Impact of Co-Registration on the Histogram Analysis of ADC maps in MRI/MRS Brain Tumor Diagnostics

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Target audience – Neuroradiologists and scientists focussing on: brain tumors, combination of MR spectroscopy and MR imaging, Apparent Diffusion Coefficient (ADC) histogram analysis and co-registration methods.

Purpose – MR-spectroscopy and MR-diffusion have proven to provide important information for initial brain tumor diagnostics as well as for tumor progression evaluation. For advanced longitudinal analysis of brain tumor patients, tools enabling *combined* advanced image and spectral analysis including co-registration are of utmost importance. However, image co-registration may have negative impact on the information extracted from ADC-maps. The purpose of this study is therefore to analyse the impact of co-registration on the histogram analysis[1, 2] of ADC maps of brain tumor patients examined by MRS.

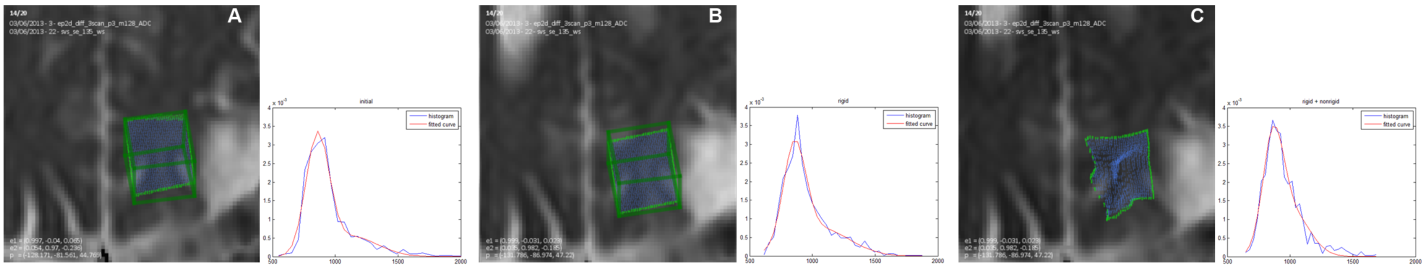

Figure 1 – Example showing the impact of the rigid and non-rigid co-registration on both the spectroscopic voxel and on the histogram. ***A*** corresponds to the initial state, ***B*** to the state after rigid registration and ***C*** to the state after both rigid and non-rigid registration. For ***A*** and ***B*** it is presented both the projection of the spectroscopic voxel and the intersection with the image slice. For ***C*** it is presented only the intersection of the spectroscopic voxel with the image slice. The histograms are presented with the corresponding fitted curves. The ADC intensity values are in $\mu m^2/s$ and the vertical axis values correspond to the normalized observed frequencies.

Methods – A novel custom java application that controls an external co-registration application and that is able to apply the same image transformations of the co-registration to the spectroscopic voxels was developed. The algorithm used for the co-registration was the open-source NiftyReg[3,4]. In order to be able to adapt the encapsulated region to the non-rigid deformations, the volume contained in the spectroscopic voxel was filled with a cloud of equally spaced points (Figure 1). The location of these points before and after deformation was used to extract the voxels for the histogram analysis. From the intensity values, both direct features (mean, standard deviation, skewness, kurtosis) and fitting parameters (two-component Gaussian mixture model) were collected. The fitting was performed using a constrained minimization algorithm. A total of 74 ADC maps were analysed at the location of the spectral voxel of patients with glioma. In all cases the single voxel spectroscopy (SVS) was placed in the tumor infiltrated area. The image reference chosen for co-registration was another ADC map of the same patient acquired at another time point. The histogram analysis was performed for each ADC map before registration, after rigid registration and after rigid followed by non-rigid registration. A two-tailed paired t-test was performed between the parameters obtained for the initial image and the ones obtained after co-registration. The results with p-value<0.05 were considered significant.

Results – The obtained results are resumed in Table 1. The performed study showed significant differences for the standard deviation after rigid and non-rigid registration, as well as for the mean but for this parameter only after non-rigid registration. The other histogram parameters analysed were not found to be significantly different.

Table 1 – Mean Root mean squared errors (RMSE), mean relative differences and results of the two-tailed paired t-test for the parameters extracted from the histogram analysis comparing the initial results with the ones obtained after rigid registration (top) and with the ones obtained after rigid followed by non-rigid registration (bottom). Miu1, sigma1, miu2, sigma2 and K correspond to the parameters of the two-component Gaussian mixture model.

		mean	**std. dev.**	**skewness**	**kurtosis**	**miu1**	**sigma1**	**miu2**	**sigma2**	**K**
Rigid	**RMSE**	469.60	1374.71	0.18728	9.21739	6019.75	5444.97	82583.54	19112.34	0.06613
	Rel. Diff.	-0.00022	-0.03730	2.23249	-0.22093	0.01776	0.35522	-0.00417	0.49464	0.87137
	p-value	0.63868	**0.00004**	0.28090	0.55626	0.08597	0.85323	0.24203	0.79758	0.84302
Rigid + Non-rigid	**RMSE**	6536.31	6325.06	0.52388	15.45	11673.44	5268.78	105118.99	41785.99	0.07326
	Rel. Diff.	-0.01736	-0.05461	0.89137	-0.31361	0.02353	0.27418	0.00233	0.71356	1.07854
	p-value	**0.01015**	**0.00060**	0.17905	0.18646	0.19353	0.23000	0.32732	0.37075	0.58859

Discussion – The results presented demonstrate that the co-registration of the ADC maps can have a significant impact on the parameters derived from the corresponding histogram analysis. Therefore, future studies using the histogram analysis of co-registered images should not neglect this effect and should evaluate the impact the registration step on the analysis being performed. Another alternative for evaluating consistently a certain region in a follow up study might be to maintain the images intact and perform the required transformations only to the contours of the Region of Interest (ROI). This can be done by using the co-registration method just to map one image to the other and obtaining the corresponding transformation. The transformations can then be applied just to the ROI, leaving the image information unaltered.

Conclusion – The presented study allowed showing that co-registration of the ADC-maps can have a significant impact on the parameters obtained from the histogram analysis. Therefore care has to be taken combining co-registration with histogram analysis of ADC-maps.

References – 1. Pope, Whitney B., et al. "Recurrent Glioblastoma Multiforme: ADC Histogram Analysis Predicts Response to Bevacizumab Treatment 1." Radiology 252.1 (2009): 182-189. **2.** Nowosielski, Martha, et al. "ADC histograms predict response to anti-angiogenic therapy in patients with recurrent high-grade glioma." Neuroradiology 53.4 (2011): 291-302. **3.** Ourselin, Sébastien, et al. "Reconstructing a 3D structure from serial histological sections." Image and vision computing 19.1 (2001): 25-31. **4.** Modat, Marc, et al. "Fast free-form deformation using the normalised mutual information gradient and graphics processing units." *High-Performance MICCAI workshop*. 2008.