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Review

The road to functional imaging and ultrahigh fields

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ABSTRACT

The Center for Magnetic Resonance (CMRR) at the University of Minnesota was one of the laboratories where the work that simultaneously and independently introduced functional magnetic resonance imaging (fMRI) of human brain activity was carried out. However, unlike other laboratories pursuing fMRI at the time, our work was performed at 4 T magnetic field and coincided with the effort to push human magnetic resonance imaging to field strength significantly beyond 1.5 T which was the high-end standard of the time. The human fMRI experiments performed in CMRR were planned between two colleagues who had known each other and had worked together previously in Bell Laboratories, namely Seiji Ogawa and myself, immediately after the Blood Oxygenation Level Dependent (BOLD) contrast was developed by Seiji. We were waiting for our first human system, a 4 T system, to arrive in order to attempt at imaging brain activity in the human brain and these were the first experiments we performed on the 4 T instrument in CMRR when it became marginally operational. This was a prelude to a subsequent systematic push we initiated for exploiting higher magnetic fields to improve the accuracy and sensitivity of fMRI maps, first going to 9.4 T for animal model studies and subsequently developing a 7 T human system for the first time. Steady improvements in high field instrumentation and ever expanding armamentarium of image acquisition and engineering solutions to challenges posed by ultrahigh fields have brought fMRI to submillimeter resolution in the whole brain at 7 T, the scale necessary to reach cortical columns and laminar differentiation in the whole brain. The solutions that emerged in response to technological challenges posed by 7 T also propagated and continues to propagate to lower field clinical systems, a major advantage of the ultrahigh fields effort that is underappreciated. Further improvements at 7 T are inevitable. Further translation of these improvements to lower field clinical systems to achieve new capabilities and to magnetic fields significantly higher than 7 T to enable human imaging is inescapable.

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Introduction

In this article, I have taken the opportunity to reflect on some of the events that shaped my career and ultimately my intense interest and involvement with ultrahigh field magnetic resonance and functional brain imaging (fMRI) at such high fields.[1] The two are intricately tied for me and the laboratory that I lead at the University of Minnesota, the Center for Magnetic Resonance Research (CMRR); one cannot separate them since as soon as our 4 T system, one of the first three to be installed at about the same time circa 1990, became

[1] Although, this article covers some of the literature on functional magnetic resonance imaging and ultrahigh fields, it is by no means meant to be a comprehensive scientific review of these topics or the relevant literature.

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operational we initiated a project we had been planning for a while, namely imaging of brain activity using the BOLD contrast described by my colleague Seiji Ogawa (see also Ugurbil, this issue). Of course, this did not happen suddenly and in isolation; the path to that development started a long time before then.

Early years leading to high field MR

I finished high school in Istanbul. Having received a bilingual education from age twelve on, I was able to explore the possibility of studying in the USA and came to Columbia University in New York City for my undergraduate studies. Initially, I was not sure what I wanted to study. But I decided to major in physics after taking a course in electricity and magnetism in the first semester of my second year, a course which used a text book titled Electricity and Magnetism (at the time known as the Vol. 2 of the Berkeley Physics Course) written by Ed Purcell, who as many would know, shared the Nobel Prize with Felix Bloch for the discovery of Nuclear Magnetic Resonance (NMR) in 1952. That was my first encounter with magnetic resonance I suppose, though I did not know it at the time. But clearly, the pleasure of learning about electricity and magnetism from this wonderful textbook is one of the reasons I decided to study physics. However, by the time I was about to finish my undergraduate studies, the bottom fell out of the support for physics research in the USA. Many physicists were getting laid off and new job opportunities were scarce. I joined the rush of physicist abandoning physics and turning to biology both because of the excitement that engulfed biological sciences in the seventies and because of funding and employment opportunities.

After getting my bachelor's degree in 1971, I worked for a year in the lab of Cyrus Levinthal, well known for, among other things, the Levinthal's Paradox. Cyrus was a high-energy physicist turned successful biological researcher who, after working in molecular biology for a while, had switched his attention to neurosciences, in particular to connectivity in the developing nervous system. He was interested in the use of graphical computational tools to reconstruct, by tracing of electron microscopy serial sections, the growth and initial connections of the optic nerve axons in the small microcrustacean Daphnia (commonly referred to as the water flea) (e.g. Lopresti et al., 1973). In a way, this was a high-energy-physics inspired approach since, at the time, laboriously digitizing pathways of particles created in accelerator experiments was already a common practice. Cyrus had one of the first computers with a graphical interface in his lab and I worked that year as a programmer on this platform. I find it interesting that after many years, I now work towards tackling analogous problems, but with high and ultrahigh[2] field MR imaging and humans in the Human Connectome Project (http://humanconnectome.org/consortia/) that was recently awarded by NIH to a consortium lead by Washington University and University of Minnesota with David Van Essen and I as the principal investigators.

