# Accelerated Microstructure Imaging via Convex Optimization (AMICO) in crossing fibers

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**PURPOSE.** Mapping the local microstructure properties of the tissue in the brain is crucial to understand any pathological condition from a biological perspective. In recent years, microstructure-imaging techniques aimed at extracting such precious information by using explicit biophysical modeling of the decay patterns in different tissue compartments, e.g. axons, glial cells and extra-axonal space[1]. In particular, the ActiveAx technique[2] allows the estimation of the density and the average diameter of the axons with diffusion MRI, but the non-linear routines usually employed to fit the model to the data are computationally very intensive and cause practical problems for their application in clinical studies. Moreover, the model assumes a single axon orientation while numerous regions of the brain actually present more complex configurations, e.g. fiber crossing. ActiveAx was later extended to allow axon diameter mapping also in regions with crossing fibers[3], but the fitting time is still prohibitive for practical applications. Thus, there is an evident need for developing advanced techniques enabling *fast and accurate reconstructions* of the tissue microstructure properties not limited to regions known to contain only parallel fibers as for instance the corpus callosum. Recently, Daducci et al[4] presented a flexible framework for Accelerated Microstructure Imaging via Convex Optimization (AMICO) to reformulate these microstructure imaging techniques as linear systems that can be solved using fast convex optimization methods. The purpose of the present study is to extend the AMICO framework[4], which in its current formulation assumes only one fiber population per voxel, to *recover microstructure parameters also in regions with multiple fiber populations*.

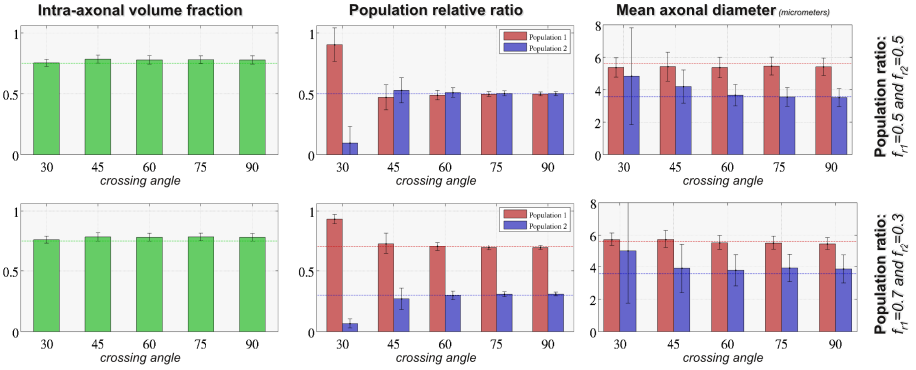
**METHODS.** The reconstruction problem for microstructure features from diffusion data in presence of crossing fibers is presented here as an extension of AMICO. In the AMICO framework[4], the microstructure mapping problem is re-formulated as a system of linear equations of the form $\boldsymbol{y} = \Phi\boldsymbol{x}$, (being $\boldsymbol{y}$ the vector of measurements, $\boldsymbol{x}$ the coefficients to be estimated and $\boldsymbol{\Phi}$ the linear operator or dictionary) and solved as a regularized least-squares problem as follows:

$$\min_{x\geq 0} \frac{1}{2}||\Phi x - y||_2^2 + \lambda\frac{1}{2}||x||_2^2$$

where $\|\cdot\|_2$ is the standard $\ell_2$ norm to promote Tikhonov regularization. As a proof of concept, we extend this formulation to allow axonal diameter mapping with the ActiveAx model[3] also in case of multiple fiber populations within a voxel. The reconstruction problem is decoupled into two simpler sub-problems. First, the number and orientation $\mu_i$ of the fiber populations in each voxel is estimated using standard Constrained Spherical Deconvolution[5]; please note that any alternative reconstruction method could be used in this step. For sake of simplicity, in this work only 2-fiber crossings are considered, acknowledging that the model can be generalized for any arbitrary number. In the second step, we build the linear operator $\Phi$ to express ActiveAx as a linear system being able to map microstructure features also in case of multiple fiber populations. To this end, the dictionary $\Phi$ is built from different sub-matrices: $\boldsymbol{\Phi} = [\Phi_1^r \mid \Phi_1^h \mid \Phi_2^r \mid \Phi_2^h]$, where $\Phi_i^r$ and $\Phi_i^h$ (i=1,2) model the intra-axonal and extra-axonal contributions to the diffusion signal along the direction of fiber population $\mu_i$. The microstructure indices defined by Alexander et al[2] can be estimated for each individual fiber population from the recovered coefficients $x$ by partitioning them as $[x_1^r \mid x_1^h \mid x_2^r \mid x_2^h]$ and then follow the procedure defined in AMICO[4] (further details can be found in the corresponding manuscript).

To evaluate the effectiveness of our formulation, we have tested it on synthetic data generated using the Monte-Carlo diffusion simulator system available in Camino[6], with the imaging protocol corresponding to a gradient strength $G_{max}$=140 mT/m with 270 measurements divided into 3 shells with b-values={1930,3090,13190} s/mm$^2$, corresponding to G={140,131,140} mT/m, $\delta$={10.2,7.6,17.7}, $\Delta$={16.7,45.9,35.8}ms and same TR/TE=5000/60 ms for all images. We simulated voxels with two fiber populations crossing at different angles (from 30° to 90°). Each fiber population consists of a distribution of different axon diameter, as done in Alexander et al[2], and several white-matter substrates have been tested. For each configuration, different relative ratios of the 2 populations have been evaluated. In each case, we computed the mean and standard deviation of the estimated microstructural parameters over 1000 repetitions, contaminating the signal with independent Rician noise realizations corresponding to SNR=30, and compared them to the ground-truth. For compactness, we report here only results corresponding to relative volume fractions $f_{r_1} = \{0.5, 0.7\}$ and fiber populations with 2 different radii distributions - gamma distributions with parameters $(3.27, 4.9 \cdot 10^{-7})$ and $(4.82, 2.6 \cdot 10^{-7})$, respectively corresponding to average axon diameters about 5.6 and 3.6 micrometers. Results on the other substrates are consistent.

**RESULTS AND DISCUSSION.** We have compared the microstructure indices (mean axon diameter, intracellular volume fraction and ratio between fibers) with the ground-truth in the experimental settings described above. Plots show the mean and standard deviation of the estimated parameters as a function of the crossing angles between the two fiber populations; dashed lines correspond to the corresponding ground-truth parameters. The intra-cellular volume fraction can be estimated very accurately for all crossing angles (slightly over-estimated by about 4%). Nonetheless, the accuracy in recovering the fiber orientation has a direct impact on the microstructure features estimation. In fact, the relative ratio of the two fiber populations can be estimated pretty robustly only for crossing angles larger than 45° but, when the two orientations are too close (≈30°), the algorithm fails to correctly disentangle them. As expected, this has an impact also on the estimation of the axon diameter index. The algorithm provides in fact accurate and precise estimates for crossing angles above 45°; however, as the crossing angle decreases the errors as well as the standard deviations of the estimates with respect to the ground-truth increase . Our results are in line with (and slightly improve) those previously reported by Zhang et al [3].




**CONCLUSION.** We have presented here an extension to the AMICO framework that enables *fast axonal diameter mapping* with ActiveAx also *in the presence of multiple fiber populations* within a voxel. Our results indicate that AMICO represents indeed an effective and extendable framework to obtain fast and accurate microstructural features in the white-matter. Future research will be devoted to improve the reconstruction by exploiting more advanced forms of regularization, notably to take advantage of the smoothness in the microstructural features of the fibers all over the brain.

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