; Solomon et al., 2023).

These sequences were developed to capture the diffusion characteristics of microstructures in the short- and long-time regimes (e.g., restriction and exchange). Recently, novel waveforms, such as free gradient waveforms, have been proposed, allowing the selection of suitable models for the highest contrast based on the research purpose (Chakwizira et al., 2023). Several studies have combined the long- and short-time domain forms (Novikov et al., 2011; Jiang et al., 2016; Reynaud et al., 2016; Jiang et al., 2017; Jiang et al., 2019; Johnston et al., 2019; Jiang

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et al., 2021; Jiang et al., 2022). Reports suggest that the combination of high-frequency and low-frequency OGSE with standard PGSE gradients can achieve higher microstructural detection sensitivity (Xu et al., 2012; Xu et al., 2014). For biological tissues of changeable scales, the concepts of long- and short-time regimes are relative; therefore, it is essential to choose appropriate measurement scales and sequence protocols based on the observed structure's characteristics when measuring different tissues.

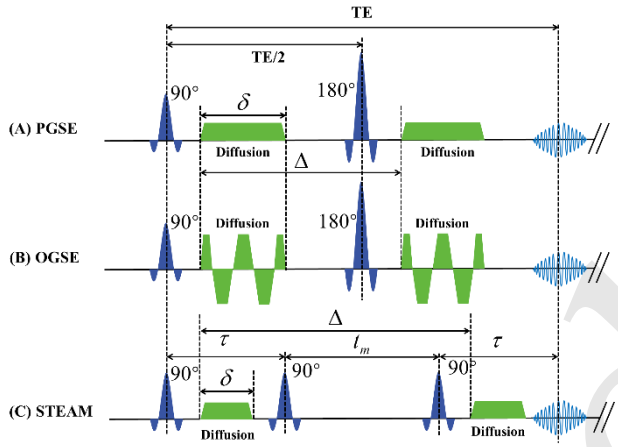

Fig. 2 Waveform of (A) PGSE, (B) OGSE, and (C) STEAM protocol. TE = echo time.

4 Simulation results and discussion

4.1 Diffusion in the short diffusion time regime

4.1.1 Physical picture: behavior of water molecules diffusing in the short-time regime

During the diffusion process in biological tissues, water molecules will continuously encounter barriers that limit or hinder diffusion. These restrictions or obstacles reflect the microscopic structure of the tissues, such as cell size and volume fraction, which in turn provide an opportunity for non-invasive exploration of tissue status. The progression of many diseases is often accompanied by alterations in cellular or subcellular microstructural characteristics. For example, differences are apparent in cell density and cell size between the substance, edema, and necrotic area of tumors and normal tissues. Neurological swelling caused by hypoxia and ischemia (Warach et al., 1995), astrocytic edema and morphological changes like bead-like formations (Budde and Frank, 2010), as well as alterations induced by mechanical pressure on the tissue are features of certain diseases (Hattori et al., 2011). Information reflected by the short diffusion time might offer greater sensitivity for detecting disease progression. Therefore, the short diffusion time provides powerful candidate indicators for the specific and non-invasive description of the cellular structural features of brain neurons, various tissue cells, and tumor cells.

4.1.1.1 Signal and ADC contrast

Many diseases can impact tissues at the cellular and subcellular scales, but alterations can be obscured by the coarse-graining effect of long diffusion times (Novikov et al., 2019b). It is evident that the short-time domain signal, typically obtained by OGSE, is different from the signal measured by PGSE and contains different microstructural information. The apparent diffusion coefficient (ADC) is a critical metric of diffusion MRI, reflecting comprehensive cellular-level information. However, in tissues, the ADC is expected to vary with the change of the b value (decreasing with increasing b value) and diffusion time (increasing for short diffusion times), and the changes of ADC over time (ΔADC)caused by the time-dependence of diffusion can also reflect additional microstructural information. Common indicators include a direct comparison between ADC_{OGSE} and ADC_{PGSE}, change in ADC (cADC = ADC_{OGSE}-ADC_{PGSE} or ΔADC), or relative change in ADC (rcADC = (ADC_{OGSE}-ADC_{PGSE}) / ADC_{OGSE}). As one of the earliest attempts to interpret ADC, diffusion tensor imaging (DTI) provides reliable microstructural indicators. The application of OGSE enables DTI to acquire new information at smaller scales hitherto unseen in typical PGSE imaging (Clark et al., 2001; Xu, 2021).

The differential diagnosis and treatment of tumors, especially brain tumors, continues to be a hot research area in medicine. In recent years, researchers have discovered that shorter diffusion times can yield a higher diffusion signal contrast or ADC differentials, providing a non-invasive method for distinguishing between benign and malignant tumors, tumors and normal tissues, and different types of tumors (Colvin et al., 2008; Colvin et al., 2011; Xu et al., 2012; Bongers et al., 2018; Iima et al., 2019; Zhu

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et al., 2023). Several mouse tumor model studies found that the tumor ADC measured by PGSE at typical diffusion times did not significantly differ from that of normal tissue , whereas the tumor ADC measured by short diffusion time OGSE was higher than that of the surrounding tissue, enhancing the contrast between tumor and normal tissue regions. Moreover, ADC_{OGSE} significantly increased during radiation and chemotherapy, corresponding to a response to treatment (Colvin et al., 2011; Xu et al., 2012; Bongers et al., 2018). These findings aligned with the results of human scan studies of various conditions such as head and neck tumors, brain gliomas and prostate tumors (Lemberskiy et al., 2017b; Lemberskiy et al., 2018; Iima et al., 2019; Zhu et al., 2023).

In addition, some studies have reported that malignant tumors exhibit more significant ADC differentials compared to benign tumors, which suggests the possibility of using ΔADC to determine the malignancy of tumors. Kamimura et al. (2023a) conducted a retrospective human study and successfully used ΔADC to distinguish between glioblastoma and brain metastasis in the enhanced region ($p < 0.01$), significantly surpassing the conventional ADC0Hz method in terms of AUC ($AUC_{\Delta ADC} = 0.877$, $AUC_{ADC0Hz} = 0.595$, $p < 0.001$). Maekawa et al. (2019) found that ADC values measured by OGSE (t_{eff} = 6.5 ms) and PGSE (t_{eff} =35.2 ms) were lower in choroid plexus cysts than in cerebrospinal fluid under short diffusion times, indicating restricted spatial diffusion and increased cystic viscosity. For non-axial brain tumors, high-grade tumors had higher ΔADC(max) and rADC(max) values for ADC absolute differences in OGSE and PGSE measurements than low-grade tumors ($p < 0.01$), while the ΔADC(max) values for normal white matter were lower than those for high-grade and low-grade brain tumors (Maekawa et al., 2020). Non-axial brain tumor studies showed that compared to meningiomas (ΔADC = 15.7 ± 4.4%) and auditory nerves (ΔADC = 12.4 ± 8.2%), pituitary adenomas (ΔADC =46.8 ± 11.3%) had the highest average (standard deviation) relative percentage change in ADC, i.e., they showed a stronger diffusion time dependency (Maekawa et al., 2023).

