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Historical Perspective

NMR Fourier Zeugmatography

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Interview with the author(s).

A video interview with the author(s) associated with this Historical Perspective and the original article can be found in the online version, at doi:10.1016/j.jmr.2011.08.006.

1. Introduction

The paper NMR Fourier Zeugmatography, J. Magn. Reson. 18, 69–83 (1973) was a joint effort by Anil Kumar, Dieter Welti, and myself. I am grateful to Professor Anil Kumar that he left me free hands to write a rather personal account of our work and its circumstances. Dr. Dieter H. Welti, unfortunately, deceased after many fruitful years with Nestlé Research Center, Lausanne.

My return to Switzerland in spring 1968 was for me a personal and scientific disaster. I left Varian Associates in Palo Alto, convinced that I made some significant contributions to the advancement of NMR by introducing Fourier transform (FT) NMR, together with Wes Anderson [1], noise decoupling [2], and on-line computer techniques for system control and data processing [3,4]. Coming home to Switzerland, my expectations were in no way fulfilled. I was not received as a "National Hero" but rather as a "lost son". Without a decent NMR spectrometer available in the Laboratory of Physical Chemistry at ETH Zürich, without adequate finances, without mentorial support, I tried desperately to put to good usage the remaining lose ends of my FT NMR work from Palo Alto. But I did not have the means to start any new project. Eleven months later, I suffered a serious nervous break-down from which I only slowly recovered.

At that moment, I was convinced that the one-dimensional world of NMR was nearly exhausted in terms of finding novel spectroscopic tools. It seemed to me indispensable to advance to "new dimensions" for maintaining the pioneering excitement and creativity of the past course of NMR methodology.

I hoped that double resonance experiments might reveal fruitful avenues for future NMR developments. Two variable frequencies could be used for scanning a two-dimensional frequency space. These two-dimensional dreams had to do with what one might call "systematic double resonance". By varying systematically two frequencies, a two-dimensional plot could be created. I tried to experimentally implement the graphical concepts developed by Anderson and Freeman [5,6]. They took advantage of schematic two-dimensional plots for explaining double resonance effects in their famous papers in the Journal of Chemical Physics, such as spin tickling. I intended to measure by experiments "Anderson–Freeman plots".

In 1971, surprisingly, Jean Jeener presented his famous lecture on a pulse pair technique at the AMPERE School II in Basko Polje, Yugoslavia, September, 1971: "*Pulse pair techniques in high resolution NMR*" [7]. It is not astonishing that Jeener's lecture had a stimulating effect on my "prepared mind". I asked my gifted, theoretically inclined student Enrico Bartholdi to explore theoretically the possibilities of the novel form of "two-dimensional NMR". It became soon obvious that we had unwittingly opened a nearly inexhaustible treasure box. Thousands of experiments came to our mind for how to take advantage of two frequency variables. It was for us like a glimpse into an entirely new world through a narrow key hole. I have never been more excited in my life about science than at this miraculous moment. However, we hesitated to put into print our spectacular results before giving Jean Jeener a fair chance for publishing his revolutionary ideas himself. However, our waiting was fruitless; Jean Jeener did not publish!

In 1974, our situation of respectfully waiting was changed at the 15th Experimental NMR conference at North Carolina State University, April 28–May 1, 1974, by a lecture of Paul Lauterbur. He demonstrated an entirely different approach for attaining two- and three-dimensional "NMR images" by NMR Zeugmatography. His ground-breaking lecture "*Zeugmatography – Spatial Resolution of NMR signals*", together with C.S. Dulcy, C.M. Lai, W.V. House, F.W. Porretto, and M.A. Feiler, described a revolutionary way for attaining three-dimensional images of objects and living beings. Actually, Lauterbur had published some of his ideas already one year before in Ref. [8]. However, at that time, I was not aware of his earlier publication, and I was exposed to NMR Zeugmatography for the first time at the 15th ENC.

