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Dr. Pettigrew has been elected to membership in the National Academy of Medicine, the National Academy of Engineering (NAE), the National Academy of Inventors, the American Academy of Arts and Sciences, and the National Academy of Sciences, India. His awards include gold medals from the Academy of Radiology Research and the Radiological Society of North America, the Arthur M. Bueche Award from the NAE and the Vannevar Bush Award from the National Science Board.

Expanding Boundaries

A lady approached Michael Faraday after one of his lectures on electromagnetism at the Royal Institution, and asked, "But, Professor Faraday, even if the effect you explained was obtained, what is the use of it?". According to Sir Richard Gregory, Faraday replied with Benjamin Franklin's apothegm: "Madam, will you tell me the use of a newborn child?" [1]

Sir Richard Gregory: Discovery, the spirit of science (London, 1916)

Pushing the envelope

In the last three decades, MRI has not only fulfilled its initial promise as a non-invasive imaging modality that can yield images with exquisite soft-tissue contrast in an impressive fashion; it has also become a versatile imaging tool that can provide insights into tissue in terms of its structure, function, and metabolism, and its magnetic, electrical, thermal, and mechanical properties. While the feasibility and demonstration of many advanced MR imaging methodologies often stem from academic settings, the engineering and technological refinements necessary for widespread clinical adoption require close collaboration between academics and industry partners. The fact that MRI systems are arguably among the most technologically and methodologically complex medical equipment you will find *routinely* used by clinicians around the world – with operational equipment specifications often prescribed in units of parts per million (ppm) – is a testament to the effective collaboration between scientists in academia and industry. Just in the last two decades, this collaboration has contributed to impressive performance boosts in nearly every aspect of MRI hardware. There have been significant advances in main field strength, gradient performance, multi-channel radio-frequency coil arrays, and software – acquisition methodologies and reconstruction – to further our understanding of human health. It is worth noting that such impressive progress is not a mere byproduct of the technological advances that are bound to occur with time but advances that had to reckon with the bounds imposed by the biological effects due to exposure to electromagnetic fields. These span six or more orders of magnitude both in terms of amplitude (from several Tesla for static magnetic fields to µT for RF fields) and frequency (from gradient field oscillations at a few kHz to the RF field variations on the order of hundreds of MHz

that are characteristic of an MR experiment). Regulatory bodies and the MR community prescribed conservative limits for RF exposure, such as specific absorption ratio (SAR) or peripheral nerve stimulation (PNS), to minimize any potential harm. The MR community – both in academia and industry – has pushed the envelope far beyond what was once considered possible in nearly every aspect of MRI. For example, in 1979, based on theoretical models of dielectric and inductive losses in a human sample, it was suggested that: *"…frequency of operation of the spectrometer with the human samples should be less than about 10 MHz" (~ 0.25T)* [2]. A mere few years later, in 1983, the first whole-body MRI scanners with field strengths of 1.5T that were capable of scanning the human head were introduced. Since that time, the strength of the main magnetic field of MRI scanners has increased five fold [3, 4]. The challenges of increased SAR and B_1^+ field inhomogeneity intrinsic to imaging at ultra-high fields are being met by methodological advances, such as techniques to lower the RF exposure while preserving tissue contrast and technological advances such as multi-array transmit solutions to minimize B_1^+ field homogeneity [5–7]. The SNR gains at ultra-high fields, as well as the increased sensitivity and specificity of the BOLD signal at ultra-high fields, have made it possible to image at resolutions capable of probing the columnar and laminar structures – believed to be the cortical processing units (CPU) – of the cortex [8]. This has also made it possible to couple blood flow dynamics in micro vessels of the brain to function [9], and to improve functional and structural images of the brain stem. From a clinical perspective, the increased sensitivity at ultra-high field imaging has broadened the range of potential applications: e.g., brain imaging with high spatial and contrast resolution to visualize various intracranial pathologies, to resolve metabolites hitherto undetectable at lower field strengths [10], measure pH in vivo, and evaluate neurovascular pathologies which may be contributing factors in many neurodegenerative [11] and demyelinating diseases [12, 13].