In addition to brain tumors, studies on hepatocellular carcinoma (Wagner et al., 2020) and breast cancer (Someya et al., 2022) have also shown greater temporal changes in ADC in the pericancerous area. Malignant tumors have higher ΔADC values than benign tumors (Iima et al., 2020a), and the ΔADC performance in different molecular types of breast cancer also differs (Iima et al., 2021).

Another major use for short diffusion time diagnostics is in strokes. As a sensitive method for diagnosing stroke, dMRI has been widely applied, and it has been reported that the contrast between ischemic lesions and normal tissue decreases with shorter diffusion times (Baron et al., 2015; Boonrod et al., 2018). Given PGSE's high sensitivity to stroke, short diffusion time OGSE imaging might not replace stroke diagnosis, but could provide new insights into stroke lesions (Xu, 2021). The difference in signal contrast between short and long diffusion times potentially results from stroke-related occurrences such as neural beading and axonal swelling (Warach et al., 1995; Budde and Frank, 2010; Baron et al., 2015; Boonrod et al., 2018). Simulations and animal experiments have shown that ADC measurements from high-frequency OGSE can provide differences in contrast between cell layers (Aggarwal et al., 2012; Wu et al., 2014); cADC was significantly higher in the ipsilateral region of oxygen-glucose deprivation damaged brains, potentially indicating sensitivity to subcellular structures (Aggarwal et al., 2014; Wu et al., 2014; Wu et al., 2018b), a result confirmed by human experiments (Gao et al., 2020; Xu, 2021).

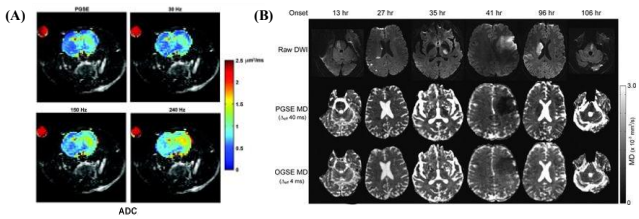

Fig. 3 (A) Color ADC maps of rat brain tissue inoculated with glioblastoma cells. A smaller td provides an increased contrast and shows more spatial heterogeneity inside brain tumors. Reprinted from Colvin et al. (2008). (B) Images of raw DWI, PGSE MD and OGSE MD of human brain with ischemic stroke. Reprinted from Baron et al. (2015)

In addition, the signal contrast brought about by

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shorter diffusion times, direct comparison between ADC_{OGSE} and ADC_{PGSE}, as well as the change in ADC values have provided new insights into the microstructural differences between different brain tissue structures (Grussu et al., 2019; Foo et al., 2020), and diagnoses of diseases such as NPH (normal pressure hydrocephalus), epidermoid cyst, multiple sclerosis, and Duchenne muscular dystrophy (Mcdowell et al., 2021; Xu, 2021). In animal and human experiments, OGSE DTI studies have consistently found that shorter diffusion times lead to significant increases in DTI eigenvalues of grey matter, and declines in the FA of white matter (Kershaw et al., 2013; Baron and Beaulieu, 2014). In one animal experiment, the frequency dependence of the vertical diffusion rate in the corpus callosum was significantly higher, and high-resolution 3D diffusion tensor images obtained from high-frequency oscillating gradients could be used to distinguish different cellular layers in the brain and cerebellum (Aggarwal et al., 2012). Recently, a study discovered that the time-dependence of diffusion tensor imaging is related to age and gender differences (Téreault et al., 2020). Frequency-dependent DTI using OGSE in whole-body gradient systems can be used for *in vivo* human research, but is restricted to relatively lower b values and/or oscillation frequencies (i.e., $f_{max} \times b_{max} \leqslant 0.035\ \mu m^{-2}$) (Dai et al., 2023).

Note that Xu et al. (2012) observed competing effects at different length scales in live tissue using diffusion MRI technology, with high-frequency OGSE being more sensitive to subcellular scales and PGSE being more sensitive to cellular scales. The signal expression in the mid-frequency range may be affected by changes in cell density and intracellular structure. Given the complexity and heterogeneity of biological tissues, the settings of effective diffusion times (Lemberskiy et al., 2018; Iima et al., 2019; Kamimura et al., 2023b) and the selection of thresholds (Shi et al., 2018) have a significant impact on the classification results based on ΔADC for distinguishing different tumors. Generally, variation brought by different diffusion times shows tremendous potential for distinguishing and diagnosing tumors using ADC values. However, since there is no standardized comparison sequence or ADC/signal intensity threshold for different diseases, differences stemming from different diffusion times are more suitable as auxiliary diagnostic information (Iima et al., 2020a). More quantitative research and long-term clinical validation are still needed to standardize the process of data analysis, improve the accuracy of differentiation, reduce the risk of misdiagnosis, and eventually achieve individualized, precise disease diagnosis and prognosis.

4.1.1.2 Frequency dependency of *D*(*t*)

Measuring diffusion signals and diffusion metrics over a wide range of frequencies and diffusion times can obtain the diffusion spectrum, which is the ideal parameter for describing the comprehensive information of tissue microstructures (Xu, 2021). If we consider $t \approx 1/\omega$, then at the high-frequency range ($\omega \to \infty$), the equation derived by Mitra et al. (1993) and Parsons et al. (2006) in porous media can be generalized under both PGSE and OGSE as $D(t) \sim \omega^{-1/2}$ (Novikov and Kiselev, 2011; Xu et al., 2011). In the short-time domain, its expression is as follows (Novikov and Kiselev, 2011):

$$D(\omega) \cong D_0\left(1 - \frac{4}{3d\sqrt{\pi}} \cdot \frac{S}{V}\sqrt{\frac{D_0}{\omega}}\right), D_0 \equiv D|_{\omega\to\infty}$$

The validity of surface-to-volume ratio (S/V) estimates was verified on sedimentary rocks and beads (Reynaud, 2017). Note that studies have shown that although in extremely short diffusion times, subcellular structures such as the cell nucleus may affect the accuracy of the expression, the relative apparent *S/V* still provides a valuable parameter to describe the microstructure of tissues (Xu et al., 2011; Reynaud et al., 2016). In cellular models, an average ADC dispersion rate in the range 50–250 Hz demonstrated sensitivity to the treatment of colorectal tumor SW620 with barasertib (Reynaud, 2017). In mouse models, high frequency oscillating gradient images revealed different frequency dependencies for different cellular layers (Aggarwal et al., 2012; Wu et al., 2014). For example, in a model of demyelination, structures with high frequency dependent ADC increases were pronounced in demyelinated mice (Aggarwal et al., 2012).

