

# 3D Variography of Human White Matter and the Influence of Age

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## Introduction

Magnetic resonance imaging is an excellent tool for the non-invasive acquisition of *in vivo* images with high soft tissue contrast. However, regarding a single tissue type, visual inspection is not the appropriate tool to gain information. This applies especially to healthy human white matter (WM). Indeed, in  $T_2$  weighted images of elderly patients one can frequently observe hyperintensities in the white matter (WMH). These findings seem to be the result of advanced changes in the vascular microstructure of the tissue [1]. Providing a tool which allows for the quantification of structural parameters of WM would be beneficial for the investigation of processes underlying ageing and might reveal structural changes of the tissue before they manifest as WMHs. In the present work a method widely used in geostatistics [2,3] and referred to as variography is employed in order to quantify the homogeneity and spatial correlation of WM tissue from MP-RAGE images. Fifteen female volunteers of various age are analysed and compared.

## Materials and Methods

Comparing MP-RAGE images of WM to Gaussian noise only one can hardly find any significant visual differences [Fig.1]. Nevertheless, both samples differ in the essential property of spatial correlation: the intensities of two arbitrarily chosen voxels from the noise image vary independently from their distance while two voxels in WM tend to have more similar intensities if they are closer together. This might be intuitive since the measured intensity is the mean value over the internal substructure of a voxel which also influences its environment, and therefore, the intensity of adjacent voxels. Such a spatial correlation can be depicted by a variogram. The value,  $\gamma$ , of the variogram for a certain distance,  $d$ , can be estimated by:  $\gamma(d) = \frac{\sum (I(x_1) - I(x_2))^2}{2n}$ , with  $|x_1 - x_2| = d$ , and represents the variance of the intensities,  $I(x)$ , of all  $n$  voxel pairs displaced by  $d$ . In order to interpret the variogram shape, one can use numerical samples consisting of randomly placed spheres of diameter,  $D$ , with Gaussian distributed intensities. Such samples give rise to a variogram that increases monotonically from zero distance to the diameter,  $D$ , while the value for larger distances remains constant.  $D$  is said to be the correlation distance of the sample and the value of the variogram for large distances represents the variance of the used intensities for the single spheres. In Figure 2 the variograms for spheres of diameter 3 and 9mm are shown exemplarily. The actual quantitative value for the correlation distance can be extracted from the variogram by fitting an appropriate function such as the commonly used spherical model ( $\gamma(d) = \sigma^2(3d/2d_c - d^3/2d_c^3)$  if  $d \leq d_c$  and  $\gamma(d) = \sigma^2$  otherwise), where  $d_c$  is the correlation distance and  $\sigma^2$  the variance. Interestingly, this technique also applies for a mixture of samples [Fig.2 (bottom)]. Thus, the sum of several samples gives rise to a variogram that is the sum of all single variograms. By defining a meaningful range of expected  $d_c$ 's and employing a nonnegative least square (NNLS) algorithm, one can decompose a variogram into several elementary variograms, each representing a region of correlation with a certain size and amplitude. The result can be depicted as a correlation spectrum [Fig.2 (right)]. Applying this methodology to white matter images, one can detect regions of correlation within the tissue and quantify their size and degree of homogeneity. The variograms were obtained from MP-RAGE images ( $\alpha=9^\circ$ ,  $TI=900ms$ ,  $TR=2250ms$ ,  $TE=3.03ms$ ,  $1 \times 1 \times 1 mm^3$  voxels) of 15 healthy female volunteers (age=39.9+15.5y) acquired with a 3T scanner (Siemens Medical, Erlangen, Germany). In order to preserve the comparability of the calculated variograms from the different subjects, a comprehensive preprocessing of the images is required: WM was segmented and inherently bias corrected by a SMP8 routine [4]. The mean intensity of the WM was scaled to 100 and the noise level of the image was determined in order to correct the variogram for these influences. For the estimation of  $\gamma(d)$ , only those pairs of voxels were considered which have a direct connection through the tissue, so that misinterpretations of the voxel distance due to the concave shape of WM is prevented. Finally, correlation spectra are inferred by means of a NNLS algorithm [5] using correlation distances from 0 to 100mm in steps of 0.1mm.