High-performance gradients for brain imaging: the lesson therein

Along the same lines, the potential to probe tissue microstructure via diffusion-weighted imaging (DWI) accelerated the quest to develop high-performance gradients with high peak gradient strengths (G_{max}) to impart sufficient diffusion sensitivity in relatively short times, *and* high slew rates (SR) to rapidly encode the diffusion-weighted signal with an echo-planar readout. At present, the commercial *whole-body* gradient systems available on the market can reach peak gradient amplitudes of around 80 mT/m and a maximum slew rate of 200 T/m/s [14]. Increasing the gradient performance of whole-body MR systems beyond this level has been recognized as a significant challenge. With increasing coil radius (r), the coil inductance increases dramatically (by a factor of r^5), necessitating substantial power to drive the gradient coil (and mechanisms to dissipate the concomitant thermal load effectively). In addition, PNS thresholds decrease with increased imaging volume thereby restricting the range of G_{max}/SR accessible for imaging. Many research MRI systems boast gradient inserts that cover a small region, e.g., an adult head, that can outperform whole-body gradient systems by a factor of four or more. Nearly a decade ago, the Human Connectome Project (HCP, funded by the National Institutes of Health) pushed the boundaries of DWI by customizing the gradient coil and gradient power amplifiers of commercial whole-body 3T scanners from Siemens Healthineers. The aim was to increase the maximum gradient strength from 40 mT/m to 100 mT/m [15] early on, with an even bolder version built as academically proposed with a maximum gradient strength of 300 mT/m [16]. Both systems boast a clean inner bore size of 56 cm with linearity of the gradient field (about 5% at 20 cm FOV) to image an adult head. It is no exaggeration to say that the technological and methodological advancements with the HCP have transformed the field of mapping connections within the brain and have yielded unprecedented insights into how the brain circuitry changes with aging and in disease. A more advanced version of the high-performance gradient system (dubbed Connectome 2.0[1]), with a G_{max} of 500 mT/m, a maximum SR of 600 T/m/s, and a slightly smaller inner diameter of 44 cm, is being developed [17] to study the functional architecture of the brain at multiple scales – from probing cellular geometries at microscopic levels to improving the robustness of estimates of fiber connectivity at macroscopic levels. Dedicated head-only systems with impressive gradient performance have now been demonstrated by several groups [18–22]. Overall, high-performance gradient systems have a high likelihood of becoming the new standard for neuro imaging, not just in research and academic settings but also in routine clinical practice.

High-performance gradients for whole-body imaging: what the future may hold

Indeed, the advent of high-performance gradients has contributed to opening new vistas of scientific inquiry to probe brain structure and function with unprecedented spatial and contrast resolutions. However, the role of high-performance gradients in body imaging has remained somewhat stagnant due to the inherent challenges of attaining sufficient gradient linearity over a large FOV, lower thresholds for PNS, and possible cardiac stimulation. However, the methodological improvements and technological expertise gained with high-performance gradients in neuroimaging can open new frontiers in the study of

structures outside the brain in the body. Several years ago, I advocated for developing high-performance gradients suitable for whole-body imaging and proposed what led to the creation of the 3T MAGNETOM Cima.X system[1], which will attain a gradient strength of 200 mT/m with a slew rate of 200 T/m/s. Compared to neuroimaging, the body-imaging challenges imposed by physiologic motion from cardiac pulsation, respiration, and blood flow, and by the substantial air-tissue interfaces in the thorax that introduce field inhomogeneities are substantial. Nonetheless there are several compelling reasons to investigate the role of high-performance gradients in the body.

First, as in neuroimaging, *even small reductions in TE* to attain a prescribed diffusion weighting may significantly mitigate the confounding effects of tissue motion and artifacts arising at susceptibility interfaces. Several clinical applications may immediately benefit from the availability of high-performance whole-body gradient systems. Multiparametric MRI of the prostate – the recommended initial diagnostic test for men with suspected prostate cancer – would benefit where imaging guidelines prescribe that diffusion MRI at b-values ~1400 s/mm^2 be obtained to improve the diagnostic confidence [23]. A concern, however, is that the presence of air in the bowels can substantially degrade the quality of prostate diffusion-weighted MRI. In our preliminary experience with human volunteers on the MAGNETOM Cima.X platform[1] [24], we successfully tested and demonstrated the feasibility of obtaining diffusion weighting > 2400 s/mm^2 (TE ~55 ms). The reduction in TE provides higher SNR for imaging and helps minimize the impact of T2 weighting in DWI.

