

# Chapter 6

## Morphometry

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### Abstract

This chapter covers three principle morphometric methods, that will be called *voxel-based*, *deformation-based* and *tensor-based* morphometry.

Deformation-based morphometry (DBM) is a method for identifying macroscopic anatomical differences among the brains of different populations of subjects. The method involves spatially normalizing the structural MR images of a number of subjects so that they all conform to the same stereotaxic space. Multivariate statistics are then applied to the parameters describing the estimated nonlinear deformations that ensue.

Tensor-based morphometry (TBM) is introduced as a method of identifying regional structural differences from the gradients of deformations fields. Deformation

### 6.2.3 Canonical Correlation Analysis

To characterize differences among groups of subjects, one usually uses CCA, which is a device that finds the linear combination of dependent variables (in this case the deformations) that is maximally correlated with the explanatory variables (e.g., male vs. female). In a simple case of one categorical explanatory variable (e.g., sex) this will be the deformation field that best discriminates between the groups. Note that this is not the same as simply subtracting the deformation fields of two groups. This is because (i) the MANCOVA includes the effects of confounds that are removed and (ii) some aspects of the deformations may be less reliable than others (CCA gives deformations that explicitly discount error in relation to predicted differences). The canonical deformations can either be displayed directly as deformation fields, or can be applied to some image to “caricature” the effect detected.

Canonical correlation analysis (CCA) is used to measure the strength of association between two sets of variables. In this case, the variables are  $\mathbf{X}_a$  and  $\mathbf{Y}_a$ , which are the data and design matrix from Section 6.2.2 after having been orthogonalized with respect to a set of confounding effects. The first canonical variate pair is the linear combination of columns of  $\mathbf{X}_a$  and the linear combination of columns of  $\mathbf{Y}_a$ , that has the maximum correlation. The second canonical variate pair consists of linear combinations that maximize the correlation subject to the constraint that they are orthogonal to the first pair of canonical variables. Similarly, all subsequent pairs maximize the correlations and are orthogonal to all the previous pairs.

The weights used to determine the linear combinations are derived from the unitary matrices ( $\mathbf{U}$  and  $\mathbf{V}$ ) obtained by singular value decomposition:

$$\mathbf{USV}^T = \left(\mathbf{X}_a^T \mathbf{X}_a\right)^{-\frac{1}{2}} \left(\mathbf{X}_a^T \mathbf{Y}_a\right) \left(\mathbf{Y}_a^T \mathbf{Y}_a\right)^{-\frac{1}{2}}$$

Then the weights ( $\mathbf{A}$  and  $\mathbf{B}$ ) are derived by:

$$\mathbf{A} = \left(\mathbf{X}_a^T \mathbf{X}_a\right)^{-\frac{1}{2}} \mathbf{U} \text{ and } \mathbf{B} = \left(\mathbf{Y}_a^T \mathbf{Y}_a\right)^{-\frac{1}{2}} \mathbf{V}$$

The canonical variate pairs are obtained from the columns of  $\mathbf{X}_a \mathbf{A}$  and  $\mathbf{Y}_a \mathbf{B}$ .

When the number of variables approaches the number of observations, the problem needs to be regularized. This can be done by computing the canonical variates from data that has been compacted using singular value decomposition as in Section 6.2.2. If  $\mathbf{X}$  has been decomposed such that it can be approximated by  $\mathbf{X} \simeq \mathbf{U}^* \mathbf{S}^* \mathbf{V}^{*T}$ , and canonical correlation analysis performed on  $\mathbf{U}^*$  and  $\mathbf{Y}$  to give weight matrices  $\mathbf{A}^*$  and  $\mathbf{B}^*$ , then the weights to be applied to the original data ( $\mathbf{X}$ ) can be reconstructed by  $\mathbf{V}^* \mathbf{S}^{*-1} \mathbf{A}^*$ .

Figure 6.2 shows CCA as it would be used to graphically describe the differential features of three groups. However, it can also be used to aid classification. Once derived, the same weighting matrix ( $\mathbf{A}$ ) can be applied to new data-sets that were not involved in its derivation. If there are only two groups involved in a study, then CCA can be used directly to assign group memberships to new observations<sup>4</sup>. With more groups, CCA serves as a graphical aid for assigning new observations to the groups.

## 6.3 Tensor-Based Morphometry

There is a near infinite number of ways in which the shapes of brains can differ among populations of subjects. Many thousands or millions of parameters are required to precisely describe the shape

<sup>4</sup> Providing that the signs of the canonical variates are adjusted accordingly.