However, *ex vivo* experiments performed on kidney and liver tissue showed very little contrast with dispersion rate compared to conventional ADC

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(Reynaud, 2017).

In humans, the diffusion time required for the spatial scale of human muscle fibers (30-50 μm) is several hundreds of milliseconds, making short-time domain research viable (Novikov et al., 2011). The Mitra mechanism range of human brain fibers may be less than 1 ms, thus requiring frequencies greater than 1 kHz. In clinical MRI systems, due to the limitation of gradient strength, short diffusion time mechanisms are often less suitable for detecting the mesoscale structures in biological tissues.

Therefore, the power law form of the short-time domain is more suitable for reflecting structural features, differentiating between long- and short-time domains, or being applied as a constraint condition in models such as RPBM (Novikov et al., 2011) or POMACE (Reynaud et al., 2016).

4.1.1.3 Frequency dependency of *K*(*t*)

In addition to the frequency dependence of ADC or DTI eigenvalues, studies have found that kurtosis values also show frequency dependence. Numerous simulations and animal experiments have observed the non-monotonic behavior of kurtosis changing with time, increasing in the short-time domain and decreasing in the long-time regime (Aggarwal et al., 2020; Lee et al., 2020b). However, this phenomenon has not yet been observed in human experiments.

Even under the OGSE sequence with the highest frequency of 47.5 Hz, Dai et al. (2023), using the high-performance MAGNUS gradient magnetic resonance imaging system, observed frequency dependence of diffusion rates and kurtosis in both entire and localized WM and GM areas of humans, but the kurtosis always showed a decreasing trend over time.

In mouse experiments, Wu et al. (2018a) reported that OGSE kurtosis measurements could provide more information about microstructural changes after ischemic stroke. However, due to technical challenges such as the performance of gradient systems, discoveries from simulation and animal studies regarding time/frequency-dependent diffusion MRI have not been fully translated into *in vivo* human research (Borsos et al., 2023; Dai et al., 2023).

4.1.2 Models and applications

Within the short-time regime, novel insights into the diagnosis of various diseases rely mainly on signal contrast, the time dependence of the signal in the short-time domain, and the quantified biophysical indicators of cell structural features.

Microstructure modeling in the short-time domain typically assumes Gaussian diffusion and simplifies cells into basic geometric structures, such as axonal cells viewed as cylinders, or tumor cells viewed as spheres or hollow spheres. The signal expression measured by the PGSE sequence in simple geometries was first derived by Stejskal and Tanner (1965). Jiang et al. (2016) recently updated the expression measured using the OGSE sequence, meeting the need for signal analytical expressions at shorter diffusion times. Based on these expressions, there are currently three models that are widely used preclinically or clinically: IMPULSED (Jiang et al., 2017), POMACE (Reynaud et al., 2016), and VERDICT (Panagiotaki et al., 2014).

4.1.2.1 POMACE

The POMACE model is a two-compartment model in the absence of exchange (Reynaud et al., 2016). It measures a high-frequency OGSE to estimate the surface-to-volume ratio and free diffusion rate D_0, and then fittings are made to the model of impermeable spheres soaked in ECS, with low-frequency OGSE and PGSE measurements assessing four model parameters (ECS, R_{cell}, D_{ICS}, and D_{ECS}). POMACE is used mainly for tumor models.

In vivo and *in vitro* experiments on the GL261 glioma mice model showed that the measured ECS matched previous research and correlated well with microscopic optics. Additionally, cell sizes broadly aligned with EM measurements. However, the high oscillating frequency of OGSE makes clinical translation of POMACE a great challenge (Reynaud, 2017). As yet, there are no cases of POMACE being used in humans.

4.1.2.2 IMPULSED

The IMPULSED model is also a two-compartment model without exchange (Jiang et al., 2017). It collects OGSE measurements at various frequencies and a single PGSE measurement at a relatively longer diffusion time. This model quantifies microstructural parameters such as cell size,

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density, and intercellular and extracellular diffusion coefficients, with a primary focus on size estimation. Its basic form is

$$S/S_0 = f_{in}S_{in}(d, D_{in}) + (1 - f_{in})S_{ex}(D_{ex0}, \beta)$$

where f_{in} is the relaxation-weighted intracellular signal fraction and S_{in}/S_{ex} is the intra-/extracellular signals. S_{in} is modeled by diffusion within spheres of diameter d, with intrinsic cytosol diffusivity D_{ex0}. S_{ex} is modeled as

$$S_{ex}(D_{ex0}, \beta) = exp[-b(D_{ex0} + \beta)]$$

The IMPULSED model is applied mainly to brain, breast, and liver tumor models. Initial experiments on mouse erythroleukemia (MEL) and human K562 early granulocytic leukemia cells demonstrated a high consistency between cell diameters estimated by the model and cell sizes obtained from optical microscopes (Jiang et al., 2017). Jiang et al. (2017) further demonstrated that the IMPULSED model, using a high-frequency f = 150 Hz (t_{eff} = 1.7 ms) OGSE, low-frequency f = 50 Hz (t_{eff} = 5 ms)OGSE, and PGSE (t_{eff} = 46.7 ms) in *in vivo* tumor models, showed a positive correlation between the histology of tumor cells and IMPULSED derived cell density (Spearman coefficient = 0.81; $p < 0.0001$). They also found that using MRI to derive cell size could detect significantly reduced triple-negative breast tumors after treatment ($p < 0.05$). This demonstrated the feasibility of applying the IMPULSED method for deriving quantitative microstructural parameters in preclinical tumor models and its capacity as a biomarker to describe cancer characteristics and prognosis, and to detect radiotherapy responses (Jiang et al., 2017; Jiang et al., 2019; Xiaoyu et al., 2020; Jiang et al., 2024).

Xu et al. (2019) reported the first application of OGSE imaging in human breast tumors *in vivo* with t_d ranging from 8.77 to 66.7 ms. They mapped microscopic indicators such as breast tumor cell size, and assessed variation in cell size within tumors of breast cancer patients (Xu et al., 2020). They also reported the first application of OGSE imaging in human livers *in vivo* with t_d from 2.5 to 38.7 ms (Jiang et al., 2020). Studies thereafter demonstrated the clinical feasibility of characterizing the cell microstructure using the IMPULSED model. Zhang et al. (2023) measured the IMPULSED signals using OGSE (f =50 Hz and 25 Hz) and PGSE (t_{eff}=30 ms) sequences while limiting the acquisition time to about 4.5 min. Their study showed a good correlation between IMPULSED-derived fin and histological results (r = 0.7, $p < 0.000$ and found that the cell density derived from IMPULSED (cellularity = diameter/f_{in}*100) had the highest AUC (0.91) in distinguishing high and low-grade gliomas, outclassing traditional indicators. Ba et al. (2023) also verified that in breast cancer cells, the correlation between IMPULSED estimated diameter and histological values was very good (r = 0.84, $p < 0.0001$), and the size of breast tumors derived from the IMPULSED model had significance in distinguishing breast tumor molecular subtypes, with estimated d significantly higher than that in the HER2-positive group and LN-positive group ($p < 0.05$). They also reported the high requirements of the IMPULSED model in clinical trials for sequence aspects such as minimum diffusion time and SNR.

