

# Ph. D. Dissertation Proposal

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## 1. Dissertation Title:

High Resolution Methods for the Data Processing in Liquid NMR Experiments and Quantum Dynamic Calculations  
(Advisors: Professor V. A. Mandelshtam and Professor A. J. Shaka)

## 2. Project Description

This dissertation is mainly concerned with the development of two nonlinear high resolution methods of spectral analysis, namely, the Filter Diagonalization Method (FDM) and Regularized Resolvent Transform (RRT), and their applications to the data processing in liquid Nuclear Magnetic Resonance (NMR) experiments and quantum dynamic calculations.

NMR is one of the most powerful non-destructive techniques available today for probing the structure of matter. High-resolution NMR is valuable for determining the structure of chemical compounds; it is the only method capable of determining the 3-D structure of biomolecules in solution. While the sensitivity has been consistently improved due to new advances in NMR hardware designs, the fundamental resolution depends solely on the attainable magnetic field strength and has seen only very limited improvement over the same time frame. Conventional Fourier Transform (FT) spectral analysis has severe limitations, such as spectral resolution limited by FT uncertainty principle separately in each dimension; and typical high resolution methods are computationally expensive and numerically unstable. Recently, the Filter Diagonalization Method (FDM) has emerged as a new high resolution method for spectral analysis of multidimensional time signal [1–5]. FDM solves the nonlinear Harmonic Inversion Problem (HIP) (i.e. fitting a time signal by  $C(t) = \sum_k d_k e^{-it\omega_k}$  with unknowns  $d_k$  &  $\omega_k$ ), by pure linear algebra of diagonalizing some *small* data matrices, and can potentially overcome all the said limitations. While the fundamental theory of FDM is already established, crucial problems exist when applied to noisy experimental data. One of the most important goals of my dissertation project is to study and improve the stability and performance of the original FDM algorithm. Another goal is to apply it to various NMR techniques with the focus on those which are important in structural determination of big molecules such as proteins.

RRT emerges naturally from FDM. RRT uses the same data matrices as FDM, but constructs the spectral representations directly without obtaining the intermediate spectral parameters. RRT is a direct transform of time domain data to frequency domain spectra. It brings appealing simplicity and can be implemented very efficiently. In addition, RRT can be further modified to calculate various interesting spectral representations. My dissertation project involves the development of RRT, and its applications to both processing NMR experimental signals and inverse Laplace transform of time cross-correlated signals which occur in quantum dynamic calculations.

### 3. Progress to Date

The stability and performance of FDM have been significantly improved due to several important developments such as multi-window implementation, *Multi-Scale* FDM and the regularized FDM (FDM2K). The results have been published on *J. Chem. Phys.* and *J. Magn. Reson.* (see Ref. [6,7]). 1D FDM is now essentially a well-developed method which is generally reliable, sufficiently fast and can deliver resolutions beyond the FT uncertainty principle. In multidimensional cases, fully converged spectra can be obtained with single calculation of FDM2K or RRT, provided that the data set is large enough (typically still too short to yield a well resolved FT spectrum) and the signal to noise ratio (SNR) is sufficiently high. However, more quantitative studies still need to be done with regard to the stability and reliability of FDM in case of very short signal and/or low signal to noise ratio.

At the same time, several novel NMR techniques have been successfully designed to be combined specifically with FDM data processing. Revised version of several important NMR techniques for protein structure determination including *Full-Sweep* Constant-Time HSQC and double Constant-Time triple resonance experiments, such as HNCQ, HNCA and HCACO, have been developed. The most recent results show that fully resolved HNCQ spectra of human Ubiquitin can be obtained with as few as 5 by 5 increments in  $^{15}N$  and  $^{13}C$  dimensions! These new results show the promise of obtaining full resolved multi-dimensional spectra of proteins within extremely short experimental time. This will be particularly important for bigger proteins in high field as they will relax much faster. One paper has been submitted to *J. Biomol. NMR* (Ref. [9]) with several others in preparation (Ref. [10]).

RRT has been successfully developed with the method published on *J. Magn. Reson.* (see Ref. [8]). It has been proved to be a very efficient and reliable method which can provide higher resolution than Fourier Transform. In addition to its application in data processing in NMR, it has also been applied to extract excited vibrational energy levels of polyatomic molecules by inverse Laplace Transform of time cross-correlated functions computed by quantum path integral Monte Carlo method. Up to 4 excited levels can be obtained with high accuracy and the results will be published soon (Ref. [11]).

### 4. Plan/Primitive Schedule

Summer&Fall '01	Finish up the remaining projects and write papers (see Section 3).
Winter '02	Thesis writing/more paper writing
Spring '02	Ph. D. Defense

### References

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- [1] D. Neuhauser, "Bound-state eigenfunctions from wave-packets - time-energy resolution", *J. Chem. Phys.* **93**, 2611-2616 (1990).

- [2] M. R. Wall and D. Neuhauser, "Extraction, through filter-diagonalization, of general quantum eigenvalues or classical normal-mod frequencies from a small number of residues or a short-time segment of a signal .1. Theory and application to a quantum-dynamics model", *J. Chem. Phys.* **102**, 8011-8022 (1995).
- [3] V. A. Mandelshtam, and H. S. Taylor, "Harmonic inversion of time signals and its applications", *J. Chem. Phys.* **107**, 6756-6769 (1997).
- [4] V. A. Mandelshtam, and H. S. Taylor, "Multidimensional harmonic inversion by filter-diagonalization", *J. Chem. Phys.* **108**, 9970-9977 (1998).
- [5] V. A. Mandelshtam, "FDM: the filter diagonalization method for data processing in NMR experiments", *Prog. Nuc. Magn. Reson. Spect.* **38**, 159-196 (2001).
- [6] J. Chen and V. A. Mandelshtam, "Multiscale filter diagonalization method for spectral analysis of noisy data with nonlocalized features", *J. Chem. Phys.* **112**, 4429-4437 (2000).
- [7] J. Chen, V. A. Mandelshtam and A. J. Shaka, "Regularization of the two-dimensional filter diagonalization method: FDM2K", *J. Magn. Reson.* **146**, 363-368 (2000).
- [8] J. Chen, A. J. Shaka and V. A. Mandelshtam, "RRT: the regularized resolvent transform for high-resolution spectral estimation", *J. Magn. Reson.* **147**, 129-137 (2000).
- [9] A. A. De Angelis, J. Chen, V. A. Mandelshtam and A. J. Shaka, "A Method to Obtain High Resolution  $^{13}\text{C}$  CT-HSQC Spectra of Proteins with a Short Constant-Time Period", *J. Biomol. NMR* (submitted).
- [10] J. Chen, D. Nietlispach, V. A. Mandelshtam, and A. J. Shaka, "Ultra-high quality HNC0 spectra with very short constant times", in preparation.
- [11] J. Chen, V. Mandelshtam and D. Neuhauser, "Calculating excited vibrational levels of polyatomic molecules by diffusion Monte Carlo", in preparation.