Despite my exposure to biology and neurosciences early on, I still did not pursue graduate studies in these topics. Instead, I drifted back to more physics with some biology included, doing my PhD with Richard Bersohn in the Chemistry Department at Columbia. Richard was a physical chemist who had done a lot of theoretical and experimental work with molecular beams, but was getting interested in biological problems at the time. During my PhD, I studied the structure and function of a cupper-containing electron transfer protein from bacteria. My PhD experience was quite broad. I carried out many aspects of the work alone, isolating and purifying the protein of interest and conducting studies of that protein with techniques like NMR, optical detection of triplet states, and fluorescence; I even worked on and with nanosecond lasers to measure rotational correlation times of the protein in solution, a parameter that is important for relaxation mechanisms in NMR, though this work was never published.

My exposure to biological problems at the cellular level came when I joined Robert (Bob) Shulman, Seiji Ogawa and Truman Brown at Bell Laboratories in the effort Bob had initiated in the department he led, the Biophysics Department, to apply MR spectroscopy to study intracellular processes in intact cells. Later, Jan den Hollander, Sheila Cohen and Bob Gillies would join us, and Gil Navon as well early in the effort. We employed ^{31}P and ^{13}C NMR spectroscopy to study energetics and metabolism in *Escherichia coli* and yeast cells in suspension (e.g. Ugurbil et al., 1978a, 1978b, 1982; Shulman et al., 1979). The work from this lab together with the contemporaneous effort from the laboratory of George Radda at Oxford pioneered *in vivo* magnetic resonance spectroscopy or MRS that many employ today to study metabolism in the human body using high and ultrahigh magnetic fields. Led by Bob, who is one of the greatest talents I have known in recognizing an important new scientific direction, we were immersed in, totally excited about, and energized by the realization that we were pushing the boundaries of NMR. This atmosphere, together with presence of superb colleagues in Bell Labs, created an extremely rich intellectual environment and a rigorous scientific "culture".

Bell Labs in general was truly a unique place[3]; in this large laboratory, owned and operated by a telephone company (AT&T), basic science research thrived with immense support given without demanding short-term returns. I particularly remember our lunches because they were almost always accompanied with long and interesting discussions among colleagues with diverse backgrounds, pursuing interesting questions, untethered with expectations of immediate return. Biological research flourished in Bell Labs because Bob Shulman had pointed out that a telephone company is ultimately interested in "information" and biological systems stored and utilized immense amount of information. Indeed a very long-term view in investment! This approach ultimately paid off not only in the great number Nobel prizes awarded to Bell Labs scientists, but also in the immense number of practical new technologies and consequent commercial returns. Max Perutz is quoted as saying "*Creativity in science, as in arts, cannot be organized. It arises spontaneously from individual talent. Well-run laboratories can foster it but hierarchical organization, inflexible bureaucratic rules, and mounds of futile paperwork can kill it. Discoveries cannot be planned; they pop up, like Puck in unexpected corners*". Bell Labs knew about these principles from its inception; it was a well-run laboratory that fostered creativity. It is a model that department chairmen, deans, directors of labs etc. and especially those who formulate science and funding policy should be mindful of, especially these days when we appear to be rapidly sacrificing a long-term vision for possible short-term gains and, at the same time, increasing "inflexible bureaucratic rules and mounds of futile paperwork". My Bell Labs experience was probably the most formative with respect to the development of my scientific interests and my approach to science, and is ultimately responsible for the push towards very high magnetic fields for human studies.

When I later moved to Columbia University as a faculty member and, subsequently, to the University of Minnesota in 1982, I continued the work I started in Bell Labs with *in vivo* spectroscopy but I switched from using cells in suspension to *ex vivo* perfused hearts and subsequently to whole animal models, in the latter case employing spatially localized spectroscopy, the introduction of which also dates back to Bell Labs years (Brown et al., 1982). I was, of course, always interested in expanding this effort ultimately to humans. However, these spectroscopy studies were being conducted at very high

[2] The terminology is based on that used for classifying radiofrequency (RF) bands. The frequency range 300 MHz to 3 GHz is defined as Ultra High Frequency (UHF) (see http://en.wikipedia.org/wiki/Ultra_high_frequency). The hydrogen nucleus resonance frequency at 7 T is ~300 MHz i.e. in UHF band and hence, 7 T can be defined as Ultra High Field (UHF).

[3] Bell Labs, as it was in those days, disappeared with the break-up of AT&T.

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