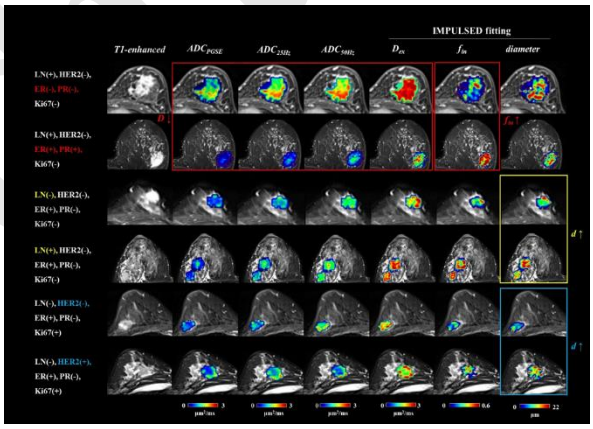

Fig. 4 IMPULSED-derived microstructure properties of breast tumor. Reprinted from Ba et al. (2023).

However, IMPULSED simplifies cancer cells as spheres and assumes that the average cell size derived from the use of IMPULSED includes all cell types (such as cancer cells, matrix cells, and lymphocytes). It is challenging to specifically distinguish between cancer cells and other cells without anticipating the distribution of cell sizes. Refinements to the IMPULSED model would need to consider estimating cell morphology, cell distribution (Xu et al., 2021), membrane permeability (Jiang et al., 2022), modeling of extracellular space (Xu et al., 2023), and the effects of IVIM and T2 relaxation. The improvements in modeling assumptions and clinical use with TDS to some extent enhance the accuracy and stability of the

model. Some researchers are working to improve the stability and accuracy of model fitting in the fitting algorithm to enhance the robustness of fitting under a low SNR (Wu et al., 2023). However, the microstructural parameters estimated by each model have not been compared clinically, and the effectiveness of the model needs to be more extensively tested.

4.1.2.3 VERDICT

VERDICT is a biophysical, multi-compartment model fitted on DW-MRI measurements (Panagiotaki et al., 2014). This model focuses on diffusion times of t_{eff} = 10-40 ms, a timeframe achievable by PGSE sequences, thus making it more suitable for clinical application. The VERDICT model measures PGSE sequences in various directions and at multiple b-values. Characteristically, it considers vascular modeling, giving it more parameters and increased complexity. Its basic form is as follows:

$$S/S_0 = f_{ic}S_{ic}(d, D_i) + f_{EES}S_{EES}(D_e) + (1 - f_{ic} - f_{EES})S_{vasc}(D_{vasc})$$

where D_i, D_e, and D_{vasc} are the intrinsic diffusivities, and f_{ic}, f_{EES} and f_{vasc} are relaxation-weighted signal fractions ($f_{ic} + f_{EES} + f_{vasc} = 1$) of the intracellular space, extracellular space and vascular ADCs, respectively. d is the cell diameter. In practical applications, several parameters are usually fixed to enhance parameter fitting stability including D_i, D_e, and D_{vasc}.

VERDICT is applied mainly to diseases rich in vascular changes, such as prostate cancer. Its *first in vivo* application was to quantify and map histologic features of tumors. Results showed that the intracellular volume fraction derived from VERDICT is extremely close to microstructural parameters obtained from histological stained slices, with cell volumes being slightly larger – possibly due to shrinkage during tissue slice preparation. Experimentation on colorectal adenocarcinoma xenografts in mice indicates that different tumors yield significantly different VERDICT-derived intracellular volume fractions, cellular size indices, and pseudo-diffusion coefficients, demonstrating VERDICT's potential for studying tumors on a region-based level and revealing underlying heterogeneity.

Panagiotaki et al. (2015) demonstrated the feasibility of applying VERDICT to prostate cancer in a clinical setting. They found significant increases in estimated f_{ic} and f_{vasc} and a decrease in the f_{EES} (p = 0.05) for malignant peripheral zones compared with benign peripheral zones. This finding has been replicated by multiple research groups and inspired more researchers to explore the application of the VERDICT model in prostate cancer (Johnston et al., 2016; Bailey et al., 2018; Johnston et al., 2019; Singh et al., 2022).

However, key challenges to VERDICT's clinical application remain, including the specific assumptions about cell structure and substantial signal loss due to relaxation during long spin-echo times. While a discussion has emerged around different modeling approaches for each part concerning the goodness-of-fit of data, the adoption of the Ball-Ball-Sphere (BBS) model for the three compartments may better explain microstructural characteristics of prostate bone metastatic tumors (Bailey et al., 2018), reflecting the need to fine tune model assumptions in various clinical applications. Palombo et al. (2023) developed the relaxation-optimized model (rVERDICT), which provides T1/T2 estimates and microstructural parameters unaffected by tissue relaxation properties. In particular, due to the complexity of VERDICT models, pre-fixed parameters are generally used in clinical use, or more appropriate fitting tools are applied and developed to enhance their clinical feasibility (Fokkinga et al., 2023). Nonetheless, VERDICT requires acquisition optimization for high b-values (up to ≈3000 s/mm^2) and various Δ, δ along with potential TE in its recent extensions, suggesting it still relies on extended acquisition schemes that might be impractical in clinical scenarios with limited scanning time.

4.1.2.4 Other models

In addition to the primary models referenced above, there are other models applicable to brain tumor and cerebral fiber imaging. The SSIFT model (Devan et al., 2022) uses the area encased by signals at different times to distinguish brain tumors from peritumor edema and radiation necrosis due to the model's sensitivity to cell size. Karkar et al. (2018) suggested that estimates of axon diameter from using OGSE ActiveAx are more accurate and precise than those from using SDE. Herrera et al. (2022) proposed

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a model for studying human axons with diameters in the 1-2 μm range using OGSE sequences. This model emphasizes the necessity of axonal orientation dispersion, demonstrating closer fitting results than ActiveAx and histological outcomes.

