G-Ratio mapping as a tool for neuroscience research: potential and current hurdles

Siawoosh Mohammadi Organizer
University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Department of Neurophysics, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Martina Callaghan Co-Organizer
University College London
London, United Kingdom

Overview

Recent advances in quantitative MRI and biophysical modelling of the MR signal have taken us a step closer to the promise of in vivo histology using MRI, i.e. the microstructural characterization of the living human brain. One of the parameters these techniques can provide is an MRI-based aggregated estimate of the g-ratio reflecting the degree of myelination of an axon relative to its cross-sectional size. Modelling of neuronal signal propagation has shown that the g-ratio is one of the most important parameters influencing neuronal conduction velocity, a key determinant of cognitive function, sensory integration and motor skills. Hence, we are now at a point where in vivo estimates of the g-ratio can be interpreted in the context of human function and behavior, in both health and disease. Extensive work has been done to derive and validate MRI markers of myelin composition, axonal distribution, and the g-ratio, however, challenges remain. Therefore, this symposium will describe some promising quantitative MRI approaches to mapping myelin and axonal volume fractions and the g-ratio, as well as the relationship between the g-ratio and conduction velocity. It will outline methods using calibrated volume-fractions and methods directly (i.e. not requiring calibration) mapping the g-ratio, highlighting their assumptions as well as their current and potential applications and limitations. This symposium is comprised of four lectures: highlighting the relevance of the g-ratio for conduction velocity and neuronal modelling; giving an overview of techniques used to date, applications, and validation; introducing a method for directly (i.e. not requiring calibration) mapping the g-ratio from the gradient-echo signal; investigating the calibration step in volume-fraction-based g-ratio mapping and how it can be improved. At the end, there will be a panel discussion with all the speakers intended to start a fruitful discussion about the perspectives of g-ratio mapping that involves the audience and will continue beyond this symposium.

Lecture 1: *Linking non-invasive characterization of white matter and axonal transmission - the g-ratio as important input for mechanistic models of brain function*

Thomas Knösche Presenter

Mechanistic and biologically plausible modeling of networks of interacting neural populations are an important means of constraining cognitive theories, of linking the domains of cognition and neurobiology, and of studying mechanisms of brain disease. Such models depend on accurate descriptions of neural transfer functions, including those along long axonal connections. For this, the acquisition of individual microstructural parameters through non-invasive brain imaging is of great importance.

The microscopic structure of brain white matter governs the transmission of action potentials, and thereby brain dynamics and information processing. This link can be mechanistically quantified using biologically realistic models of axonal transmission. The single axon is characterized by the velocity of action potentials travelling along it, which depends on numerous microstructural parameters, the most important ones being axon diameter, g-ratio, node and internode lengths. An entire axon bundle is characterized by a multivariate distribution of these parameters, and may additionally feature ephaptic coupling between axons. Distributed delays as well as synchronizations between the action potentials may result.
Using a framework in which we replace the Hodgkin-Huxley dynamics by a spike-diffuse-spike model allowed us to study in detail the influence of the various model parameters on the action potential velocity and on the entrainment of action potentials between ephaptically coupled fibers. The axon diameter is the strongest determinant of the transmission velocity and we confirm the known dependencies for unmyelinated and myelinated axons. The distance between the nodes of Ranvier (internode length) in myelinated axons is known to correlate with axonal diameter such that the internode length matches the cable constant. Our simulations show that a fixed ratio between internode and node lengths (about 40) ensures optimal transmission, while the velocity decreases over the empirical range of node lengths (about 1-3 microns) by about 20 %. Hence, influences of the node and internode lengths may be relatively moderate. In contrast, we find that the velocity depends more strongly on the g-ratio than was suggested by previous theoretical studies. Moreover, we demonstrate that ephaptic coupling between axons influences synchronization and velocity of spike volleys.
In summary, given the fact that direct access to axon diameter distributions appears to be relatively limited, the g-ratio may be the most promising candidate for the non-invasive characterization of long range fiber connections in the brain, in particular since it is also known that there is a relatively tight (non-linear) relationship between g-ratio and axon diameter. Hence, since long range connectivity is a crucial constituent of any mechanistic model of the brain, the determination of the g-ratio in the individual brain is an important prerequisite for a deeper understanding of how the structural and physiological properties of the brain give rise to its stunning functionality, including cognition.

