Third–Generation Nuclear Magnetic Resonance: Diffusion Tensor Magnetic Resonance Tomography and Cerebral White Matter Tractography

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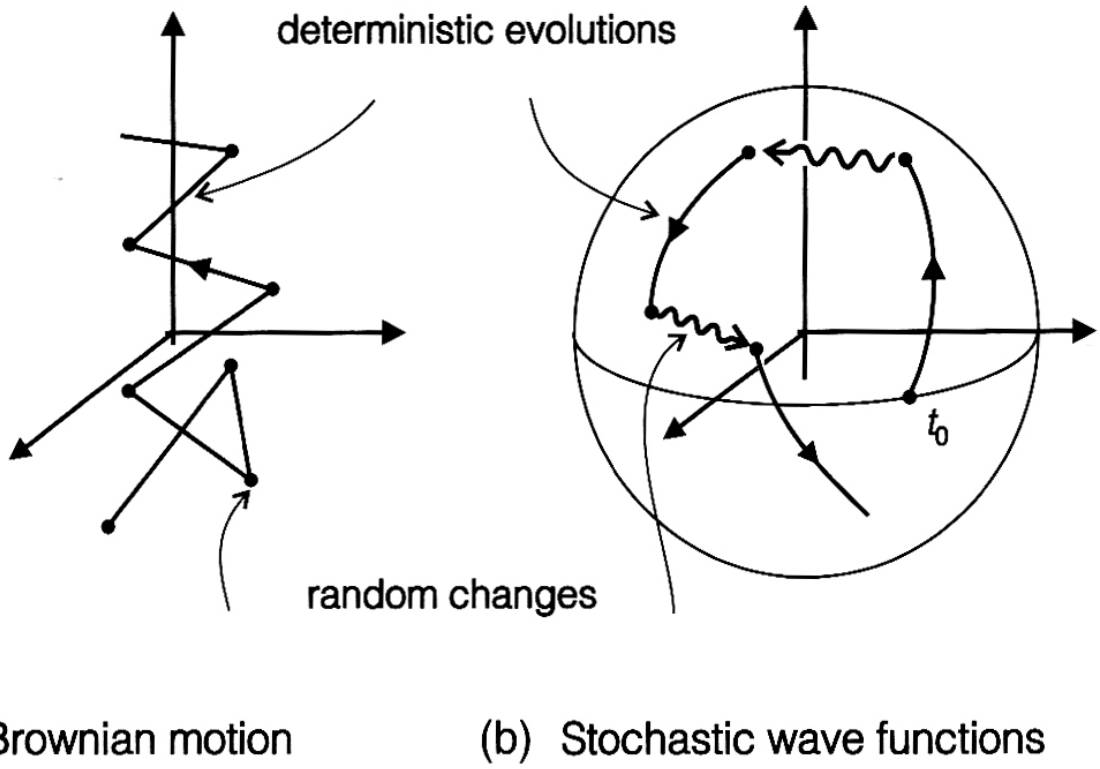
Abstract

The method of nuclear magnetic resonance (NMR) is one of the most versatile experimental methods in chemistry, physics and biology, providing insight into the structure and dynamics of matter at the molecular scale. Its second–generation imaging variant, magnetic resonance tomography (MRT), provides a unique window to quantify the diffusional characteristics of a wide range of biological specimens. Anisotropic diffusion of water molecules in neural fibers such as nerve, white matter in spinal cord, or white matter in human brain forms the basis for the utilization of diffusion tensor imaging, sometimes referred to as DTI, to track fiber pathways. The fact that molecular water diffusion within confining cellular structures is sensitive to the underlying tissue microstructure provides a unique technique of measuring the orientation and integrity of these neural fibers which may be useful for assessing a variety of neurological disorders and monitoring the course of these diseases.

Diffusion in the context of diffusion–weighted MRT refers to the processes of stochastic thermal motion and random collisions of molecules or atoms in fluids and gases, a phenomenon also known as linear Brownian random motion. The Brownian random displacements of molecules in biological tissues results in phase shifts that are widely dispersed and therefore the phase dispersion can be used as an internal signum of contrast. The molecular displacements are over distances comparable with the cell's dimensions and reflect the geometry and spatial organization of tissue compartments. Anisotropic diffusion allows to gather functional insight concerning exchanges between these compartments in various normal physiological or pathophysiological states.