4.2 Diffusion in the long diffusion time regime

4.2.1 Physical picture: behavior of water molecules diffusing in the long-time regime

Long-term diffusion approximates the tortuous limit of water molecule diffusion within tissues, leading to a coarse-graining effect at the cellular and subcellular scale. Given that the theoretical diffusion distance of water molecules surpasses cell size, the permeability of the cell membrane might emerge as a new index affecting the expression of the diffusion coefficient. On the other hand, local fluctuations in the weak heterogeneous media determine the asymptotic approximation of the diffusion coefficient to the tortuous limit. This provides an angle to noninvasively infer the global diffusion dimension of water molecules and the distribution of tissue structures. Some of these insights include identifying mesoscale structures affecting water diffusion in muscle and brain tissue based on specific values of the dynamic index during MRI measurement, or explicating structural changes underpinning the drop in diffusion coefficient during ischemic stroke (Novikov et al., 2014), and reflecting demyelination levels through changes in membrane permeability (Nedjati-Gilani et al., 2017).

Note that in numerous scenarios, these two mechanisms compete, i.e., water exchange phenomena exist between two compartments undergoing separate coarsening. Several articles have discussed this particular phenomenon (Lee et al., 2020b; Jelescu et al., 2022; Olesen et al., 2022). Lee et al. (2020b) discussed these two situations based on the water exchange time tex. In the long domain, if $t_d \ll t_{ex}$, the dominance of structural disorder is considered. If $t_d \cong t_{ex}$, the water exchange process plays a dominant role in signal expression.

4.2.2 Models and applications

4.2.2.1 Power-law

Mitra et al. (1993) and Parsons et al. (2006) proposed a power-law expression of the time dependence of the internal diffusion coefficient in the short-term domain. As the diffusion time increases, the power law might be affected by $D(t) \sim f^1$ or higher order quantities (Parsons Jr. et al., 2006; Xu et al., 2011). In the tortuous limit, weakly heterogeneous media exhibit local fluctuations, implying perturbative solutions to its diffusion time dependence. Novikov et al. (2014) supported the proposal that the dynamic index of the instantaneous diffusion coefficient $\mathcal{D}(t)$ altering over time can distinguish among universal categories of mesoscopic structural complexity.

$$\mathcal{D}(t) \sim D_\infty + A \cdot t^{-\vartheta}, \vartheta = \frac{p+d}{2}$$

Here, A is the associated strength of the structural disorder, which is being effectively coarse-grained (Novikov et al., 2019a) by the molecules traveling over an increasing diffusion length, and the structural exponent p determines the structural universality class in d spatial dimensions. The dynamical exponent ϑ characterizes diffusion in the long-time limit. dMRI typically measures the cumulative diffusion coefficient $D(t)$, which is the time-integrated instantaneous diffusion coefficient $\mathcal{D}(t)$. Therefore, a ϑ greater than 1 would be obscured by 1. The interpretation of ϑ determines the disorder in the placement of restrictions, enabling the identification of their exact source and the selection of the most suitable model based on the measurements. For example, $\vartheta = 1/2$ is the signature of a short-range disorder in 1D diffusion, and was observed in both healthy rat brains and those with large-scale ischemia. This indicates the decrease of the diffusivity in lesions is due to structural changes affecting the diffusion along randomly oriented narrow neurites, such as beading (Novikov et al., 2014; Lee et al., 2020b). On the other hand, the slope A reflects the role of disorder, and can be interpreted as changes in restriction properties, though the specific relationship requires further exploration (Lee et al., 2020a). Note that in different measurement directions, the power and slope may vary. For instance, while diffusion along the fiber in fresh *ex vivo* muscle tissue samples is unrestricted, the transverse components demonstrate dispersion with $\vartheta = 1/2$ in 2D diffusion. Therefore, it is crucial to evaluate dispersion effects in the main

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direction (Novikov et al., 2014; Lee et al., 2020a).

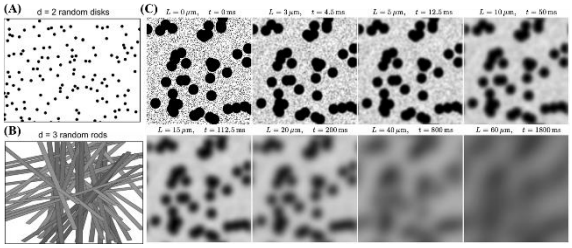

Fig (A, B) different structural universality classes in dimension d = 2 and d = 3. The figure is reprinted from (Lee,2020). (C) The coarse-graining illustrated by the diffusion in a medium where the mesoscopic structure is created by randomly placing black disks of two different radii. The figure is reprinted from (Novicov,2018).

Power laws provide theoretical support for understanding water diffusion patterns in brain, tumor, and muscle tissues. As mentioned above, ϑ = 1/2 has been demonstrated in both healthy and globally ischemic rodent brains (Does et al., 2003; Novikov et al., 2014; Wu and Zhang, 2017). Lee et al. (2020b) reported similar power in the cortical gray matter of humans, suggesting that short-range disorder with p = 0 in one dimension is a common microscopic characteristic of mammalian neuronal heterogeneity. Specifically, the diffusion in gray matter is dominated by intracellular diffusion, which is hindered mainly by spines and beads along dendrites and axons. The value of ϑ= 1/2 was also observed in the structure of mouse leg muscle fibers in the long-time range (Winters et al., 2018), indicating the characteristic of the extended permeable membranes (barriers) disorder class. This corresponds to 2D diffusion occurring between lines drawn at random angles on a plane. In the context of cancer, power-law behavior with ϑ = 1 has been reported in prostate cancer. The mean diffusivities in both benign and malignant peripheral zones decrease significantly with time according to a power law (t^{-1}) (p < 0.029), while this behavior is not observed in the benign transition zone. This could potentially reveal differences in microstructure characteristics among prostate regions. Additionally, the time dependence of t^{-1} could inform the selection of diffusion times in measurements to maximize the detection of significant differences in tumor grade (Lemberskiy et al., 2017b).

Recent studies have further explored the law. In measurements of both *in vivo* and *in vitro* animal experiments using PGSE (considered as 0 Hz) and OGSE (50-250 Hz), Xu et al. (2012) found that ADC had an approximately linear relationship with frequency. Hence, including PGSE as 0 Hz could potentially overshadow the frequency/time dependency of the measured ADC (Van et al., 2014). ϑ =1/2 (Arbabi et al., 2020) and a trend toward ϑ < 1(Baron and Beaulieu, 2014) have been observed in the *in vivo* human brain using f = 0-60 Hz and f = 0-50 Hz OGSE. In global white matter and some cortical ROIs, Dai et al. (2023) noted that the kurtosis index (ϑ_K) deviated from 0.5 or 1.0, indicating that in human cortex, the transition time of kurtosis from short to long time limits could be between 14.2 and 21.2 ms, during which a mixed effect of size restriction and water exchange could occur (Lee et al., 2020b; Dai et al., 2023).

