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Diffusion Magnetic Resonance Imaging (dMRI) is the only available imaging technique for probing the brain tissue microstructure *in-vivo.* Through the years, dMRI has been used for both estimating brain connectivity via the use of tractography algorithms [1] and to obtain indices that represent numerically the brain tissue microstructure. Examples of such indices are the Fractional Anisotropy and Mean Diffusivity [2] which are commonly used in clinical practice. In order to better investigate the brain tissue, the dMRI community is interested in the estimation of more fine-scaled indices such as the intracellular volume fraction, and the extracellular parallel and perpendicular diffusivity. These indices are calculated by fitting a multi-compartment non-linear model to the diffusion signal, which has been proved to be challenging [3]. Microstructural indices are inherently rotation invariant, meaning for example, that the intracellular volume fraction in a voxel does not depend on the orientation of the axonal bundles underneath it. However, dMRI signal is very sensitive to the neurons orientation. The same axonal bundle oriented in two different directions has the same microstructural indices but completely different diffusion signal.

To overcome this limitation, our group developed a series of algebraic independent rotation-invariant features (RIF) from the diffusion signal Spherical Harmonics (SH) expansion [4]. The use of our RIF in combination with multicompartmental models was able to increase the accuracy of the microstructural indices estimation [4].

Fully connected neural networks (FC-NN) have also been successfully trained on the diffusion signal in each brain voxel to fit microstructural indices [5]. Golkov and colleagues [5] were able to achieve the same performance of a multi-compartment model with FC-NN using fewer diffusion signal samples as input.

In this work, we propose to combine the FC-NN and the new invariants testing if the combination of these two approaches improves the estimation of the microstructural indices with respect to each method taken by itself. In order to test this hypothesis, we created a set of 300000 synthetic voxels simulated using the state of the art multi-compartment models to train 12 FC-NN with an increasing number of perceptrons and hidden layers. The output of the networks are three microstructural features, namely the intracellular volume fraction, the extracellular parallel diffusivity, and the extracellular perpendicular diffusivity. We considered three inputs for the FC-NN: the raw diffusion signal (rds) as in [5], the 15 SH coefficients representing the rds approximated by a 4th-order SH, and the 12 RIF derived from the same 15 SH coefficients. We considered FC-NN with 2, 3, 4, and 5 hidden layers with 16, 32, 64, and 128 perceptrons per layer respectively. We split the dataset into 80% training and 20% testing considering batches of 100 voxels and trained the networks for 100 epochs using the Adam optimizer and MSE loss.

Our results show that all the networks are able to outperform the classical fitting using multi-compartment models.

RIF-based FC-NN is able to obtain better performances with respect to SH-coefficients and signal based FC-NN for all the networks with less than 64 perceptrons per hidden layer. Increasing the number of perceptrons leads to a convergence of the accuracy of the estimation of the microstructural indices for the three networks.

In conclusion, increasing the number of hidden layers from 2 to 5 leads to a general improvement of the estimation of the indices for all the inputs.

This work has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (ERC Advanced Grant agreement No 694665 : CoBCoM - Computational Brain Connectivity Mapping).

This work has been supported by the French government, through the 3IA Côte d'Azur Investments in the Future project managed by the National Research Agency (ANR) with the reference number ANR-19-P3IA-0002

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