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# Preface to Special Issue: "Computational Methods in Magnetic Resonance Spectroscopy (MRS)"

Magnetic Resonance (MR) represents one of the most important modern medical diagnostic modalities. In particular, it has become an indispensable non-invasive tool in clinical oncology. Besides anatomic imaging through Magnetic Resonance Imaging (MRI), the horizons for diagnostics are widened by using Magnetic Resonance Spectroscopy (MRS) and Magnetic Resonance Spectroscopic Imaging (MRSI) to acquire invaluable biochemical information from the examined tissue. However, further progress in MR imaging and spectroscopy is hampered by almost exclusive reliance upon conventional signal processors, i.e. the fast Fourier transform (FFT) which:

- is a low-resolution spectral estimator,
- as a linear transform, imports noise unaltered from the measured time domain data to the frequency domain,
- as a non-parametric estimator, yields only a shape spectrum,
- is customarily supplemented, in quantification problems, by various fitting recipes that are all non-unique leading to spurious peaks (over-fitting) and to missing genuine peaks (under-fitting), both of which are truly unacceptable to clinicians,
- can detect only a relatively small number of metabolites.

Regarding MRS, this Special Issue explores the possibilities provided by recent mathematical advances in signal processing based upon the fast Padé transform (FPT) for both parametric and nonparametric estimations of spectra. The FPT for a general power series is defined by the unique quotient $P/Q$ of two polynomials $P$ and $Q$ that can be extracted from the given time signal. In this Special Issue, the exact and explicit analytical expressions are reported for the polynomials $P$ and $Q$ using time signals of any length. Therefore, any frequency spectrum can be now obtained by a simple usage of these closed algebraic formulae from the FPT, thus bypassing altogether mathematical ill-conditioning, which otherwise severely hampers quantification problems in MRS.

As opposed to a single polynomial from the FFT, it is essential for signal processing in MRS that the FPT, via its polynomial quotient $P/Q$, can analytically continue Taylor and/or Laurent series outside their original convergence regions. While the FFT has no extrapolation features whatsoever, the FPT is simultaneously an interpolator and extrapolator, since the Padé complex spectrum $P(\omega)/Q(\omega)$ can be evaluated at any frequency $\omega$. All signals encoded with equal acquisition times $T$ lead to Fourier spectra with the same resolution $2\pi/T$ which, of course, has nothing in common with the fundamental frequencies $\{\omega_k\}$ as the building components of the signal. The Fourier resolution is the minimal distance between any of the two adjacent frequencies $\Delta\omega_{\min} = 2\pi/T$. By means of reliable extrapolation, the FPT can provide invaluable inferences about the time signal beyond the measured $T$, and this feature alone can yield a resolution better than the Fourier limit $2\pi/T$. This should not be confused with the quantum-mechanical uncertainly principle which requires two measurable quantities. In MRS, only the time signal is measured, whereas the corresponding spectrum is obtained theoretically, i.e. via computations. In such computations, the Fourier limitation $2\pi/T$ is attributed to linearity of the FFT. This limitation is successfully circumvented by

e.g. non-linearity of the FPT. Specifically, in a local spectral analysis, the resolution provided by the FPT is equal to the average distance $\Delta\omega_{\rm ave}$ among peaks in the investigated frequency interval. In practice, one usually finds that $\Delta\omega_{\rm ave} < \Delta\omega_{\rm min}$ and this leads to an improved resolving power of the FPT relative to the FFT in the examined frequency window. Similarly in MRI, one can resolve smaller spatial distances of the scanned tissue than what the uncertainty relation would permit judging upon the wavelength of the applied radiation field. Again, this apparent paradox is resolved simply by observing that resolution in MRI is not determined by measuring devices e.g. collimation and/or focusing of the applied beam, but rather by spectral analysis.

In contrast to other parametric estimators that are typically unstable, often undergoing very wild oscillations with totally unacceptable results before they eventually saturate, i.e. converge if they do at all, the FPT exhibits a remarkably stable convergence. Moreover, the FPT greatly improves upon the convergence rate of the FFT. Such a robust performance of the FPT encounters no undesirable surprises via spikes or other artificial metabolites that are anathema to clinicians. In the inverse or quantification problem in MRS, the measured time signal is used to reconstruct its constituent harmonic components by determining their number as well as the four key parameters (position, height, width and phase) of every genuine spectral resonance or metabolite. The solutions to this problem cannot be trusted at all unless supplied by the error analysis of known validity. Such an error analysis in the FPT is carried out both analytically from the available error estimate and empirically by computing the residual or error spectra that are shown in this Special Issue to be indistinguishable from the background random noise.

In this Special Issue, thorough and multifaceted comparisons are made between the FPT and FFT using experimentally encoded time signals from MRS. The resolution improvement and extremely stable convergence of the FPT are demonstrated relative to the FFT for clinical MRS signals. It is thereby proven that the FPT can offer substantial advantages of clinical importance for MRS as a diagnostic tool. *Inter alia*, the main features of FTP are summarised as follows:

- markedly enhanced resolution and signal-to-noise ratio via merely algebraic processing,
- exact regularisation of all spurious roots with preservation of the entire information,
- as a parametric estimator provides most precise numerical values for all peak parameters (position, height, width and phase) for every retrieved genuinely physical metabolite,
- specification of the exact number of metabolites from the encoded time signal together with unequivocal identification of the constituent components of overlapping spectral peaks,
- computation of metabolite concentrations most accurately due to the established one-to-one correspondence between frequencies and amplitudes, which are obtained analytically,
- striking robustness and stable convergence for varying fractions of the full signal length, yielding major percentages of the final, fully converged concentrations of the main metabolites even for severely truncated time signals,
- treatment of both Lorentzian and non-Lorentzian spectra on the same footing.

Overall, in Magnetic Resonance Spectroscopy, with the emergence of the parametric fast Padé transform, more information becomes now available to clinicians from experimentally measured time signals than what is currently extractable with the standard fast Fourier transform, when supplemented by any of the conventional fitting and peak searching algorithms.

Therefore, it is our hope that this Special Issue will be an impetus to further developments and applications of the presently reviewed, most recent mathematical advances to Magnetic Resonance Spectroscopy with an anticipated benefit for clinical medicine.

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Guest Editors