The stochastic wave functions emitted by pulse stimulated *spin tagged* water molecules provide

a *quantum field* theoretic description of anisotropic quantum diffusion processes which is similar to a classical random walk. Indeed, between two photon emissions, the quantum wave functions obey a phase coherent *deterministic* evolution, just as a Brownian particle obeys a free flight between any two collisions. The quantum phenomenon of photon emission is considered in gradient controlled directions inside the coherent magnetic field which is externally driven by the MRT scanner, just as the collisions experienced by a Brownian particle.



Random flights: (a) A classical particle under the influence of collisions with gas molecules interrupting free flights. (b) Feynman diagram of a stochastic wave function under the influence of stimulated photon emissions. The stochastic wave function is normalized and therefore the motion is on the Bloch sphere $\mathbb{S}_2$

In the pioneering work of Felix Bloch (1905 to 1983) and Edward Mills Purcell (1912 to 1997) on NMR in bulk matter, Bloch's experimental design was couched in more dynamical terms, which can be seen as deriving the spin choreography from the Bloch sphere $\mathbb{S}_2$. Reorienting nuclear magnetic moments was the conceptual image that influenced Bloch's experimental design in his discovery of the NMR phenomenon. Quantum field theory, spin factors, and Feynman diagrams visualizing the interaction between vectors and spinors were still not available in the fall of 1945 when NMR in bulk matter was a reality. However, unbeknownst to each other at that time, the experimental achievements of Bloch and Purcell opened up a very active area of

physical research and contributed to the theoretical development which inspired all the subsequent research studies on these matters until today.

In clinical MRT, stochastic molecular motion can be observed through the phenomenon of signal attenuation caused by the phase dispersion. This fact was first recognized in the seminal spin–echo experiment performed by the NMR pioneer Erwin Louis Hahn in 1950, long before the invention of magnetic resonance as a non–invasive *imaging* modality for the *in vivo* visualization of soft tissue. Hahn explained the reduction of signal intensity of the spin–echo in terms the dephasing of spin populations caused by translational diffusion within an inhomogeneous magnetic field and proposed that one could measure the diffusion coefficient of a solution containing spin–labeled molecules. A few years later, Hermann Y. Carr and Edward Mills Purcell refined Hahn's spin–echo experiment by describing diffusion–weighted NMR experiments. However, without the inclusion of the excitations by spin–echo carrier π pulse sequences into the spin choreography, the recently accomplished quantum *entanglement* transfer between macroscopicically separated mechanical oscillators and their spin motion could not be successfully realized.

In the experiment formerly considered by Carr and Purcell, a constant magnetic field gradient is applied through the entire Hahn spin–echo experiment. As a result of the Larmor precession at the magnetic field superimposed by the constant gradient, the protons undergo a phase shift in the clockwise direction on the plane perpendicular to the direction of the main magnetic field. Therefore the net phase shift that influences the NMR signal at the echo time $\mathrm{T_E}$ is related via spinorial resonance to the motional history of the water molecules in the ensembles. By exploiting this resonance phenomenon, the NMR spin–echo gets sensitive to the effects of diffusion within the underlying tissue microstructure. This elevated NMR as a *gold standard* for measuring molecular diffusion. Quantum field theory leads via the Bargmann–Fock representation of the three–dimensional real Heisenberg unipotent Lie group $\mathcal{N}$ to the fundamental spinorial version of the Lévy–Hinčin representation associated with the real vector space duality $(\mathrm{Lie}(\mathcal{N}), \mathrm{Lie}(\mathcal{N})^*)$ and its canonical $\mathbb{R}$–bilinear form of MRT *gradient control*

$$\boxed{\mathrm{Lie}(\mathcal{N}) \times \mathrm{Lie}(\mathcal{N})^* \ni (v, \ell) \mapsto \ell(v) \in \mathbb{R}}$$

In the control by means of superpositions of linear gradients on the main magnetic field, the dual vector space $\mathrm{Lie}(\mathcal{N})^*$ is assumed to be transversally fibered under the *coadjoint action* $\mathrm{CoAd} = {}^t\mathrm{Ad}$ of the Heisenberg Lie group $\mathcal{N}$. This action provides $\mathrm{Lie}(\mathcal{N})^*$ with a bipartite principal fibration.

