Short History of QMSA

By

Reino Laatikainen, University of Eastern Finland, Kuopio, Finland

Pekka Laatikainen, Spin Discoveries Ltd, Kuopio, Finland

Soon after the discovery of NMR, it was understood that *energetics* of nuclear spins of a molecule located in magnetic field and moving isotropically in solution, can be treated quantitatively using quantum mechanical theory (QM), using only the chemical shifts and coupling constants [1-3]. The computer program LAOCOON3 was published 1964[2] and became a standard for years. However, handling of spin-systems of more than 8 coupled protons was computationally slow and clumsy. The next landmark in the history of QMSA (Quantum Mechanical Spectral Analysis) was formed by the program NUMARIT [3,4], which allowed an efficient use of symmetry and *X-approximation*. The softwares were so far frequency-based, until the *Total-Line-Shape* programs like DAVINS [5] and DAISY [6], for which the spectrum were given in digital form. The first approach toward 'Automatic analysis', meaning start of analyses from rough trial parameters, the using of ('global') Fourier integral transforms was introduced already in 1975 [7]. The ('local') transforms based on the Bartlett integrals were introduced in PERCH Software in 1996 [8]. Gradual narrowing of the integral width ('broadening'), together with the principal component analysis, allows starting of the iterative analysis from rather poor trial parameters and guides the iteration to the nearest local minimum, which is also global one if the order of trial chemical shifts is correct. For structural analyses the NMR parameters can be predicted from 3D or even 4D structures [9], but the performance of the present prediction tools is jammed to ca 0.1 ppm for protons (our unpublished protocol combining *ab initio* methods and our 4D tool goes well below 0.10 ppm). The correct order forms a challenge for systems like biofluids. A general but laborious solution for the order prediction, as based on empirical correlations of shifts, has been presented for urine [10].

Spin-system of 12 protons still forms the practical upper limit that can be handled without any approximations. However, the present QMSA tools like ChemAdder software [8,11,12] allow treatment of large spin-networks, like steroids, peptides, and mixtures of tens or even hundreds of components, with ordinary personal computers.

See https://www.chemadder.com/presentations/ChemAdder_LargeSystems.pdf

For example, simulations of cholesterol spin-network of 46 protons and urine spectrum of 1000 shifts both take a few seconds with ChemAdder software. When also optimizable response factors, baseline, linewidths and line-shape are added to the analyses, QMSA allows simulation of an experimental spectrum into very details, using the field independent NMR-parameters. In new ChemAdder signals which has not quantum mechanical structure (like lipoprotein signals or albumin spectrum), can be included into the model – which combines the QMSA and the traditional deconvolution (TLS fitting). The parameters can be then arranged into field (instrument) independent *Adaptive Spectral Libraries*, to be used as storage of reference spectra.

The NMR method is *metric*, which means that the NMR signal area is proportional to the number of nuclei, independently of the compounds, on the condition that the spectra are measured properly. This also means that the spectrum of a mixture is sum of the spectra of the components, forming the basis of quantitative QMSA (qQMSA). However, the spectra and the parameters depend significantly on conditions like solvent, concentrations, and pH, which complicates the analysis of complex mixtures and is the reason to that the analysis is done iteratively and is still computationally challenging.

QMSA allows analyses of otherwise analysable complex symmetrical spin-systems and yields diagnostic spectral parameters with a very high accuracy, offering a powerful tool for structure identification, even without pure reference compound spectra. *The Adaptive Spectral libraries* allow storage of spectra in greatly packed instrument independent form. In mixture analyses impurity spectra hiding under spectral jungle can be revealed, identified and quantitated. No calibration samples and pure reference compounds in large amounts (for weighting accuracy) are needed, if a few percents uncertainties in concentrations are tolerated.

The principles of QMSA and qQMSA are reviewed in ref. [11] and in

https://www.chemadder.com/letters/QMSA%20Letters%203(2023)%20Art%20of%20qQMSA%20-20CSBC2022.pdf
https://www.chemadder.com/letters.html
https://www.chemadder.com/presentations/ChemAdder_QMSA%20BASICS.pdf
https://www.chemadder.com/presentations.html

REFERENCES

1. Anderson, W., & McConnell, H. M. (1957). Analysis of High-Resolution NMR Spectra. *J. Chem. Phys.* 26, 1496–1504 (1957). https://doi.org/10.1063/1.1743568,

2. J. D. Swalen and C. A. Reilly, J. Chem. Phys., 1962, 37, 21. Analysis of Complex NMR Spectra. An Iterative Method.

3. S. Castellano and A. A. Bothner-By, J. Chem. Phys., 1964, 41, 3863. Analysis of NMR Spectra by Least Squares.

4. J. S. Martin and A. R. Quirt, J. Magn. Reson., 1971, 5, 318. NUMARIT by A.R. Quirt, J.S. Martin and K.M. Worvill was published as Version 771 in Fortran IV for IBM computer systems, by the SERC NMR Program Library, Daresbury, in 1977.

5. D. S. Stephenson and G. Binsch, J. Magn. Reson., 1980, 37, 409. Automated analysis of high-resolution NMR spectra. II. Illustrative applications of the computer program DAVINS.

6. U. Weber and H. Thiele, 'NMR-Spectroscopy: Modern Spectral Analysis', Wiley-VCH: Weinheim, 1998.

7. P. Diehl, S. Sykora, and J. Vogt, J. Magn. Reson., 1975, 19, 67. Automatic analysis of NMR spectra: An alternative approach.

8. Laatikainen, R., Niemitz, M., Weber, U., and Sundelin, J., Hassinen, T., and Vepsäläinen, J., General Strategies for Total-Line-Shape Type Spectral Analysis of NMR Spectra Using Integral Transform Iterator, J. Magn. Reson. A120, 1-10 (1996).

9. Laatikainen, R. et al., Comprehensive Strategy for Proton Chemical Shift Prediction: Linear Prediction with Nonlinear Corrections, J. Chem. Inf. Model. 2014, 54, 419−430, https://dx.doi.org/10.1021/ci400648s.

10. Panteleimon G. Takis, Hartmut Schäfer, Manfred Spraul and Claudio Luchinat, Deconvoluting interrelationships between concentrations and chemical shifts in urine provides a powerful analysis tool, Nature Communications (2018), 8: 1662, DOI:/10.1038/s41467-017-01587-0.

11. Laatikainen R, Tiainen M, Korhonen S-P, Niemitz, M, "Computerized Analysis of High-resolution Solution-state Spectra" in Encyclopedia of Magnetic Resonance, eds R. K. Harris and R. E. Wasylishen, John Wiley: Chichester. Published 15th December 2011. DOI:/10.1002/9780470034590.emrstm1226.

12. Tiainen M, Soininen P, Laatikainen R, Quantitative Quantum Mechanical Spectral Analysis (qQMSA) of ^{1}H NMR Spectra of Complex Mixtures and Biofluids, J. Magn. Reson., 2014, 242, 67-78.