4.2.2.2 RPBM

RPBM (Random Permeable Barrier Model) is a method that does not assume specific cellular geometric shapes. Novikov et al. (2011), who developed the RPBM model, found the disordered extended restrictions in d = 2 dimensions seemed to provide an adequate sketch of a cross-section of myofibers. This method assumes that the muscular membrane is the primary restriction for water movement, typically using STEAM sequences to cover diffusion times from tens to hundreds of ms. RPBM is characterized by three parameters: the free diffusion coefficient D_0, the membrane permeability κ (assumed to be the same for all membranes), and the ratio of membrane surface to volume S/V. Its basic expression is:

$$\mathcal{D}(\omega) = \frac{D_0}{1+\zeta+2z_\omega(1-z_\omega)\left[\sqrt{1+\frac{\zeta}{(1-z_\omega)^2}}\right]}, z_\omega = i\sqrt{i\omega\tau}$$

It is represented by three parameters D_0, ζ, and z_ω, where the effective "volume fraction" $\zeta = (S/V)/d$ occupied by the membrane (here d denotes the dimension of diffusion), and $\tau = D_0/(2\kappa)^2$. The real part of $\mathcal{D}(\omega)$ is determined by the signal measured by OGSE, while the results of PGSE are used for the fitting of the cumulative diffusion coefficient $D(t)$ (Novikov et al., 2011; Fieremans et al., 2017).

This model is used mainly in muscle tissues and

cancer models. A significant correlation between the measured *S*/*V* and the perimeter-to-area ratio (*P*/*A*) obtained from histology was found in murine leg muscle fibers *in vivo* ($r = 0.56$, $p = 0.025$) and *ex vivo* ($r = 0.71$, $p = 0.01$), suggesting a significant correlation in restriction size and revealing that muscle cell size and membrane permeability could be important microstructural indicators of muscle growth (Winters et al., 2018). Some studies in humans that explored the feasibility of clinical applications found that the microstructural markers explained by RPBM could potentially be used to reveal chronic exertional compartment syndrome (Sigmund et al., 2014), calf and shoulder muscle atrophy (Fieremans et al., 2017; Lemberskiy et al., 2021), and other potential insights into pathological changes in muscle tissue. Recently, RPBM was applied to *in vivo* studies of oropharyngeal squamous cell carcinoma, revealing a strong correlation between tumor *V*/*S* and histological results ($r = 0.47$, $p = 0.014$). It was shown to correlate with the clinical staging of OPSCC/OCSCC and could possibly be used to quantify microstructural parameters and the early response of cancer cells to treatment (Cao et al., 2024).

4.2.2.3 Kärger model

One crucial assumption of most biophysical models within the short-time domain is that water exchange between cells can be neglected, yet this assumption may not hold in the long-time regime (Nilsson et al., 2009; Jelescu et al., 2022). As a result, specific models incorporating intra- and extracellular water exchange should be developed. The most classic model is the two-compartments model with exchange capability, namely the Kärger Model (KM) (Kärger, 1985; Kärger et al., 1988). This model assumes that spins of two components occupy space at ratios of f_1 and f_2 respectively, with position-independent exchanges occurring. The diffusion coefficients are D_1 and D_2. Coupled Bloch–Torrey equations are used to describe the changes in dual-component magnetic density at any location in space. When the residue times τ1 and τ2 of the spins in the two compartments meet the equilibrium condition ($f_1\tau_2 = f_2\tau_1 = \tau_{ex}$) the equations give a double exponential form of signal attenuation:

$$M_t/M_0 = f_1' e^{-D_1' q^2 t} + f_2' e^{-D_2' q^2 t}$$

In this formula, Mt denotes diffusion-weighted transverse magnetization, and M_0 represents the value without diffusion weighting. The weighted volume fractions $f_{1/2}'$ and diffusion coefficients D_(1/2)^' are determined together with f_1, f_2, D_1, D_2, τ_1, τ_2, and the diffusion gradient vector $\boldsymbol{q}$.

A number of computer simulations have validated the effectiveness of the KM in the long-time domain and made corrections for the time-dependent restrictions of compartments within KM and the impact of T2 relaxation (Price et al., 1998; Stanisz et al., 1998; Meier et al., 2003; Harkins et al., 2009; Fieremans et al., 2010; Haddar et al., 2016). Results of cell experiments (Andrasko, 1976; Tanner, 1983), animal experiments (Paran et al., 2004; Jespersen et al., 2018; Jelescu et al., 2022; Olesen et al., 2022; Li et al., 2023), and human brain experiments (Nilsson et al., 2009; Lee et al., 2020b; Jelescu et al., 2022) indicate the applicability of KM in the context of red cells, brain white and gray matter, and tumor models, validating its effectiveness in capturing water exchange phenomena. According to the results based on KM fitting, water exchange in healthy human brain white matter is considered to be at the second or sub-second levelE, while demyelination leads to a reduction in exchange time (Nedjati-Gilani et al., 2017). Recently, KM has revealed that water exchange could be an indicator to measure microstructural characteristics in stroke patients (Lätt et al., 2009), developing brains or neurodegenerative diseases (Brusini et al., 2019; Olesen et al., 2022).

Note that, even though KM can be considered approximately valid in brain and muscle tissues (Fieremans et al., 2010), studies have found that KM fails in cases of rapid exchange (Fieremans et al., 2010; Nedjati-Gilani et al., 2017). Therefore, when KM is applied in processes involving rapid exchange, or applied to tissues with complex microstructures, the definition of multi-site exchange models seems ambiguous and needs careful discussion (Gardier et al., 2023).

4.2.2.3.1 Time dependent diffusion kurtosis imaging (TDKI)

DKI (Diffusion Kurtosis Imaging) reveals the non-monotonic changes of kurtosis values in water exchange, which increase in the short-time domain

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and decrease in the long-time domain (Jensen et al., 2005; Jensen and Helpern, 2010). When the diffusion coefficient of the object under study does not change with time, indicating complete coarsening, it means that the applicable range of KM has been reached, and thus the water exchange time can be fitted from the time-dependent tail change of $K(t)$:

$$K(t) = K_0 \cdot \frac{2\tau_{ex}}{t}\left[1 - \frac{\tau_{ex}}{t}\left(1 - e^{t/\tau_{ex}}\right)\right] + K_\infty$$

where K_0 represents the intrinsic kurtosis, t_{ex} is the exchange time, and K_∞ signifies the situation where non-exchanging compartments remain.