Actually nilpotent harmonic analysis, Lie sphere geometry and the *symbolic calculus* of quantum field theory reveal to form the natural framework for establishing the spinorial version of the Lévy–Hinčin formula for the expectation operator

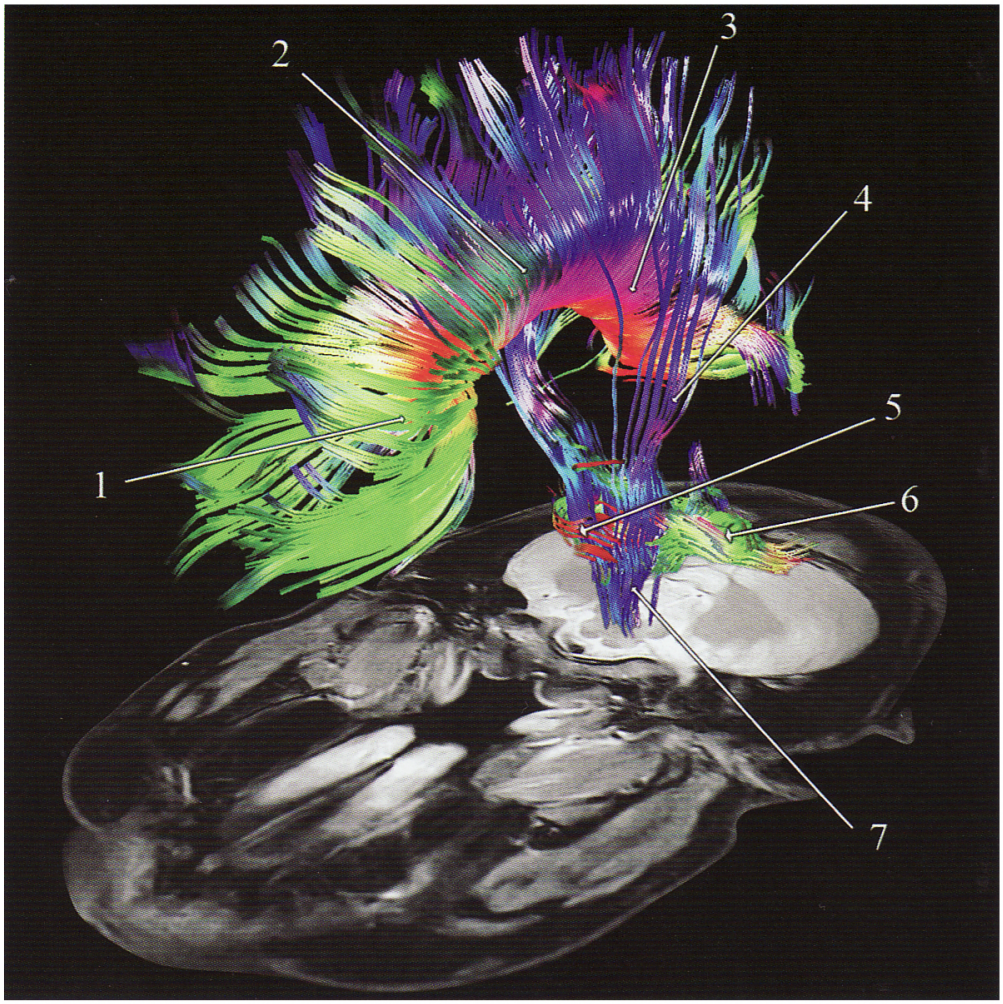
$$\boxed{\mathbb{E}(\mathbf{e}(\ell(X_t)),\mu) = \exp\Big(-t\,(\frac{1}{2}Q(\ell) + i\gamma(\ell) + \int_{\mathrm{Lie}(\mathcal{N})} (1 - \mathbf{e}(\ell(v)) + i\ell(v)\mathbf{1}_{\mathcal{B}}(v))\,\mathrm{d}\lambda(v))\Big) \quad (t \in \mathbb{R}_+)}$$