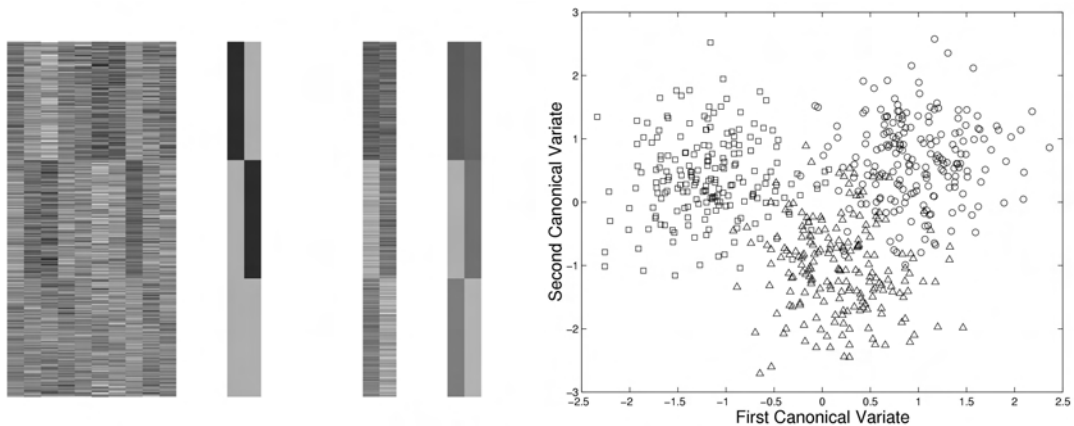


Figure 6.2: This figure illustrates canonical correlation analysis using simulated data. The two matrices on the left are a  $600 \times 10$  data matrix ( $\mathbf{X}_a$ ) and a  $600 \times 2$  design matrix ( $\mathbf{Y}_a$ ) after centering by orthogonalizing with respect to a column of ones as described in Equations 6.1 and 6.2. The design matrix represents a partitioning of the data into three groups. The canonical variates for  $\mathbf{X}_a$  and  $\mathbf{Y}_a$  are shown in the third and fourth matrices ( $\mathbf{X}_a \mathbf{A}$  and  $\mathbf{Y}_a \mathbf{B}$ ). The left-hand columns of these two matrices contain the first canonical variate pair, whereas the second pair are in the right-hand columns. The graph on the right shows the two columns of  $\mathbf{X}_a \mathbf{A}$  plotted against each other, where the different symbols used represent memberships of the three different groups.

of a brain at the resolution of a typical structural MR image. Given, say, 10 schizophrenic and 10 control brain images, there are lots of ways of inventing a measure that would differentiate between the groups. In most cases though, this measure will not provide any distinguishing power in a comparison between further groups of schizophrenics and controls. In other words, the measure would be specific to the subjects included in the study, and not generalizable to the populations as a whole. It is therefore not feasible to use methods that try to detect *any* difference. One has to be specific about the types of differences that are searched for.

The multivariate methods described in Section 6.2 require that the deformations are parameterized by only a few “eigen-warps”, on which the statistical tests are performed. This only allows inferences about those eigen-warps included in the analyses, so much of the information in the deformation fields is lost.

A more useful analysis involves identifying focal differences in the form of a statistical parametric map (SPM). SPMs of univariate statistical measures often allow relatively simple questions to be addressed, such as where is there significantly more of a particular measure that happens to correlate with a particular effect of interest. Standard parametric statistical procedures (t-tests and F-tests) can be used to test the hypotheses within the framework of the general linear model (GLM – see Chapter 7), whereby a vector of observations is modeled by a linear combination of user specified regressors [16]. The GLM is a flexible framework that allows many different tests to be applied, ranging from group comparisons and identifying differences that are related to specified covariates such as disease severity or age, to complex interactions between different effects of interest.

Performing comparisons at each voxel results in many statistical tests being done. Without any correction, the number of false-positive results would be proportional to the number of independent tests. A Bonferroni correction would be applied if the tests were independent, but this is not normally the case because of the inherent spatial smoothness of the data. In practice,

the effective number of independent statistical tests is determined using Gaussian Random Field (GRF) theory [15, 25] (see Chapters 14 and 15). By using GRF theory, a correction for multiple dependent comparisons can be made to produce the appropriate rate of false-positive results.

