ABSTRACT

NMR spectroscopy is one of the most powerful and versatile tools for the study of biomolecules. The wide applicability of this method covers determination of structures of proteins and their complexes with other molecules, investigation of various aspects of internal molecular dynamics, and detection and characterization of interactions of biomolecules. NMR also plays an increasingly important role in the currently booming area of structural genomics. The present dissertation concerns methodological advances in NMR by focusing on the development of the Multi-Dimensional Decomposition (MDD) method and its contribution to the NMR field based on its remarkable performance and robustness.

The dissertation is composed of two major parts. The first part mainly concerns a specific type of MDD for 3D NMR interpretation, which is referred to as three-way decomposition (TWD). An application of TWD with the goal to extract relaxation times for a large protein with 370 residues, the maltose binding protein (MBP), shows that this method is superior to conventional approaches in resolving overlapped signals and in dealing with spectral artifacts. This enables a substantial number of additional probes to be available for characterizing the relaxation behavior of this protein. Another project presented in the dissertation consisted of performing a systematic investigation of TWD using simulated relaxation and NOESY data. By using accuracy and precision as main criteria, robustness and performance of the method is evaluated with respect to the influence of the following parameters: signal-to-noise ratio, overlap of signals and incorporation of a regularization procedure with the algorithm. The simulations demonstrate that TWD exhibits a robust behavior in situations with severe signal overlap and/or poor signal-to-noise. Moreover as a complement to this study, comparisons are also carried out between TWD and other methods that achieve the same type of results.

The second part of the dissertation is about the application of MDD in combination with non-uniform sampling to a 4D ^{1}H-^{13}C-^{13}C-^{1}H NOESY spectrum of a 12 kDa protein produced in a structural genomics effort. The main question in this study is whether the resolution and sensitivity of the complete reference 4D spectrum can be retained in a spectrum reconstructed using only a fraction of FIDs (free induction decays). A systematic evaluation shows that both sensitivity per unit time and resolution are well preserved, even when the measurement time is reduced to as little as 15% of the time required for the reference spectrum. An in-depth investigation of a spectrum reconstructed with MDD from an input with only 30% of data of the reference spectrum shows that all of the above-noise spectral intensities in the complete reference spectrum are correctly reproduced in the reconstructed spectrum, and no false peaks appear. The dissertation also includes a concise manual of mddNMR, the software package developed to implement MDD.

Keywords: NMR, multi-dimensional decomposition, three-way decomposition, NOESY, relaxation, non-uniform sampling, structural genomics

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