## Results

Figure 3 shows a typical WM correlation spectrum with peaks at 0mm, ~1.7mm, ~2.6mm, 5-10mm and ~20mm. Thus, it appears useful to divide the peaks into distance classes. The first class, referred to as short range, implies all peaks below 2mm representing the variance approximately within a voxel (space diagonal= $\sqrt{3}$ ). The second class, called mid range, contains correlation distances from 2-5mm and finally the wide range goes from 5 to 10mm. The last peak observed at approximately 20mm is most likely due to an inherent correlation of the MP-RAGE sequence. This was concluded from the analysis of datasets from homogeneous water phantoms. The values of the short and mid range class show a significant correlation ( $R>0.5$ ,  $p=0.02$ ) with subject age as depicted in Figure 3. Accordingly, WM heterogeneity increases systematically with age on the length scales mentioned. The wide range variance offered no significant correlation with age.

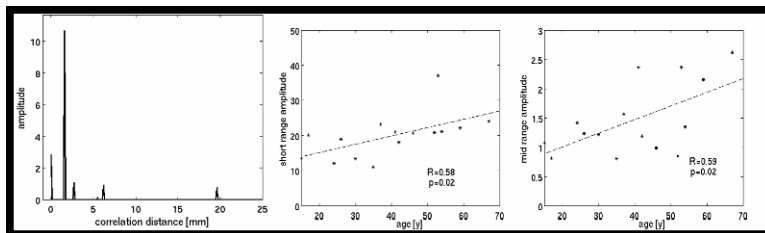


Fig.3: typical white matter correlation spectrum (left), short and mid range amplitudes vs. age from 15 volunteers (middle, right).

Spatial Data, John Wiley&Sons, Inc 1993; [3] A.G.Journel, Ch.J.Huijbregts, Mining Geostatistics, 5. Printing, The Blackburn Press 2003; [4] J.Ashburner, K.J.Friston, Unified segmentation, NeuroImage 26(2005):839-851; [5] MATLAB, The MathWorks, Natick, MA.

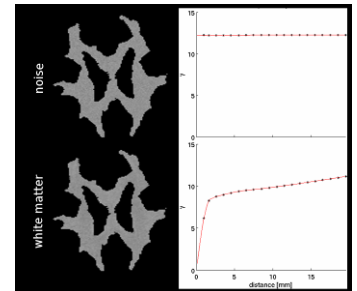


Fig.1: comparison of the spatial correlation of WM and noise.

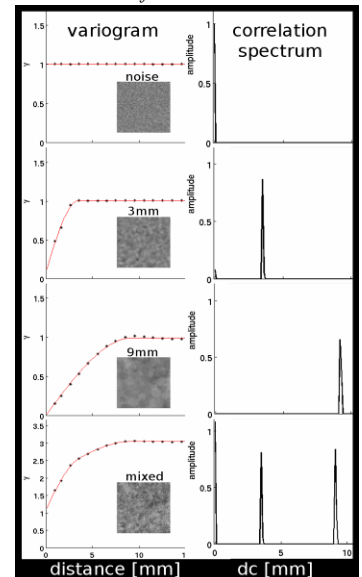


Fig.2: variograms and correlation spectra from various numerical samples.

## Conclusions

It has been demonstrated that the variogram method presented is able to reveal information about the WM spatial structure of different subjects beyond that obtained from visual inspection. Furthermore, the heterogeneity of correlated regions of different sizes was shown to be correlated significantly to age. This is an observation that is supported by the frequent occurrence of WMH in elderly patients. A thorough analysis of further volunteers in the future will serve to enhance the statistical significance of these results.

## References

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