

PhD Thesis Subject: A unified biophysical modelling framework for white matter tissue characterization using multiparametric MRI

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Keywords: Magnetic Resonance Imaging, biophysical modelling, Monte Carlo simulations, inverse problem solving, white matter microstructure

PhD thesis description:

Magnetic Resonance Imaging (MRI) noninvasively probes biological tissues by exploiting the nuclear magnetic resonance of hydrogen spins in water and macromolecules (e.g., lipids and proteins). The measured MR signal arises from spin dynamics governed by relaxation, molecular diffusion, and chemical exchange, all of which are modulated by the underlying microenvironment. Quantitative MRI (qMRI), combined with biophysical modeling of the MR signal, enables the decomposition of this aggregate signal into distinct proton populations by representing spins with similar relaxation, diffusion, or exchange properties as separate compartments¹. In this framework, each compartment corresponds to a specific microstructural environment (e.g., axonal, extra-axonal, or myelin). Estimating biophysical properties through quantitative parameters such as relaxation times, diffusivity coefficients, and exchange rates provides indirect access to tissue microstructure and composition, offering a valuable approach to characterize and monitor tissue state in both health and disease. In particular, the estimation of compartmental volume fractions serves as an important indicator of the relative density of underlying microstructural constituents, such as axons, myelin, and glial cells.

State-of-the-art biophysical models of white matter have provided important insights into tissue microstructure and organization. However, they predominantly rely on single-contrast mechanisms, probing parameters of relaxation, diffusion, or chemical exchange in isolation through dedicated MR acquisition sequences that selectively sensitize the signal to one of these processes. As a result, each class of models captures only a partial view of the underlying microstructure and requires strong simplifying assumptions about tissue composition and compartmental interactions. These simplifications lead to parameter degeneracy and ultimately limit the specificity of the inferred microstructural features. For instance, relaxation-based approaches typically model white matter as two water pools, often associated with myelin water and the remaining tissue water². Diffusion-based models, in contrast, distinguish between intra-axonal and extra-axonal compartments but remain largely insensitive to myelin-associated water³. Similarly, chemical exchange-based methods probe interactions between bulk water and macromolecules, without explicitly separating distinct microstructural compartments⁴.

In the PHENIQS team (Physics and digital technologies for quantitative imaging of the central nervous system) in CRMBM, we work on the development of a novel MRI acquisition sequence that simultaneously sensitizes the MR signal to relaxation, diffusion, and chemical

exchange mechanisms. The objective of this PhD project is to design and validate a unified biophysical model of white matter that jointly accounts for these mechanisms, providing a more realistic description of tissue microstructure while reducing the biases inherent to single-contrast approaches. The biophysical model of white matter will comprise five compartments: water proton populations in the intra-axonal, extra-axonal, and myelin-associated spaces, and macromolecular proton pools in the extra-axonal and myelin compartments. The biophysical model will be interpreted by a mathematical model that combines Bloch–McConnell equations⁵ (for relaxation and chemical exchange) and Bloch–Torrey equations⁶ (for relaxation and diffusion) into a single formalism.

In practice, realistic 3D *in silico* models of white matter, together with the mathematical framework describing MR signal behavior, will be used in an open-source Monte Carlo simulator⁷ to simulate the MR signal produced by the newly developed MR acquisition sequence. This approach allows a controlled and quantitative assessment of how the sequence interacts with the tissue microstructure, prior to any *in vivo* experiments. The *in silico* models of white matter will be generated with varying compositions of myelin, axons, and glial cells using open-source tools⁸ and will be assigned different biophysical properties of relaxation, diffusivity and chemical exchange. A sensitivity analysis will be performed by systematically varying the acquisition variables of the MRI sequence across wide ranges to identify the optimal acquisition settings that provide sufficient sensitivity to discriminate the five compartments defined in the unified biophysical model.

To extract meaningful tissue properties from experimentally measured MR signals, the inverse problem must be solved. The relationship between the signals and the underlying biophysical parameters is nonlinear and sensitive to noise, and the large number of parameters to estimate (22 in total) requires robust strategies for numerical stability. Extensive datasets will be acquired on a calibrated physical phantom that replicates the five compartments described by the unified biophysical model. Acquisitions will be guided by the sensitivity analysis without any time constraint and performed on the 7T preclinical MRI scanner in the CRMBM. Data subsets and parameter groupings will be iteratively refined based on their impact on identifiability and fitting performance, until the estimated biophysical parameters converge toward the ground-truth values.

Translation for *in vivo* experiments on mice will be considered in the last part of this PhD project. For this purpose, the acquisition protocol will be optimized using analyses such as the Cramér–Rao lower bound, with the final goal of reducing the acquisition protocol to maximum 2 hours. The final protocol will then be applied to healthy mice, and repeatability analyses will quantify robustness to physiological and experimental variability. Validation will be achieved by correlating compartment-specific MRI metrics with corresponding histological markers for myelin, axons, and glia (performed by collaborators in the Institute of NeuroPhysiopathology in Marseille).

The ideal candidate should have a strong background in physics, biomedical engineering, or a related quantitative field, with solid knowledge of MRI physics and signal modeling. Experience in quantitative MRI and skills in scientific programming (Julia, Python, MATLAB) are expected. The candidate should be rigorous, autonomous, and comfortable working in an interdisciplinary environment at the interface of physics, mathematics, and biomedical applications. Familiarity with numerical modeling, simulations, or inverse problems is a plus. Good communication skills in English are required.

The innovative nature of this research project will offer the candidate valuable opportunities to publish in leading international journals in the field (e.g., *Magnetic Resonance in Medicine*, *Imaging Neuroscience*, *NMR in Biomedicine*), and to present their work at major international and national conferences in the field, including ISMRM, ESMRBM and SFRMBM.

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