Figure 17.5: Partitioning the ventricles into 3D surface elements. A model of the lateral ventricles is shown, in the context of a coronal anatomic image and a smoothed cortical surface mesh. The ventricles are partitioned into 14 connected surface elements, whose junctions reflect tissue type boundaries at the ventricular surface. For example, caudate, thalamic, and septal tissues (as well as callosal fibers) surround the superior ventricular horn, and each exhibits different patterns of variation and asymmetry. To ensure that these parameters are not confounded, each ventricular element is modeled separately. (For a color version of this Figure see Plate 28 in the color section of this book.)
hemispheres. Additional gyral boundaries are represented by parameterized curves lying in the cortical surface. The ventricular system is modeled in [29] as a closed system of 14 connected surface elements whose junctions reflect the cytoarchitectonic boundaries of the adjacent tissue (Fig. 17.5). Information on the meshes’ spatial relations, including their surface topology (closed or open), anatomical names, mutual connections, directions of parameterization, and common 3D junctions and boundaries is stored in a hierarchical graph structure. This ensures the continuity of displacement vector fields defined at mesh junctions.

17.5.3 Automated parameterization

A major goal in brain mapping is to find surfaces of brain structures automatically. If an identical regular grid structure can be imposed on anatomic surfaces from different subjects (Fig. 17.4), the explicit geometry can be exploited to compute shape measures and correspondence maps that associate anatomic points in different subjects. Accurate labeling of anatomy, especially at the cortex, requires detailed case-by-case rules that are difficult to formulate computationally [25, 26, 41, 42, 115]. Current approaches for automated parameterization of brain structures fall into two major categories: (1) deformable templates, and (2) voxel coding. Deformable templates are covered in detail in Chapters 3 and 6. Briefly, the shape of a prototype model, such as a parametric curve or surface, is tuned until a measure of fit is optimized, suggesting that the target object has been found in the image. Probabilistic brain atlases can assist these algorithms, in that (1) stored information on empirical shape variability can guide deformable templates [116], and (2) a validation test-bed of existing models can be used to optimize algorithm parameters. Bayesian approaches have also been developed to identify the corpus callosum in each image in an MRI database [44, 117]. In [44], the shape of a deformable curve (Fig. 17.6, panel 7) is progressively tuned to optimize a mathematical criterion measuring how likely it is that it has found the corpus callosum. The measure includes terms that reward contours based on their agreement with a diffused edge map (panels 7-9), their geometric regularity, and their statistical abnormality when compared with a distribution of normal shapes. As described by Cootes et al. [116] and Jain et al. [118], a preference for specific shapes is expressed by specifying a probability distribution on the parameters of the deformation function. Since the best algorithm parameters may depend on the image noise (e.g., the size of the connectivity filter for edge suppression), optimal values were determined empirically from simulations on a database of 104 brain images. The performance of the algorithm is shown in Fig. 17.6. As we shall see later, by averaging corpus callosum contours derived from an image database, structural abnormalities associated with Alzheimer’s disease, schizophrenia, and fetal alcohol syndrome can be identified and visualized [28, 29, 41, 42, 47].
Figure 17.6: Probabilistic labeling of brain structures. An atlas storing information on anatomic variability is used to guide an algorithm in finding the corpus callosum boundary (panel 9) in each image in an anatomic database (N=104; [44]). The output of an edge detector (panel 2) is run through a connectivity filter that suppresses the smallest connected sets of edge pixels. The filtered edge image is then diffused over time (panels 4-6) and a deformable curve (panel 7) is adapted to optimize a matching measure (panel 10). This measure penalizes curve shapes that are (1) too bent or stretched, that (2) fail to overlap the diffused edge image, or that (3) are unlikely based on a statistical distribution of normal corpus callosum shapes. Given an image database, algorithm parameters (such as the size of the connectivity filter; panel 11) can be tuned based on their overall performance on an image database. Their optimal values differ depending on how noisy the images are. Boundaries can then be averaged from patients with dementia or schizophrenia to detect anomalies. Using separate sets of training and test images, these algorithms can both invoke and generate information on structural variation and pathology. (For a color version of this Figure see Plate 29 in the color section of this book.)
17.5.4 Voxel coding