The lecture by Lauterbur at ENC was truly revealing to me and inspired my mind for finding better or at least different ways of imaging. I instinctively disliked the original projection–reconstruction approach by Paul Lauterbur. It was clear to me that radial projections cannot efficiently cover a two- or three-dimensional space because of the dense sampling in the centre of the imaging parameter space and the low sample density at the periphery. (k-space

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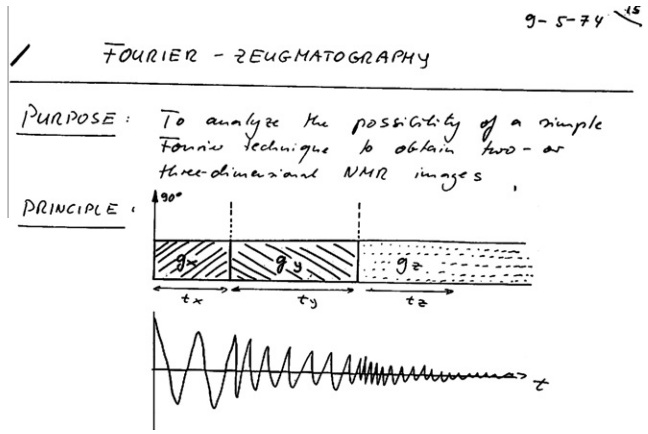

Fig. 1. Page 15 of Notebook of Richard R. Ernst with the very first note on Fourier-Zeugmatography, 9 May, 1974.

terminology was not yet familiar in 1974.) At 14:30 on Tuesday, April 30, 1974, during Lauterbur's lecture, *Fourier Zeugmatography* was born. I was convinced that systematic variation of gradients in two or three dimensions would provide a cleaner and mathematically simpler coverage of the imaging space. Eight days after the ENC, on 9 May 1974, I was writing down my idea in my notebook as is shown in Fig. 1. My proposal, Fourier Zeugmatography, uses a very simple scheme by applying in sequence gradients along the *x*-, *y*-, and *z*-directions. By varying the time durations of the two "evolution periods" t_x and t_y, two- or three-dimensional data matrices could be measured that led after two- or three-dimensional Fourier transformation to two- or three-dimensional images. I was convinced that this scheme is superior to the projection–reconstruction technique proposed by Lauterbur. Unfortunately, I have lost in the mean time the notebook from which Fig. 1 was taken. Most likely it has been stolen by one of my "adorers"! Its retrieval could be quite relevant for science history [9].

It became rapidly clear that the two techniques, 2D spectroscopic NMR and NMR Zeugmatography are methodologically surprisingly similar: They use the same data processing software. The experiments differ by the application of radiofrequency pulses in 2D NMR to delineate the evolution and detection periods, whereas in NMR tomography, magnetic field gradients are switched between different orthogonal directions in space. The spectroscopic 2D experiments were performed by the gifted graduate Walter P. Aue [10], while the imaging experiments were implemented by the highly creative post doctoral fellow Dr. Anil Kumar [11]. Walter P. Aue used our Varian DA60 high resolution NMR spectrometer, equipped with home-made pulse equipment, and attached to a Varian 620i computer, for recording 2D spectra with only 64×64 data points. The first Fourier Zeugmatography experiments, on the other hand, were implemented on our Bruker SXP4-100 high power pulse spectrometer, interfaced to a Varian 620/L-100 computer system. The pulsed field gradients were produced by the shim coils of the Varian 15-in. electromagnet and switched by home-made pulsing equipment.

In the course of June 1974, the first imaging experiments on samples consisting of two parallel cylindrical sample tubes were successfully done by Anil Kumar with the support by Dieter Welti. On August 2, 1974, the manuscript of a paper was submitted to the Journal of Magnetic Resonance [11]. We did not receive any negative comments by referees but, nevertheless, it took nine months for the final appearance of the paper in the April 1975 issue! Being horrified by the excessive delay, we submitted two related papers to different journals in the meantime [12,13].

The main motivation for performing these imaging experiments was not so much our conviction of their particular relevance, but it was more the need of making a decent presentation at the *VIth International Conference on Magnetic Resonance in Biological Systems*, Kandersteg, Switzerland, September 16–21, 1974. Kurt Wüthrich asked me to join the Organizing Committee. I thought this would save me from having to deliver a lecture; however, Kurt felt it would make sense for me also to say a few words on our research at the Laboratory of Physical Chemistry of ETH Zürich to profile myself as a respectable member of the NMR community. I did not announce a lecture, and there is none mentioned in the Book of Abstracts. I was asked to chair Symposium E on "New Methods", on Sept. 19, with some incredible speakers: Rex E. Richards, John S. Waugh, Paul C. Lauterbur, and James S. Hyde. I took the (authorized) liberty of smuggling in another brief lecture, entitled "*Fourier Zeugmatography and Pulse Pair Fourier Transform Spectroscopy*". My hand-written notes for the "non-lecture" start as follows: "*I would like to describe two methods which are strongly related. One technique is an alternative possibility to obtain Zeugmatograms, the other delivers information of the type usually obtained in double resonance experiments. For the first one, we got the idea during a talk at last ENC. For the second one, the idea is stolen from Prof. Jeener. Let me first briefly describe conventional Zeugmatography in a bit unconventional terms to show the differences between conventional and Fourier Zeugmatography.*" Then follows a sequence of 17 slides; and my notes terminate as follows: *Both methods are very demanding with regard to data storage. There are possibilities to somewhat reduce the requirements. But after all, these are two intriguing possibilities, particularly if you own stocks of a computer company or if you need an excuse to buy more memory for your own lab computer.*"

