(Nuclear) Magnetic Resonance ((N)MR) is a non-invasive technique that has been used to acquire spatially resolved images of living organisms. Another application of clinical MR is MR Spectroscopy (MRS) in which chemical information can be extracted from a well-defined region (e.g. a voxel) in for example the human brain [de Graaf, 1998]. Brain tumors [Nelson, 1999], multiple sclerosis, epilepsy and Alzheimer constitute some very important research areas where MRS can identify the pathology, provide insight in the underlying biochemical processes or monitor the effect of medication. Depending on the measurement protocol used, so-called single-voxel or multi-voxel (multiple signals acquired simultaneously over a larger region, one per voxel) long- or short-echo-time proton signals (see Figure 1) are obtained. Applying spectral analysis methods can provide quantitative information about the metabolites. However the quantification is hampered by a low signal-to-noise ratio, deviations from the theoretical model function and the presence of disturbing components (like residual water and lipids). Moreover, the exact number of spectral components is unknown. To complicate matters further, short-echo-time signals are characterized by the presence of an unknown broad baseline underlying the resonances of the metabolite signals of interest and by heavily overlapping metabolite signals. To exploit the full potential of MRS the reliable determination of the metabolites present and their concentrations is essential. We discuss the state of the art of data processing methods for long- and short-echo-time proton measurements including techniques to remove unwanted features that hamper the quantification.

Figure 1: Above: Long-echo-time proton measurement (after Fourier transform). Below: Short-echo-time proton measurement (after Fourier transform).
Due to the fact that short-echo-time proton measurements are more complicated in nature than long-echo-time proton signals, short-echo-time proton signals require more advanced quantification techniques.

### 3.1 Long-echo-time proton signals

The oldest and still widely used quantification method in the frequency domain is the integration of the area under the peak of interest of the Fourier transformed time-domain signal. The advantage is that no assumptions have to be made concerning the lineshape of the signal. The major drawback is the low estimation accuracy. In recent years, frequency- and time-domain methods have been presented that rely on a model function ([Mierisová, 2001], [Vanhamme, 2001]). Although time- and frequency-domain methods are equivalent from a theoretical point of view, in practice mathematical operations are usually less computationally demanding when performed in the time domain. Hence we focus here on time-domain methods.

The model function most often used to represent long-echo-time proton signals is the following:

\[
y_n = \sum_{k=1}^{K} a_k e^{j\phi_k} e^{(-d_k + j2\pi f_k) t_n} + e_n, n = 0, \cdots, N - 1
\]

where \(K\) represents the number of resonance frequencies. The amplitude \(a_k\) is proportional to the number of nuclei contributing to the spectral component with frequency \(f_k\). The damping \(d_k\) provides, among others, information about the mobility and macromolecular environment of the nucleus, \(\phi_k\) is the phase and \(t_n\) are the sampling time points. In MRS applications prior knowledge concerning relations between spectral components (e.g. derived from quantum mechanics), like for example, amplitude and damping ratios, frequency and phase shifts, is often available.

The majority of existing time-domain analysis methods models the MRS signals using the above model function (or a modified version of it) and subsequently determines the parameters using an optimization-based or a black-box approach. Optimization-based methods are very flexible and allow the use of alternative model functions and prior knowledge can easily be incorporated. The most important drawbacks are the need for user interaction and the fact that no methods exist that guarantee convergence to the global minimum in a reasonable amount of time. Black-box methods on the other hand require minimal user involvement or expertise. A disadvantage however is that the model function is restricted to a sum of damped complex exponentials. Although recent developments [Laudadio, 2004] allow the incorporation of some prior knowledge by translating the extra information into linear algebraic concepts such orthogonal projections onto subspaces, canonical angles, subspace intersections, not all available prior knowledge can be exploited in this way. As a consequence black-box methods are often used to remove in an automated way, unwanted components such as residual water or lipid. In many cases the water peak is heavily distorted and as a result can not be parameterized as a single peak. Black-box quantification algorithms that use several damped exponentials to parameterize the water signal have been successful in reconstructing the water signal. Alternative approaches consist of the use of suitable filters, such as Finite Impulse Response filters ([Sundin, 1999], or wavelets [Coron, 2001]).
2.2 Short-echo-time proton signals

Methods ([Bartha, 1999], [Provencher, 1993], [Young, 1998]) that have been developed to process short-echo-time spectra differ a.o. in the model function used to model the metabolites, the domain in which the analysis is carried out (time or frequency domain), the way in which is dealt with the inevitable line distortions present in in-vivo spectra and the presence of unknown components (the so-called baseline). One approach is an extension of the optimisation-based methods developed for long-echo-time proton signals and consists of using extensive amounts of prior knowledge to quantify the short-echo-time proton signals in the time domain [Mierisová, 1998]. The approach most often used is an optimization-based approach in the frequency domain [Provencher, 1993] that analyzes the signal as a linear combination of metabolite solutions in vitro (a so-called basis set, measured under the same experimental conditions). By using complete spectra, rather than just individual peaks, full use is made of the available prior knowledge. The method makes use of a parameterized model for peak distortion and for the baseline and uses a constrained regularization method to stabilize the analysis. Various models for the baseline have been proposed by different authors ([Auer, 2001], [Soher, 2001], [Hofmann, 2002], [Seeger, 2003]) and the influence of the choice of basis set is also under study.

3. CONCLUSIONS

A substantial amount of research has been carried out in the area of long- and short-echo-time proton data analysis in either time or frequency domain. The majority of existing analysis methods models the MRS signals and subsequently determines the parameters using a black-box or an optimization-based approach. An active area of research is the use of data quantification in order to extract appropriate features from proton measurements to be used in brain tumor diagnosis [Lukas, 2004].

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