Voxel-coding [119, 120] provides a fundamentally different approach for automated structure parameterization. Rather than starting with an a priori geometric model of the target structure, low-level image operations, such as erosion and dilation, are applied at a voxel-by-voxel level to gradually build up parametric surface grids. The term voxel-coding derives from the procedure of repeatedly assigning numerical codes to voxels. These codes are used to sort voxels efficiently, find the shortest paths in 2D and 3D, and accelerate mathematical morphology operations such as erosion and skeletonization. This approach by-passes the complex mathematics of deformable templates, is computationally fast, and extracts parameterized models of multiple surfaces in a 3D image at once. A related approach can be used to extract sets of curved lines representing the superficial sulcal pattern. In view of the interest in deformable surfaces to parameterize deep sulcal anatomy [57, 121], a voxel-coding approach was recently developed to address the problem ([119]; Fig. 17.7). In this approach, a supervised classifier is used to derive a binary map of gray matter and cerebro-spinal fluid (CSF) which contains the sulci. In each 2D slice a fast algorithm propagates a distance field from the image exterior to the sulcal beds. Local maxima of the distance function are identified, and from these points shortest voxel paths to the exterior are identified. These paths are adjusted to a medial course by reference to a second distance field propagated from the sulcal banks. A third distance field is then traversed to establish local object connectivity between slices, and the resulting voxel set is uniformly reparameterized and triangulated [20]. Topological issues of ambiguous or multiple connectivity, e.g., when objects merge or divide, are addressed by introducing a simplified skeleton extracted from a region that defines interslice differences [120]. Automatically extracted models agreed well with manual-derived data, and their local accuracy was mapped using an adaptive approach based on Hotelling’s $T^2$ random fields to encode patterns of manual error [25, 26, 119]. Work is underway to integrate this approach into an automated image analysis pipeline for analyzing disease-related patterns of anatomy.

17.5.5 Model-based deformable atlases

Parametric models can also be used to measure cross-subject anatomical differences by computing the amount of deformation required to reconfigure one anatomy into the shape of another. A recently developed surface-based 3D image warping algorithm [29, 80, 81] matches complex anatomical surface boundaries when driving one brain into the shape of another. Specialized approaches are used to match gyral patterns of the cortex across subjects (see Section 17.7) constraining the anatomical transformation with anatomical landmark points, curves, surfaces, and even curves within surfaces. For each surface mesh $M_i$ in a pair of scans $A_p$ and $A_q$ we define a 3D displacement field:
Figure 17.7: Automated sulcal surface parameterization. (Data from [119]). Parametric models of deep sulcal surfaces can be derived automatically from MRI data. An MR image (panel 1) is tissue classified to produce a binary map (panel 2) of gray matter and cerebro-spinal fluid (CSF). Shortest paths are generated to points that are local maxima of a distance field from the exterior (panel 3) and adjusted to a medial course (panel 4). Recursive generation of voxel codes based on distance fields (panels 5-8) imposes a serial order on these voxels, which are triangulated (panel 9) after resolving connectivity ambiguities between image slices. Multiple surfaces are obtained simultaneously. These surface meshes can be uniformly reparameterized for subsequent measurement and analysis [20]. (For a color version of this Figure see Plate 30 in the color section of this book.)
carrying each surface point \( r_t^p(u, v) \) in \( A_p \) into structural correspondence with \( r_t^q(u, v) \), the point in the target mesh parameterized by rectangular coordinates \((u, v)\). This family of high-resolution transformations, applied to individual meshes in a connected system deep inside the brain, elastically transforms elements of the surface system in one 3D image to their counterparts in the target scan. Weighted linear combinations of radial functions, describing the influence of deforming surfaces on points in their vicinity, extend the surface-based deformation to the whole brain volume (see Fig. 17.8). Recent extensions of the core algorithm to include continuum-mechanical and other filter-based models of deformation [18, 19, 29, 110, 122, 123] have yielded similar encouraging results. Figure 17.8 shows how the algorithm performs on post mortem cryosectioned data.

\[
W_{i}^{pq}[r_t^p(u, v)] = r_t^q(u, v) - r_t^p(u, v)
\]  \hspace{1cm} (17.22)

17.6 Probabilistic atlases and model-based morphometry

17.6.1 Anatomical modeling

Many morphometric studies focus on identifying systematic alterations in anatomy in a variety of diseases. These studies are complicated by the substantial overlap between measures of normal and diseased anatomy, which makes group-specific patterns hard to discern. However, recent studies suggest that disease-specific variants may be easier to localize by creating average models of anatomy, rather than deriving volumetric descriptors [25, 26, 41, 42, 47, 48, 114].