This method has been applied to the measurement of water exchange in animal and human brain gray and white matter (Aggarwal et al., 2020; Lee et al., 2020b; Li et al., 2023), and tumor cells (Zhang et al., 2021; Solomon et al., 2023). When using the STEAM sequence, the complete coarsening time ($D(t)$ is time-invariant) for mouse gray matter structure is expected to be between 100 and 200 ms. In the study by Li et al. (2023), the exchange time for *ex vivo* mouse white matter was measured to be 232.4 ± 16.0 ms ($K_\infty = 0$) and $\tau_{ex} = 17.6 \pm 10.5$ ms ($K_\infty > 0$). Zhang et al. (2021) used a diffusion time of up to 800 ms to measure the exchange time in living mouse cortex bands, which was 30-40 ms. When using the PGSE sequence, the time dependency of $D(t)$ becomes very weak for animal and human gray matter when the diffusion time exceeds 20 ms. Jelescu et al. (2022) used the PGSE sequence to measure the exchange time in rat brain gray matter cortex *in vivo* in the range of 10-45 ms, which gave τ_{ex} = 16-21 ms ($K_\infty = 0$) and τ_{ex} = 0.4-0.9 ms ($K_\infty > 0$). Lee et al. (2020b) used the PGSE sequence to measure the exchange time in human brain gray matter in the range of 21.2-100 ms, which showed an estimated exchange time of about 11 ms. As for tumors, Zhang et al. (2021) measured τ_{ex} = 68 ms in a mouse model of breast cancer and found similar exchange times (70 and 106 ms) in human experiments. Solomon et al. (2023) measured the water exchange time in clinical metastatic lymph nodes of head and neck cancer to be between 50 and 70 ms. The exchange times estimated in published studies are listed in **Table 2**.

Table 2. Application of transmembrane water exchange time estimation in different studies

ROI	Model	Exchange time (mean) [ms]	Reference
Animal brain gray matter	NEXI	22	Jelescu et al., 2022
	TDKI ($K_\infty = 0$)	21	Jelescu et al., 2022
	TDKI($K_\infty > 0$)	0.4	Jelescu et al., 2022
	TDKI($K_\infty > 0$)	41	Zhang et al., 2021
Animal brain white matter	NEXI	105	Jelescu et al., 2022
	TDKI ($K_\infty = 0$)	232.4	Li et al., 2023
	TDKI($K_\infty > 0$)	17.1	Li et al., 2023
Animal tumor	TDKI($K_\infty > 0$)	68 and 93 (breast cancer)	Zhang et al., 2021
Human brain gray matter	TDKI($K_\infty > 0$)	11	Lee et al., 2020b
	TDKI($K_\infty = 0$)	250	Lee, et al., 2020b
	Cumulant expansions	135	Chakwizira et al., 2023
Human brain gray matter	Cumulant expansions	285	Chakwizira et al., 2023
Human cerebellar gray matter	Cumulant expansions	115	Chakwizira et al., 2023
Human tumor	TDKI($K_\infty > 0$)	50-70 (head and neck cancer) 88 (breast cancer)	Solomon et al., 2023

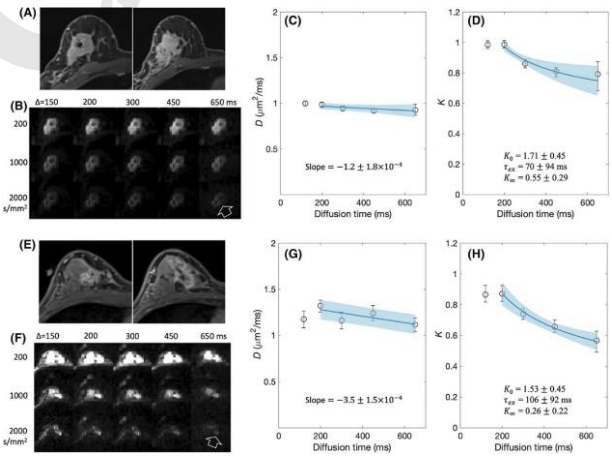

Fig. 6 tDKI data of two biopsy proven invasive ductal carcinomas in a 35-year-old woman (A-D) and a 56-year-old woman (E-H). In the long-time regime, the D(t) shows weak time dependency while K(t) drops significantly. Reprinted from Zhang et al. (2021).

4.2.2.3.2 Time dependent diffusion kurtosis imaging (TDKI)

One approach is to integrate the KM with multi-compartment models, specifying the two compartments of the KM as the intracellular (i.e., re-

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stricted) and extracellular (i.e., hindered) spaces. Sometimes a third compartment that does not participate in the exchange is added, considering the exchange between the intracellular and extracellular compartments, which better describes the phenomenon of water exchange existing in specific tissue structures such as brain gray matter, white matter, and tumors. NEXI and SMEX have been used mainly in studies of brain gray and white matter. Jelescu et al. (2022) estimated the exchange time of living rat gray matter to be 12-20 ms. The JOINT model (Jiang et al., 2022) and CEXI model (Gardier et al., 2023) have been used mainly in studies of tumor tissues. Studies have involved performing simulation verification on the application of permeable limited sphere models and cell models, aiming to simultaneously measure cell size and transmembrane exchange information. Due to the requirements of higher b-values (up to 104 s/mm2) and shorter diffusion times, NEXI and CEXI have not yet been applied in human clinical practice. Recently, a model that can extend KM to any number of compartments has been proposed, using new indicators to explain water exchange (Jensen, 2024). A measurement strategy such as the free-gradient waveform has been developed to decouple restriction and exchange (Chakwizira et al., 2023). However, the gray and white matter structure of the brain is very complex. Taking into account the volume ratio of gray and white matter, differences in T1 and T2 relaxation, the choice of diffusion time and sequence, estimates of water exchange time in different studies vary greatly. Even with the same model, different sequence parameters can yield different estimates. For example, in the four datasets used in NEXI, the water exchange time for the cortex changes in the range of 10-60 ms (Jelescu et al., 2022). Numerous studies have demonstrated the potential for exchange between multiple compartments in the gray matter and the confounding effects of microstructures, but there is a lack of histological verification for the measurement values of water exchange and an urgent need for appropriate optimization solutions to bring these models into clinical application. The activity of water exchange reflected by the water exchange time may reflect the activity of tumor cells, the level of myelination, and the acute cell swelling and final membrane breakdown after ischemic stroke and disease processes. Thus, it is critical in studies of etiology and disease mechanisms of tumors and brain diseases, early diagnosis, and monitoring progress changes in the process of drug development.

5 Future developments

5.1 Hardware and acquisition

The extension of the diffusion time spectrum depends on the implementation of OGSE with higher frequencies and b-values. Because $b \sim G^3/f^2$ (Xu, 2021), a stronger maximum gradient strength Gmax and faster slew rate (SR) are required to achieve a higher frequency f while maintaining a reasonable b value. Over the past twenty years, the development of high gradient technology has propelled the whole-body gradient system of mainstream clinical superconducting magnetic resonance scanners from a G_{max} of about 40 mT/m and SR_{max} of about 200 T/m/s to 240 mT/m and 200 T/m/s, respectively (United Imaging uMR Sagitta). In addition, the coil performance of the ultra-high gradient MRI system for head imaging has been increased to G_{max} = 650 mT/m and SR_{max} = 600 T/m/s. Under this system, the highest frequency f of OGSE can theoretically reach 250 Hz (t_d =1 ms) while keeping b = 500 s/mm^2. High-performance gradient systems can further enhance dMRI contrast and improve microstructural estimation accuracy (Wu et al., 2024).