Second, unlike neuroimaging, tissue motion – bulk motion as well as deformation – within the thoracoabdominal cavity is on the order of several millimeters of displacement. This is four or more orders of magnitude higher than the diffusive motion (micrometers) of water molecules and can result in a substantial signal loss if not treated appropriately. So, broader application of DWI in the body should consider the specific motion characteristics of the organ under investigation. One approach to increase the motion resilience is to design the diffusion-encoding gradient waveforms to be velocity (M_1) and acceleration (M_2) compensated at the cost of prolonged TE [25–28]. This cost could be partly mitigated with the availability of high-performance gradient systems. The feasibility of such M_1/M_2-compensated diffusion-encoding gradient waveforms has been demonstrated, e.g., in cardiac DWI in systems with gradient strengths of 80 mT/m. It reasonably follows that these methods could directly benefit from the availability of systems capable of delivering higher gradient performance.

In the heart, diffusion tensor imaging (DTI) can map myofibrillar disarray in patients with hypertrophic cardiomyopathy, manifested as a reduction in fractional anisotropy (FA) [29]. Fractional anisotropy is also diminished in patients with dilated cardiomyopathy compared to normal controls [30]. Cardiac DWI/DTI has shown promise in evaluating myocardial infarction in acute and chronic settings, which could offer a non-contrast alternative or complement to the widely used delayed enhancement MRI [31, 32]. The availability of increased gradient performance should improve the robustness of these methods and offer wider clinical application.

Third, diffuse pathologic changes in tissue can subtly alter the underlying tissue microstructure and microcirculation that are not evident in conventional MRI. Despite the promise of the intra-voxel incoherent model of diffusion to yield information about tissue microstructure as well as microcirculation (perfusion) from a single experiment, accurate estimation of perfusion-related parameters – perfusion fraction (f) and pseudo-diffusion coefficient (D*) – has been challenging. The reported values for a given organ system vary widely, as longer TEs associated with diffusion weighting encode relaxation-dependent effects in addition to diffusion [33]. Even modest reductions in TE with high-performance whole-body gradient systems can increase the robustness of estimating these parameters (particularly f) to yield imaging-based metrics that can help study such diffuse disease processes. For example, high-performance gradients could facilitate the development of diffusion-based non-contrast alternative metrics to extra-cellular volume fraction (ECV), a marker of diffuse fibrosis and in infiltrative cardiovascular pathologies such as cardiac amyloidosis, that is currently assessed with T1 measurements before and after the administration of an extracellular contrast agent [34]. Despite its promise, early DWI in the body has not found widespread clinical acceptance in the evaluation of diffuse disease processes. The improvements that come with high-performance gradient systems may increase the robustness of these measures enough to permit clinical adoption.

Fourth, the scale of endogenous tissue motion within the human body spans several orders of magnitude – from microscopic diffusive motion to rapid flow in large vessels that reaches many tens of cm/s. MRI scanners equipped with whole-body, high-performance gradient systems can enhance our ability to measure small tissue displacements, e.g., myocardial tissue velocities, vessel wall motion associated with cardiac pulsation, lymphatic drainage and cerebrospinal flow. The availability of (exceptionally) high gradient strengths can enhance the evaluation of microscopic externally imparted motion, e.g., to measure tissue motion caused by the acoustic radiation force at the focus of high-intensity ultrasound, or microscopic movement of

[1] *Work in progress. The product is still under development and not commercially available. Its future availability cannot be ensured.*

tissue imparted by external transducers as in the case of MR elastography [35, 36].

Finally, the advantages of having seamless access to high-gradient performance on a whole-body clinical 3T scanner herald new vistas. It is true that the full hardware capabilities of the MAGNETOM Cima.X system[1] are expected to exceed what can be clinically used in some anatomies while staying within the current PNS limits – a condition analogous to the state of brain imaging when Connectom gradients were initially delivered. We have observed that in the last 15 years, the introduction of high-performance gradient systems for neuroimaging has revolutionized our understanding of brain structure and function. The MR community has developed MR methods and solutions to problems that seemed insurmountable at the time. Similar progress should happen in the body. New approaches are being developed to include PNS models in the design of gradient hardware and more tailored gradient waveforms that can be safely used for imaging. Perhaps the day is near when patient-specific limits for PNS will be determined at the beginning of an MRI scan, similar to what is done in modern CT scanners to reduce radiation dose by modulating tube current as a function of patient body habitus. We hope the era of whole-body high-performance gradient systems will pave the way for a greater understanding of human health, earlier detection of disease, a greater opportunity for preventive intervention and thus improved delivery of healthcare.

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