Lecture 2: *The aggregate g-ratio imaging framework and beyond*
Jennifer Campbell Presenter

This talk will provide an overview of the g-ratio imaging framework, discuss its application and interpretation, and propose avenues for improvement of the technique. g-Ratio mapping can be done with MRI using either (i) generative biophysical models using the GRE signal or (ii) the volume-fraction based approach. In the latter, the fiber g-ratio is shown, via a simple tissue model, to be a function of the myelin volume fraction and the axon volume fraction. With MRI, these volume fractions have been inferred using quantitative MRI, including combinations of diffusion MRI modeling, magnetization transfer MRI, proton density, relaxometry, and complex gradient echo processing. The g-ratio imaging framework has been applied and shows promise in the study of healthy development and aging, and diseases such as multiple sclerosis. The analysis can be done using regions of interest or by connectomic analysis. These and other potential applications, such as relating structure and function, will be reviewed, with a focus on potential pitfalls in the interpretation of the g-ratio metric in cases of complex, heterogeneous tissue and disease. Potential solutions for these pitfalls will be presented, including more specific and more robust quantitative MRI metrics, and modeling to probe fascicle-specific microstructural parameters at the subvoxel scale. Finally, validation studies to date will be summarized.

Lecture 3: *Decoding MR g-ratio by integrating generative Biophysical models, Gradient Echo Signals and DWI*
Jose Marques Presenter

Myelin water imaging was first introduced in the late 90's [Mackay et al, 1994] when it was noticed that in white matter the spin echo signal decayed at two very distinct rates: a slow rate associated with water inside axons and in interstitial space, and a faster rate associated with water bound to myelin. In 2012 the Hollow cylinder model [Wharton et al, 2012] was introduced to explain the signal behaviour of gradient echo imaging, accounting for three compartments, with one being the myelin compartment which was characterized not only by a fast decay rate and an anisotropic magnetic susceptibility which in turn resulted in significant changes in the intra and extra-axonal water frequency shit. In this model it is clear that the g-ratio plays an important role in the signal amplitude and phase. This observation inspired the appearance of Myelin Water Imaging based on gradient echo data [Nam et al, 2014] and attempts to use the gradient echo signal do decode the white matter microstructural information (not only myelin water, but also fiber volume fraction and g-ratio) present in gradient echo data.
This talk will provide an overview of recent advances on myelin water imaging explicitly using the hollow cylinder model:
i) The integration of diffusion derived quantities (such as fiber orientation and dispersion, as well as ratios between diffusion restricted and hindered compartments) in combination with the hollow cylinder model as a mean of constraining the number of parameters used in multi-compartment relaxometry myelin water imaging.
-iii) The use of multiple orientation gradient echo data combined with signal models computed using realistic axonal geometries derived from microscopy such methods can be used to decode white matter microstructural information that go beyond traditional relaxometry and myelin water imaging resulting in Fiber Volume Fraction and g-ratio maps.

Mackay A, Whittall K, Adler J, Li D, Paty D, Graeb D. In vivo visualization of myelin water in brain by magnetic resonance. Magn Reson Med. 1994 Jun 1;31(6):673–7.

Wharton S, Bowtell R. Fiber orientation-dependent white matter contrast in gradient echo MRI. Proc Natl Acad Sci U S A. 2012 Nov 6;109(45):18559–64.

Nam Y, Lee J, Hwang D, Kim D-H. Improved estimation of myelin water fraction using complex model fitting. NeuroImage. 2015 Aug 1;116:214–21.

Hédouin, R., Metere, R., Chan, K.-S., Licht, C., Mollink, J., van Walsum, A.-M.C., Marques, J.P., Decoding the microstructural properties of white matter using realistic models, (2021) NeuroImage, 237, art. no. 118138, DOI: 10.1016/j.neuroimage.2021.118138

Chan, K.-S., Marques, J.P., Multi-compartment relaxometry and diffusion informed myelin water imaging – Promises and challenges of new gradient echo myelin water imaging methods, (2020) NeuroImage, 221, art. no. 117159, DOI: 10.1016/j.neuroimage.2020.117159

Lecture 4: *The calibration step in volume-fraction-based g-ratio mapping and how it can be improved*
Siawoosh Mohammadi Presenter

To ensure that the g-ratio measured with MRI is specific to relative axonal myelination, accurate calibration of its two constituent biomarkers (one estimated with myelin imaging, M, and the other with diffusion MRI, A) into volume fractions is required. Today's standard only scales M into a myelin volume fraction, neglecting a potential offset. Moreover it is assumed that A is directly mapping the diffusion-MRI-visible water fraction, i.e. that no calibration via a scaling or offset factor is required. In reality, however, each of these assumptions is probably invalid for the A and M biomarkers that have been used to date for g-ratio mapping. Here, we outline the existing calibration methods, evaluate the performance of these for different biomarkers and propose a new calibration method to calculate MR g-ratios. We show that this novel calibration method outperforms the current standard, improving the accuracy of MR-based g-ratio estimates and therefore their utility for neuroscientific research.