Acquisition needs to be further improved to avoid undesired effects in the process. For instance, in current *in vivo* human studies, the use of OGSE in whole-body gradient systems is generally limited to relatively low b values and/or oscillation frequencies. To avoid signal attenuation caused by microcirculation flow at low b values, Wu and Zhang (2017) developed the DEFOG method. Some studies have also found that the effective spoiling gradient in the STEAM sequence (responsible for shattering the remnant magnetization after storage) may affect the theoretical diffusion time at long tm (Kleinnijenhuis et al., 2018; Solomon et al., 2023). Additionally, while it avoids T2 decay, the T1 decay effect in the STEAM sequence might also be a potential factor impacting the signal (Solomon et al., 2023).

5.2 Optimization of models

A model is a simplified sketch of reality that can describe only a few relevant features of a tissue when

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its assumptions are met. Therefore, the design of models needs to focus on the main estimation parameters and sensible design of each experiment (i.e., pulse sequences, protocol parameters, etc.) to provide the most meaningful biomarkers and contrast (Jelescu et al., 2020). For example, our understanding of brain gray matter has evolved from "soma affecting the power law (Palombo et al., 2020)" to "both soma and exchange affecting the power law (Jelescu et al., 2022)."

The model fitting strategy is a critical factor to consider when assessing a model's suitability for clinical applications. If a model includes too many free parameters, it may encounter difficulties during fitting. Given the presence of inevitable noise and artifacts in clinical scan data, it is essential to develop fitting algorithms that enhance accuracy, robustness, and efficiency. The use of techniques such as AMICO, machine learning, and deep learning networks has significantly enhanced the effectiveness of model fitting (Nedjati-Gilani et al., 2017; Bonet-Carne et al., 2019; Wu et al., 2023; Zheng et al., 2023).

Model validation requires histological inspection. Unfortunately, some models, such as water exchange, cannot obtain reliable histological validation (Lee et al., 2020b; Zhang et al., 2021; Li et al., 2023). Numerical models complement physical models as they provide a controlled and flexible tool to simulate how different mechanisms, such as diffusion, exchange, relaxation, and susceptibility changes, affect the MR signal in a given microstructural geometry. The development of simulation models (Hwang et al., 2003; Cook et al., 2005; Xu et al., 2007; Lee et al., 2021) and phantoms (Solomon et al., 2023; Xu et al., 2023) have greatly fostered the validation of models.

The development of models normally aims at generating quantitative biophysically specific imaging biomarkers. Numerous novel models and associated biomarkers have been proposed and used in disease diagnosis, prognosis, and various other domains (**Table 1**). However, despite these advancements, there remains a lack of multicenter validation, and the establishment of a universally acknowledged clinical application for microstructural maps remains elusive. Additionally, some techniques yield inconsistent, poorly understood, or contradictory outcomes, such as variations in water exchange time measurements across different models and discrepancies in axon diameter assessments. Hence, there is a pressing need for revolutionary modeling and validation studies, coupled with meticulous attention to calibration and reproducibility, to fully harness the potential of non-invasive three-dimensional intravital microstructural mapping (Novikov et al., 2018).

5.3 Clinical translation

Diffusion MRI lacks standardization. For example, in the diagnosis and treatment of breast cancer, the relationship between the ADC value and b value selection has been widely recognized (Baltzer et al., 2020), solving the problem of significant differences in ADC value results from different reports (Iima et al., 2020b). However, diffusion time is still a forgotten parameter, yet has a tremendous impact (Iima et al., 2021). Some studies have reported that different measurement times can cause up to 15% differences in ADC values (Someya et al., 2022), and in an extreme case, ADC could increase at long diffusion time but decrease at short diffusion time after treatments (Xu et al., 2012). The same problem also occurs in the diagnosis of other diseases. The standardization of diffusion time is also an important issue.

To apply *in vivo* microstructure imaging to cancer patients, the acquisition time must be tolerable, for example, about 10 min or less, as other anatomical and physiological images must be acquired from the same imaging process (Cao et al., 2024). For diseases like stroke that require urgent treatment, the patient's collection time needs to be even shorter. How to reduce collection time and ensure richer structural information puts high demands on the design of models and fitting algorithms.

6. Conclusions

There have been significant advances in TDDMRI research, with the technique gaining increased recognition as a powerful tool for revealing the microstructure of tissues. Advances in hardware, sequence designs, and the development of various mathematical models and computational methods have significantly enabled its application in diverse areas. From basic research to applications in early disease diagnosis, TDDMRI has shown great potential. However, there remain challenges to overcome. We must push for more efficient scanning and data processing technologies, develop accurate models to better describe and quantify the time-dependent behavior of molecular diffusion, and strive to develop

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more clinical application scenarios. Attention to these measures will ensure that this technology continues to evolve and provide invaluable insights into molecular diffusion in biological systems.

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Author contributions

Ruicheng Ba and Dan Wu designed the research, Ruicheng Ba and Dan Wu processed the corresponding data. Ruicheng Ba wrote the first draft of the manuscript. Dan Wu helped to organize the manuscript. Ruicheng Ba and Dan Wu revised and edited the final version.

Conflict of interest

Ruicheng BA and Dan WU declare that they have no conflict of interest.

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中文概要

题　目：时间依赖性弥散磁共振成像：测量，建模和应用

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目　的：介绍 TDDMRI 的概念和基本物理原理，然后重点讨论短扩散时域和长扩散时域的测量策略和建模方法。最后，我们讨论了这一领域面临的挑战，包括对高效扫描和数据处理技术的要求、开发更精确的描述时间依赖性分子扩散的模型以及关键的临床应用。

创新点：1. 总结了弥散核磁共振成像的最新进展，尤其是包括弥散时间依赖性的研究。2.概述了近年来有关这一主题的重要研究，并概述了一些潜在的未来方向。

结　论：1. 时间依赖性弥散磁共振成像研究取得了重大进展，该技术作为一种揭示组织微结构的强大工具得到了越来越多的认可。硬件、序列设计以及各种数学模型和计算方法的发展极大地促进了该技术在不同领域的应用。从基础研究到早期疾病诊断应用，TDDMRI 显示出巨大的潜力。2. 这项技术的应用仍有一些挑战需要克服。我们必须推动更高效的扫描和数据处理技术，开发精确的模型以更好地描述和量化分子扩散的时间依赖性行为，并努力开发更多的临床应用场景。

关键词：时间依赖性扩散；扩散磁共振成像；微结构成像；微结构建模

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