of the Lévy process $(X_t)_{t\in\mathbb{R}_+}$ with respect to the probability measure μ and the Lévy measure λ on $\mathrm{Lie}(\mathcal{N})$, the positive semi–definite quadratic form Q derived from the Bargmann–Fock representation of $\mathcal{N}$, the drift coefficient γ, and the open unit ball $\mathcal{B} \subset \mathrm{Lie}(\mathcal{N})$. As usual, $\mathbf{e}(\theta) = e^{i\theta}$ for $\theta \in \mathbb{R}$ describes the phase circle within the symplectic plane $\mathbb{R} \oplus \mathbb{R} \cong \mathbb{C}$.

To switch from first–generation NMR to third–generation diffusion–weighted MRT imaging methods, there are at least three reasons why DTI forms an important visualization modality. First, macroscopic morphological MRT based on the signatures of relaxation times cannot reveal detailed anatomy of the white matter. The second reason is that, even after decades of intensive anatomical studies of the human brain, the understanding of its *connectivity* is far from complete. There are many pathophysiological conditions in which abnormalities in specific connections are suspected, but are difficult to delineate. It is anticipated that DTI tractography may provide new information about human brain connectivity. Third, DTI is a non–invasive imaging modality which admits high spatial resolution for the *in vivo* visualization.

On diffusion–weighted MRT images, structures with unrestricted diffusion such as cerebrospinal fluid are dark, while structures with restricted diffusion are bright. In the living human brain, gray matter diffusion is isotropic. White matter diffusion is variable and dependent on the relative orientation of the myelin sheats along the axonal tracts. The myelin sheats are able to restrict free diffusion. This can be used to advantage. By applying the magnetic field gradient in one direction the pulse sequence is sensitized for diffusion in that direction. Fiber tracts parallel to this direction will show maximal signal loss, whereas the effect is minimal if the gradient is perpendicular to the fiber tracts. By application of diffusion gradients in three directions the anisotropy of the white matter can be visualized in studying, for example, myelination progress; to use the values of diffusion in different directions and ensemble average the values to cancel the anisotropy and obtain so–called trace maps, for example for the diagnosis of infarctions and infections; or to maximize the anisotropy information by using multiple gradients to obtain diffusion tensor measurements, which allow the display of fiber tracts in the Cerebrum.

Close inspection of the main diffusion directions suggests that the macroscopic shape of white matter tracts can be reconstructed by connecting several diffusion orientations. By choosing a starting point within a *seed region* and following the main diffusion direction, trajectories can be constructed that visualize the fiber tracts of white matter. A typical example arises when a seed region was placed within the corpus callosum, the guiding structure of cerebral anatomy, and all fibers through the seed region were reconstructed at macroscopic resolution. The colour encoding indicates the orientation of the various fiber pathways, and the three–dimensional reconstructions demonstrate the clear discrimination of white and gray matter structures in the



Three–dimensional fiber–tracking diffusion tensor MRT of the Corpus callosum: transversal seed region (1 = Genu corporis callosi, 2 = Truncus corporis callosi, 3 = Splenium corporis callosi, 4 = Tractus pyramidalis, 5 = Pedunculus cerebellaris medius, 6 = Pedunculus cerebellaris superior, 7 = Tractus frontopontinus)

living human brain. Although the gray matter primarily contains neurons and their processes, the white matter is composed predominantly of myelinated bundles of axons. A discrimination of white and gray matter is of great value for the clinical diagnosis of multiple sclerosis where the number of nerve fibers is significantly decreased to demyelinating lesions.

The DTI modality also provides indirect insights into the brain microstructural characteristics of patients suffering of different forms of dementias, improving the comprehension of the underlying pathophysiological processes that result in macroscopic brain tissue loss over time. It has also been successfully used to provide specific markers which are able to support the diagnosis of different forms of dementias in the early stages and to monitor the course of disease. There

is, however, still a long distance for an efficient model of the Alzheimer disease.

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