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Analysis of the distribution of diffusion coefficients in cat brain at 9.4 T using the inverse Laplace transformation

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Abstract

In this work, the usefulness of the inverse Laplace transformation (ILT) in the characterization of diffusion processes in the brain has been investigated. The method has been implemented on both phantom and in vivo cat brain data acquired at high resolution at 9.4 T. The results were compared with monoexponential and biexponential analyses of the same data. It is shown that in the case of diffusion restricted by white matter axonal tracts, the resulting diffusograms are in good agreement with the biexponential model. In gray matter, however, the non-monoexponential decay does not lead to a bimodal distribution in the ILT, even though the data can be fitted to a biexponential. This finding suggests the possibility of a distribution of diffusion coefficients rather than a discrete biexponential behavior. It is shown that this distribution is sensitive, for example, to experimental parameters such as the diffusion time. Thus, the ILT offers the possibility of implementing a unique tool for the analysis of heterogeneous diffusion, that is, the analysis of the diffusion coefficient distribution, which has the yet unexplored potential of being a valuable parameter in the characterization of tissue structure.

Keywords: Laplace transformation; Cat brain; Diffusion

1. Introduction

Water self-diffusion in living tissue is a process that deviates from simple gaussian diffusion process because of the complexity of the microscopic structure of tissue. In particular, the parcellation into different tissue compartments that are permeable to exchange and the existence of physical barriers (cell membranes, intracellular organelles, etc.) that restrict the motion of water molecules give rise to a non-monoexponential attenuation of the diffusion-weighted signal with respect to b value [1,2]. In addition, the anisotropic nature of tissue structures, for example, axonal fibers in brain, introduces a direction dependence to the behavior of the diffusion measurement [3–8]. One of the most common models used to describe the diffusion signal as a function of b value is the biexponential model [1,2,9–12], which assumes a sum of two *distinct diffusion coefficients*, ADC_{fast} and ADC_{slow}, along with their associated volume fractions, f_{fast} and f_{slow}. The biexponential model is a source to much debate. Some of the points of contention regarding the biexponential model are (a) whether the biexponential model reflect a realistic distribution of diffusion times in tissue; (b) the nature of the relation between *diffusion components* in the model and tissue geometry and structure, and in particular, *tissue compartments*; (c) what dictates the parameters of the biexponential model, that is, the volume fractions and the ADCs of the two components; (d) how does the geometric anisotropy encountered in tissue, and particularly in white matter (WM) in the central nervous system, affects the quantities related to the biexponential model.

The underlying problem with multiexponential analysis of diffusion data is that it is an algebraically ill-posed problem. This makes it not only highly susceptible to noise, but also quite pliable with respect to the model used for the

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analysis. It has been shown that relaxation data from human brain can be extremely well fitted to two differing models—a biexponential model and a model that assumes a unimodal distribution of diffusion coefficients [13,14]. This particular model incorporates fast exchange between restricted compartments, where the exchange rate is fast enough to be sampled multiple times during the diffusion time. On the other hand, it has been shown that NAA, a solely intracellular metabolite, exhibits a nonexponential diffusion behavior that cannot be explained through intercompartmental exchange process [15,16].

In this work, some of these questions are addressed by measuring high-SNR diffusion data in cat brain at high field and by analyzing the resulting *diffusograms* [17–19], that is, the inverse Laplace transform (ILT) of the diffusion data. The ILT is a less biased approach than the explicit multiexponential analysis, and most of all, it allows the analysis and quantification of a *distribution* of diffusion coefficients. This feature becomes significant in in vivo measurement of diffusion properties of tissue water, where the heterogeneity of the system calls for an analysis method that would be sensitive to the distribution of the diffusion coefficients and to changes in the parameters associated with this distribution that may originate from different measurement parameters, for example, diffusion time and tissue properties such as permeability and boundaries between different compartments. Here, carefully optimized ROI-based diffusometric analyses were performed and compared the results with those obtained by standard biexponential and monoexponential fitting. The resulting diffusograms show a distinct bimodal distribution for WM, when the diffusion gradient direction is set perpendicular to the axonal fiber tract. The parameters of this bimodal distribution are in good agreement with those obtained by biexponential analysis of the same data. When the gradients are applied in parallel to the direction of the tract, a unimodal distribution is found, similar to that obtained from phantom results where there is no restriction on water diffusion. In gray matter (GM), the ILT results show a distribution of diffusion coefficients that exceeds the natural "line width" of the ILT peak and is sensitive to the diffusion time. This result is encouraging in the sense that it offers the possibility for a new parameter with a physical meaning that is related to diffusion in living tissue—that is, the distribution of diffusion coefficients.

2. Materials and methods

2.1. Phantom and animal preparation

2.1.1. Phantom

The phantom used was a bottle filled with a 0.9% saline solution in 2% agar. Temperature in the scanner was 20±2°C.

2.1.2. Animals

Four cats (800 g–1.1 kg) were first sedated with a ketamine/xylazine mixture and then orally intubated and ventilated with 1% isoflurane and 3:7 O2/N2O throughout the experiment. Body temperature was controlled via a rectal probe and kept stable around 38.5°C by means of a feedback water loop. Experiments were performed on a 9.4-T/31-cm spectrometer (Varian, Palo Alto, CA) equipped with a gradient system capable of delivering gradient strength up to 30 g/cm and a rise time of 300 μs.

2.2. Data acquisition—phantom experiment

Pulse sequence used was localized STEAM sequence with diffusion gradients positioned after the excitation pulse and before the detection pulse; $\delta=7$ ms, $\Delta=12$ ms and gradient values that generated 52 b values between 0 and 3200 s/mm^2. A magnetization transfer (MT) pulse of variable duration was positioned right before the excitation pulse. Values for the MT pulse length were 0, 0.01, 0.02, 0.04, 0.08, 0.15, 0.3, 0.6, 1, 2 and 3 s. The B_1 generated by the MT pulse was about 400 Hz.

2.3. Data acquisition—animal experiments

2.3.1. Pulse sequence: double spin-echo fully adiabatic echo-planar imaging sequence

Bipolar diffusion gradients were positioned before and after the first π pulse. MRI acquisition parameters were the following: data matrix 256×256, four segments, FOV 5×5×0.2 cm^3 (nominal resolution 195×195 μm^2 in-plane, denoised with a hanning filter), TE/TR=34 ms/5 s, diffusion $\delta=8.5$ ms, $\Delta=11.5$ ms.

2.3.2. b Values

Sixty gradient strength values were used between $g=0.75$ g/cm and $g=30$ g/cm, spanning a b value range between 5 and ~12500 s/mm^2 for two combinations of two gradients: $(X,Y,0)$ and $(X,-Y,0)$.

2.4. Data processing and analysis methods

All processing was performed using MATLAB. A well-conditioned finite-dimensional approximation of the Laplace transform is by Gauss–Laguerre quadrature. The ILT is an ill-conditioned operator, and the SVD decomposition of the finite-dimensional approximation must be truncated. Using the L-curve criteria as discrepancy principle, a seven- to eight-dimensional subspace operator has been determined to be the smallest norm operator that best approximate the ILT for all the cases that were analyzed. To ensure positivity of the solution, an iterative restoration algorithm [20] was subsequently used. The combination of two algorithms is used to ensure, firstly, a solution that has a large degree of flexibility with good stability and, secondly, a solution that is consistent with the physical assumptions (non-negativity). An example of the L curve for one of the data sets that were analyzed is shown in Fig. 1. The first inflection point of the