In response to these challenges, probabilistic atlases are research tools that retain information on anatomic and functional variability [25, 32–34, 37]. A probabilistic atlas solves many of the limitations of a fixed atlas in representing highly variable anatomy. As the subject database increases in size and content, the digital form of the atlas allows efficient statistical comparisons of individuals or groups. In addition, the population that an atlas represents can be stratified into subpopulations to represent specific disease types, and subsequently by age, gender, handedness, or genetic factors.

17.6.2 Parametric mesh models

Parametric meshes [80, 81] offer a means to create average models of anatomy. Once anatomical data is transformed to a standardized coordinate space, such as the Talairach space, a computational grid structure can be imposed on anatomical surface boundaries. These mesh models represent boundary point locations in stereotaxic coordinates (Fig. 17.4). Averaging of corresponding grid points across subjects results in an average surface model for each structure. At the same time, knowledge of each subject’s deviations from the anatomical group average can be retained as a vector displacement map (Fig. 17.4). After storing these maps from
Figure 17.8: A deformable cryosection atlas measures anatomic differences. Structure boundaries from a patient with Alzheimer's disease (top left) are overlaid on a cryosection atlas (top right), which has been registered to it using a simple linear transformation. A surface-based image warping algorithm is then applied to drive the atlas into the configuration of the patient's anatomy (bottom left). Histologic and neurochemical maps, accessible only post mortem, can be transferred onto the living subject's scan [24]. The amount of deformation required is displayed as a tensor map (only 2 components of the fully 3D transformation are shown). Tensor maps, and derived vector or scalar fields, can be analyzed in a statistical setting to examine anatomic variation, detect pathology, or track structural changes over time. (For a color version of this Figure see Plate 31 in the color section of this book.)
large numbers of subjects, local biases in the magnitude and direction of anatomic variability can be displayed as a map.

17.6.3 3D maps of variability and asymmetry

Figure 17.9 shows average maps of the lateral ventricles, again from Alzheimer’s disease and matched elderly normal populations. In these maps, the color shows the root mean square magnitude of the displacement vectors that map individuals to the group mean. Separate maps are displayed for elderly normals (mean age: 72.9±5.6 yrs.), and Alzheimer’s disease (AD) patients matched for age, gender, handedness (all right-handed), and educational level (age: 71.9±10.7 yrs.; mean Mini-Mental State Exam score: 19.7±5.7, out of 30). Clearly, the ventricles are significantly enlarged in dementia. By contrast with conventional volumetric approaches, which indicate that the ventricles are enlarged overall in AD, the region of greatest disease-related enlargement is clearly localized to the occipital horn. A second feature observable from the average anatomical models (Fig. 17.9) is that consistent patterns of brain asymmetry can be mapped, despite wide variations in asymmetry in individual subjects. This is an example of an effect that becomes clear after group averaging of anatomy and is not universally apparent in individual subjects. On average, the occipital horn extends 5.1 mm more posteriorly on the left than the right. Anatomical averaging can also be cross-validated with a traditional volumetric approach. In this subject group, occipital horns of the ventricles were on average 17.1% larger on the left in the normal group (4070.1±479.9 mm$^3$) than on the right (3475.3±334.0 mm$^3$; $p < 0.05$), but no significant asymmetry was found for the superior horns (left: 8658.0±976.7 mm$^3$; right: 8086.4±1068.2 mm$^3$; $p > 0.19$) or for the inferior horns (left: 620.6±102.6 mm$^3$; right: 573.7±85.2 mm$^3$; $p > 0.37$). The asymmetry is clearly localized in the 3D group average anatomic representations.