The response to my "non-lecture" was mixed. Some of the advanced members of the audience remarked: "Nice work, but a premature presentation"! This matched my own feelings, having presented my two preemies, and acting like a salesman for computer memory! But after all, are not most of our relevant communications "premature" and are we not acting all too often like "sales people"? Otherwise, we would remain unknown indefinitely.

In the back of my mind, I wanted to patent "Fourier Zeugmatography" from the beginning. I still had excellent consulting relations to Varian Associates, and I approached them with this possibility. They were interested and the patenting process started with Patent Application No. 559,479 on March 18, 1975. It was later abandoned and continued under the number 4070,611, leading to a Patent issued on January 24, 1978, under the title "*Gyromagnetic Resonance Fourier Transform Zeugmatography*", citing me as the inventor. I was glad to be refunded, as a consultant of Varian, by $200. Actually, I never found out how much income Varian received from this patent, but surely it was at least 4–5 orders of magnitude more in terms of royalties paid to Varian by the major MRI producers. It was fully legal and I never complained, especially not after getting my "little prize" in Stockholm. In the Nobel-Prize citation, Fourier Zeugmatography was not mentioned; quite correctly, because it would have gotten in conflict with the prize to Lauterbur and Mansfield that was still due.

I also considered an instrumental implementation of magnetic resonance imaging based on Fourier Zeugmatography. I did not trust Varian for starting a joint project with me, after my bad experiences a few years earlier with the implementation of one-dimensional Fourier NMR that was considered commercially non-viable by the authorities in Palo Alto. On the other hand, I did not yet have a connection to Bruker at that time. So the only possibility was the development of an MRI apparatus within ETH Zürich. I submitted a proposal on 27 February, 1976, to the *Kommission zur Förderung der Wissenschaftlichen Forschung* (KWF) for the development of an air-core magnet system of 0.1–0.2 T with homogeneity of 1×10^{-5} in a volume of $20 \times 20 \times 20$ cm for head imaging, using a power of 22.5 kW. A shim system was also proposed for reaching homogeneity of 1×10^{-6}. An NMR stabilizer was foreseen for guaranteeing the necessary field stability.

This proposal was rejected with the argument: "An already known principle shall be technically developed…. According to the committee, it is primarily a task for instrument manufacturers to overcome these technical hurdles." The committee misjudged the willingness of industry to invest into a high risk project with little chance of short-term profit.

I had a clever and initiative student, Peter Brunner, who would have loved to work on this engineering project. Because of the negative answer by KWF, he started a paper study comparing the sensitivities of various imaging techniques that was published in Journal of Magnetic Resonance under the title "*Sensitivity and Performance Time in NMR Imaging*" [14]. It became a fairly well cited paper, but the success was incomparable with our dream of creating one of the first well functioning imagers. May be, I would have had to found my own start-up company, would have lost a lot of money, and ended most likely in the poorhouse!

I was surprised by developments related to Fourier Zeugmatography: First of all, I had not realized the obvious possibility to vary the field gradient amplitudes instead of the gradient times. This idea led to Spin Warp Imaging, invented by Edelstein et al. [15] with quite clear advantages in comparison to Fourier Zeugmatography. Surely, I would have been led to this technique by thinking in terms of k-space, where, so to say, the area of the gradient pulses becomes the variable, replacing the variable duration of the gradient pulses. Intuitively, I used from the beginning the k-space concept in my work, but I was not aware of its generality, as formalized lucidly by Stig Ljunggren in "*A simple graphical representation of Fourier-based imaging methods*" [16].

Often, the concluding section of inventive papers lists a multitude of avenues for novel developments. This is also true for the paper in discussion. The last chapter, IV. "*Extensions of the Technique*", of Ref. [11] is a treasure trove of modified approaches, all related to Fourier imaging. It would go too far to recount all these variants on the available limited space. But it may be good advice to concentrate one's reading on the concluding sections of nearly forgotten papers. They might prove to be particularly stimulating for new or renewed ideas.

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