SPMs can also be obtained from the results of voxel-wise multi-variate tests. Instead of one variable per voxel of a subject, multivariate tests could effectively involve two or more variables. Following the voxel-wise multivariate tests, similar corrections based on GRF theory can be applied as in the univariate case. GRF theory has not yet been extended for Wilk's  $\Lambda$  fields, so approximations would need to be made that involve transforming the resulting Wilk's  $\Lambda$  fields to random fields of other statistics, such as  $\chi^2$  or F fields. Subsequent processing would then need to assume that the transformed fields have the same properties as true  $\chi^2$  or F fields. Another useful multivariate measure is the Hotelling's  $T^2$  statistic, for which GRF theory has recently been extended [9].

The objective of TBM is to localize regions of shape differences among groups of brains, based on deformation fields that map points in a template  $(x_1, x_2, x_3)$  to equivalent points in individual source images  $(y_1, y_2, y_3)$ . In principle, the Jacobian matrices of the deformations (a 2nd order tensor field relating to the spatial derivatives of the transformation) should be more reliable indicators of local brain shape than absolute deformations. Absolute deformations represent positions of brain structures, rather than local shape, and need to be quantified relative to some arbitrary reference position.

A Jacobian matrix contains information about the local stretching, shearing and rotation involved in the deformation, and is defined at each point by:

$$\mathbf{J} = \begin{bmatrix} \partial y_1 / \partial x_1 & \partial y_1 / \partial x_2 & \partial y_1 / \partial x_3 \\ \partial y_2 / \partial x_1 & \partial y_2 / \partial x_2 & \partial y_2 / \partial x_3 \\ \partial y_3 / \partial x_1 & \partial y_3 / \partial x_2 & \partial y_3 / \partial x_3 \end{bmatrix}$$

A simple form of TBM involves comparing relative volumes of different brain structures, where the volumes are derived from Jacobian determinants at each point (see Figures 6.3 and 6.4). Simple uni-variate statistics (t- or F- tests) can then be used to make inferences about regional volume differences among populations. This type of morphometry is useful for studies that have specific questions about whether growth or volume loss has occurred.

When many subjects are included in a study, a potentially more powerful form of TBM can be attained using multi-variate statistics on other measures derived from the Jacobian matrices. This use of multivariate statistics does not only test for volumetric differences, but indicates whether there are any differences among lengths, areas and the amount of shear. It may therefore be useful when there is no clear hypothesis about the nature of the differences, as may be the case when studying the effects of maturation on the human brain. This form of morphometry should be able to identify shape differences even when volumes are the same.

Because a Jacobian matrix encodes both local shape (zooms and shears) and orientation, it is necessary to remove the latter before making inferences. According to the polar decomposition theorem [21], a non-singular Jacobian matrix can be decomposed into a rotation matrix ( $\mathbf{R}$ ) and a symmetric positive definite matrix ( $\mathbf{U}$  or  $\mathbf{V}$ ), such that  $\mathbf{J} = \mathbf{R}\mathbf{U} = \mathbf{V}\mathbf{R}$ . Matrices  $\mathbf{U}$  and  $\mathbf{V}$  (called the *right* and *left stretch* tensors respectively) are derived by  $\mathbf{U} = (\mathbf{J}^T \mathbf{J})^{1/2}$  and  $\mathbf{V} = (\mathbf{J} \mathbf{J}^T)^{1/2}$ . Matrix  $\mathbf{R}$  is then given by  $\mathbf{R} = \mathbf{J}\mathbf{U}^{-1}$  or  $\mathbf{R} = \mathbf{V}^{-1}\mathbf{J}$ . For a purely rigid body transformation,  $\mathbf{U} = \mathbf{V} = \mathbf{I}$  (the identity matrix). Similarly, if  $\mathbf{R} = \mathbf{I}$ , then the deformation can be considered as *pure strain*. Deviations of  $\mathbf{U}$  or  $\mathbf{V}$  away from  $\mathbf{I}$  indicate a shape change, which can be represented by a strain tensor  $\mathbf{E}$ . Depending upon the reference co-ordinate system, the strain tensor is referred to as either a *Lagrangian* or an *Eulerian* strain tensor. When the strain tensor is derived from  $\mathbf{U}$ , it is referred to as a Lagrangian strain tensor, whereas when it is derived from  $\mathbf{V}$ , it is Eulerian. Spatial normalization of a series of source images involves