17.6.4 Alzheimer’s disease

Anatomical averaging has also been applied to identify disease-specific patterns in clinical populations. Preclinical hippocampal atrophy, for example, has been identified in patients with minimal cognitive impairment [35, 124]. To identify more focal effects, tests have recently been conducted to identify regionally selective patterns of callosal change in patient groups with Alzheimer’s disease and schizophrenia [28, 29, 47]. The midsagittal callosum was first partitioned into 5 sectors (Fig. 17.10; [125, 126]) that roughly segregate callosal fibers from distinct cortical regions. In AD, focal fiber loss was expected at the callosal isthmus (sector 2), which carries fibers that selectively innervate the temporo-parietal regions that show early neuronal loss and perfusion deficits [127]. Consistent with this hypothesis, a significant area reduction at the isthmus was found, reflecting a dramatic 24.5% decrease from 98.0±8.6 mm$^2$ in controls to 74.0±5.3 mm$^2$ in AD ($p < 0.025$). Terminal sectors (1 and 5) were not significantly atrophied, and the central
Figure 17.9: Population-based maps of ventricular anatomy. 3D parametric surface meshes [80, 81] were used to model the 14 ventricular elements, shown in Fig. 17.5, in 3D MRI scans of 10 Alzheimer’s patients (age: 71.9±10.9 yrs.), and 10 matched controls (72.9±5.6 yrs.; Thompson et al., 1998). 3D meshes representing each surface element were averaged by hemisphere in each group. (top:) The color map shows a 3D r.m.s. measure of group anatomic variability pointwise on an average surface representation for each group, in Talairach stereotaxic space. Oblique side views reveal enlarged occipital horns in the Alzheimer’s patients, and high stereotaxic variability in both groups. (lower panels:) A top view of these averaged surface meshes reveals localized asymmetry, variability, and displacement within and between groups. Asymmetries at the ventricles and Sylvian fissure emerge only after averaging of anatomical maps in large groups of subjects. These patterns can be encoded probabilistically to detect structural anomalies in individual patients or groups [25,26]. (For a color version of this Figure see Plate 32 in the color section of this book.)
midbody sector showed only a trend toward significance (16.6% mean area loss; \( p \sim 0.1 \)), due to substantial intergroup overlap. Average boundary representations, however, localized these findings directly. At the isthmus, average models in AD showed a pronounced shape inflection at stereotaxic location (0.0,-25.0,19.0) (see Fig. 17.10).

17.6.5 Gender in schizophrenia

Different shape alterations were observed in schizophrenia ([128]; Fig. 17.11). A significant bowing effect was observed, reflecting enlargement of the underlying superior and posterior horns of the lateral ventricles. By creating separate average models for male and female patients, significant gender effects also emerged (Fig. 17.11). The greater bowing effect in male than female patients was confirmed by multivariate analysis of variance and is highlighted in the average anatomic templates. As emphasized by this example, even if no sex difference is present in normal callosal morphology (see [40], for a review of this controversy), this does not preclude sex effects from interacting with morphometric abnormalities in diseased populations. In schizophrenia, there is typically a later age of onset in female schizophrenics, and hereditary factors may be unevenly distributed between the sexes [129–131]. Stratification of probabilistic atlases by gender and other genetic factors provides a computationally fast way to visualize these effects and relate them to epidemiologic data [37,51,52,57,132–134]. The capacity to resolve group features in a population-based atlas can also assist in studies of disease-specific cortical organization [25, 26, 36, 51, 52, 132, 135].

17.7 Cortical modeling and analysis

The cortex presents unique challenges in brain mapping. Extreme variations in gyral patterns make it hard to (1) identify homologous cortical regions across subjects, (2) pool cortically-derived imaging data across subjects, and (3) distinguish normal from abnormal cortical structure. The cortex is also severely affected in disorders such as Alzheimer’s disease, Pick’s disease, and other dementias, by tumor growth, and in cases of epilepsy, cortical dysplasias, and schizophrenia. A major challenge in investigations of disease is to determine (1) whether cortical organization is altered, and if so, which cortical systems are implicated, and (2) whether normal features of cortical organization are lost, such as sulcal pattern asymmetries. This requires methods to create a well-resolved average model of the cortex specific for a diseased group, and a statistical framework to compare individual and group average models with normative data.

17.7.1 Cortical matching

Cortical anatomy can be compared, between any pair of subjects, by computing the warped mapping that elastically transforms one cortex into the shape of the other. Due to variations in gyral patterning, cortical variability will be severely